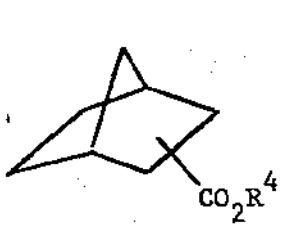
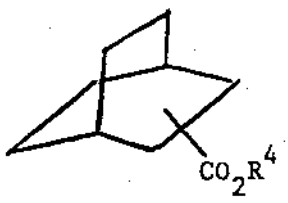
1-(2,4,6-trimethylbenzoyloxy)ethyl, pivaloyloxymethyl, phenethyl, phenpropyl, 2,2,2-trifluoroethyl, 1- or 2-naphthyl, 2,4-dimethylphenyl, 4-t-butylphenyl and 5-indanyl.

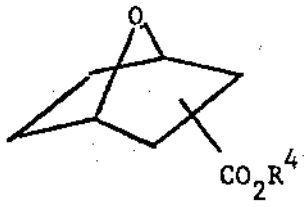
Of these a particularly preferred biolabile ester-forming group is 5-indanyl.

Compounds of the formulae (I) and (II) wherein one or both of R and R^4 are C_1-C_6 alkyl, particularly ethyl, or benzyl, are also active by virtue of their hydrolysis <u>in vivo</u>, and, in addition, are valuable intermediates for the preparation of the diacids wherein R and R^4 are both H.

Particular examples of compounds of the formula (I) wherein X is a bridged cyclic group include compounds wherein X is a group of the formula:-

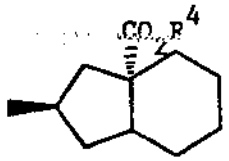






The above groups may be 2,5- or 2,6-linked, each attachment being of either endo or oxo stereochemistry.

Examples of compounds wherein X is a bicyclic group include in particular compounds wherein X is a group of the formula:



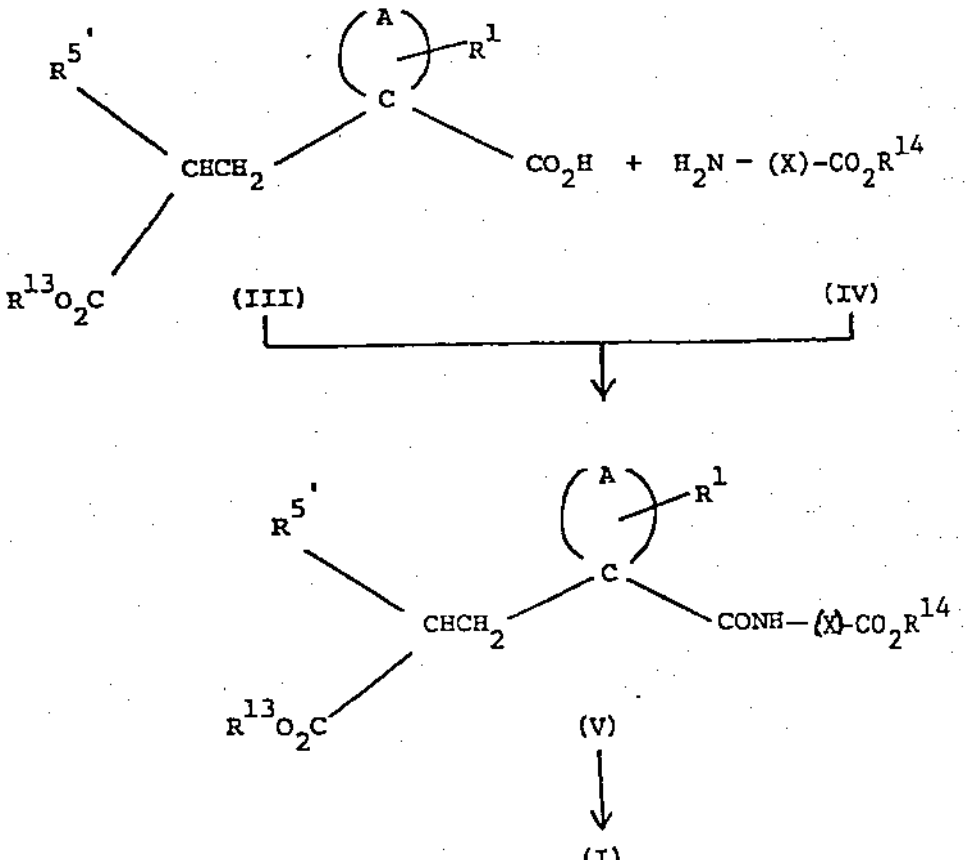
The group R^5 is preferably C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_5 alkynyl, C_5-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, C_1-C_4 alkylsulphonamido, or tetrahydrofuranyl or wherein R^5 is C_1-C_3 alkyl susbtituted by C_1-C_3 alkoxy, C_1-C_6 alkoxy(C_2-C_4 alkoxy), C_3-C_6 cycloalkyl, 4-pyridyl, 2-imidazolyl, C_2-C_4 alkanoyl, C_2-C_4 alkoxycarbonylamino, C_1-C_4 alkylsulphonyl, C_1-C_4 alkyl-sulphonamido, arylsulphonamido, heteroarylsulphonamido or benzoylamino. Thus particular and preferred examples of R^5 include methoxyethyl, 2-methoxyethoxymethyl, 4-aminobutyl and 2-methylsulphonylethyl.

Particularly preferred individual compounds of the invention include 3-{1-[6-endo-carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl} -2-(2-methoxyethyl)propanoic acid and 3-{1-[6-endo-carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl} -2-(2-methoxyethoxymethyl)propanoic acid, especially the dextrorotatory diastereoisomer of the latter compound wherein the bridged cyclic group X is resolved.

The compounds of formula (I) are prepared by a number of different processes. The basic procedure involves coupling a partially protected spiro-substituted glutaric acid derivative to an amine to give the desired glutaramide. The carboxylic acid group in the amine, if free, or any reactive groups in R^5, may require protection during the coupling step and such protecting groups are removed in the final stage of the process.

The synthetic route is illustrated in scheme 1 wherein A, is as previously defined, $R^{5'}$ is as defined for R^5 with any reactive group therein protected if necessary, $(X)-CO_2R^{14}$ is as defined for X except that R^4 is R^{14}, and R^{13} and R^{14} are as defined for R and R^4 excluding H, or they are conventional carboxylic acid protecting groups:

Scheme 1



The reaction of the compounds of formula (III) and (IV) is achieved using conventional amide coupling techniques. Thus in one process the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a carbodiimide condensing agent, for example 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as N-methylmorpholine. The reaction is generally complete after a period of from 12 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water or filtration to remove the urea biproduct and evaporation of the solvent. The product may be further purified by crystallisation or chromatography, if necessary. The compounds of formula (V) include compounds of formula (I) wherein R and R^4 are C_1-C_6 alkyl or benzyl.

In some cases the coupled product, in protected form, may be subjected to conventional chemical transformation reactions to allow preparation of further compounds of formula (V). Thus for example compounds of formula (V) wherein $R^{5'}$ is a bromoalkyl group may be reacted with sodium azide and the product reduced by catalytic hydrogenation to yield the corresponding derivative wherein $R^{5'}$ is aminoalkyl. Similarly oxidation of compounds hwerein $R^{5'}$ contains a sulphide group yields the corresponding sulphoxide or sulphone derivative. Such transformations are entirely conventional and appropriate conditions and reagents for their performance will be well known to those skilled in the art as will other variations and possibilities.

The diesters of formula (V) may be further reacted to give the monoester or diacid derivatives of formula (I) wherein one or

both of R and R^4 are H. The conditions used will depend on the precise nature of the groups R^{13} and R^{14} present in the compound of formula (V) and a number of variations are possible. Thus for example when both of R^{13} and R^{14} are benzyl, hydrogenation of the product will yield the diacid of formula (I) wherein R and R^4 are both H. Alternatively if one of R^{13} and R^{14} is benzyl and the other is alkyl, hydrogenation will yield a monoester product. This can then be hydrolysed, if desired, to again yield the diacid product. When one of R^{13} and R^{14} is t-butyl, treatment of the compound of formula (V) with trifluoroacetic acid yields the corresponding acid. The diester product wherein R^{13} and R^{14} are benzyl or lower alkyl can also be treated with trimethylsilyl iodide to produce the dicarboxylic acid product. If some other carboxylic acid protecting group is used for R^{13} or R^{14} then clearly appropriate conditions for its removal must be employed in the final step to give the ester or diacid product of formula (I). In the case where the ring A or the substituent R^5 is unsaturated, the deprotection must be effected by non-reductive methods, thus for example if either of R and R^4 is benzyl, they may be removed by treatment with trimethylsilyl iodide.

As an alternative to the above procedure the coupling reaction is performed with an amine of the formula:-

$H_2N-(X)-CH_2OH$ --- (VI)

The coupled product is deprotected as previously described and the product is then oxidised, for example by stirring with platinum in the presence of oxygen, to yield the corresponding acid of formula (I).

As well as removing any protecting group which may be present in $R^{5'}$, a number of chemical transformation reactions are possible on the final mono-ester or diacid products as previously described. In each case the product may be obtained as the free carboxylic acid or it may be neutralised with an appropriate base and isolated in salt form.

Compounds of the formula (I) wherein one or both R and R^4 is a biolabile ester forming group are prepared following similar procedures to those described above. Thus, in one variant of the process outlined in Scheme 1, a compound of formula (III) wherein R^{13} is a biolabile ester-forming group is coupled to the appropriate compound of formula (IV), wherein R^{14} is a benzyl group, and the product is hydrogenated to give the compound of formula (I) wherein R is a biolabile ester-forming group and R^4 is H.

The amines of formula (IV) and (VI) are in many cases novel compounds but they may be prepared from known starting materials by conventional synthetic procedures in accordance with literature precedents as illustrated in the Examples hereto. Thus for example the corresponding hydroxy-substituted bridged-cyclic carboxylate may be converted to the amine by sulphonylation followed by azide displacement and reduction, or a bicyclic lactone may be reduced by treatment with lithium aluminium hydride and the resulting diol converted to an aminoalcohol in a similar fashion.

The starting spiro-substituted glutaric acid mono esters of formula (III) may be prepared by a number of processes as described in European patent application 87310784.1.

As previously mentioned, the compounds of the invention are potent inhibitors of the neutral endopeptidase (E.C.3.4.24.11). This enzyme is involved in the breakdown of a number of peptide hormones and, in particular we have discovered that it is involved in the breakdown of atrial natriuretic factor (ANF). This hormone consists of a family of related natriuretic peptides, secreted by the heart, of which the major circulating form in humans is known to be the 28 amino-acid peptide referred to as α-hANP (see for example G. A. Sagnella and G. A. MacGreggor, Nature, 1984, 309, 666 and S. A. Atlas and others, Nature, 1984, 309, 717-725). Thus, the compounds of the invention, by preventing the degradation of ANF, by endopeptidase E.C.3.4.24.11 can potentiate its biological effects and the compounds are thus diuretic and natriuretic agents of utility in a number of disorders as previously described.

Activity against neutral endopeptidase E.C.3.4.24.11 is assessed using a procedure based on the assay described by J. T. Gafford, R. A. Skidgel, E. G. Erdos and L. B. Hersh, Biochemistry, 1983, 32, 3265-3271. The method involves determining the concentration of compound required to reduce by 50% the rate of release of radiolabelled hippuric acid from hippuryl-L-phenylalanyl-L-arginine by a neutral endopeptidase preparation from rat kidney.

The activity of the compounds as diuretic agents is determined by measuring their ability to increase urine output and sodium ion excretion in saline loaded conscious mice. In this test, male mice (Charles River CD1, 22-28 g) are acclimatised and starved overnight in metabowls. The mice are dosed intravenously via the tail vein, with the test compound dissolved in a volume of saline solution equivalent to 2.5% of body weight. Urine samples are collected each hour for two hours in pre-weighed tubes and analysed for electrolyte concentration. Urine volume and sodium ion concentration from the test animals are compared to a control group which received only saline.

For administration to man in the curative or prophylactic treatment of hypertension, congestive heart failure or renal insufficiency, oral dosages of the compounds will generally be in the range of from 10-1500 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2 to 300 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range 5 to 500 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above

dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

The compounds may be administered alone but may also be administered together with such other agents as the physician shall direct to optimise control of blood pressure or to treat congestive heart failure, renal insufficiency or other disorders in any particular patient in accordance with established medical practice. Thus the compounds can be co-administered with a variety of cardiovascular agents, for example with an ACE inhibitor such as captopril or enalapril to facilitate the control of blood pressure in treatment of hypertension; or with digitalis, or another cardiac stimulant or with an ACE inhibitor, for the treatment of congestive heart failure. Other possibilities

include co-administration with a calcium antagonist (e.g. nifedipine or diltiazem) a beta-blocker (e.g. atenolol) or an alpha-blocker (e.g. prazosin) as shall be determined by the physician as appropriate for the treatment of the particular patient or condition involved.

In addition to the above, the compounds may also be administered in conjunction with exogenous ANF, or a derivative thereof or related peptide or peptide fragment having diuretic/natriuretic activity or with other ANF-gene related peptides (e.g. as described by D. L. Vesely et al, Biochem. Biophys. Res. Comm., 1987, 143, 186).

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compounds of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, in particular in the treatment of hypertension, congestive heart failure or renal insufficiency in a human being.

The preparation of the compounds of the invention and of intermediates for use in their preparation is illustrated by the following Examples.

Purity of compounds was routinely monitored by thin layer chromatography. ^{1}H-N.M.R. spectra of all products were recorded using a Nicolet QE 300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

Methyl 6-exo-aminobicyclo[2,2,2]octane-2-endo-carboxylate hydrochloride

(a) A solution of 6-endo-hydroxybicyclo[2,2,2]octane-2-endo-carboxylic acid lactone (7.65 g; 50.3 mmole) in dioxan (100 ml) and 1N sodium hydroxide (200 ml) was allowed to stand at room temperature overnight. Most of the solvent was evaporated under reduced pressure at 40°C, and the residue was acidified to pH 5 with concentrated hydrochloric acid with ice cooling. The precipitate was collected by filtration and washed with water, to give 6-endo-hydroxybicyclo[2,2,2]octane-2-endo-carboxylic acid as a white solid (6.9 g, 80%), m.p. 125-125.5°C.

(b) Cesium carbonate (7.88 g; 24.2 mmole) in water (30 ml) was added to the above carboxylic acid (8.24 g; 48.4 mmole) in a 1:1 mixture of methanol and water (40 ml). The resulting clear solution was evaporated to dryness under vacuum, and the residue was dried azeotropically with toluene giving the cesium salt as a white solid. Methyl iodide (5 ml; 81 mmole) was added at room temperature to a stirred suspension of the cesium salt in dry dimethylformamide (40 ml). Water was added after 2.5 hours and the suspension was extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give an oil (8.8 g) which solidified on standing. Recrystallisation from hexane gave methyl 6-endo-hydroxybicyclo-[2,2,2]octane-2-endo-carboxylate as a white solid (7.52 g, 84%), m.p. 46-46.5°C. Found: C,65.09; H,8.83. $C_{10}H_{16}O_3$ requires C,65.19; H,8.75%.

(c) The above ester (7.11 g; 38.6 mmole) was added to an ice cold solution of 4-methylbenzenesulphonylchloride (11.04 g; 58 mmole) in dry pyridine (40 ml). After 0.5 hours the solution was allowed to warm to room temperature and, after standing overnight, the solvent was evaporated under vacuum. The residue was partitioned between ethyl acetate and water, and the organic phase was washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and water. Drying ($MgSO_4$), followed by evaporation of the solvent and recrystallisation from ethyl acetate-hexane gave methyl 6-endo-(4-methylbenzenesulphonyloxy)bicyclo[2,2,2]octane-2-endo-carboxylate as a white solid (11.65 g; 89%), m.p. 101-101.5°C. Found: C,60.29; H,6.57. $C_{17}H_{22}O_5S$ requires C,60.33; H,6.55%.

(d) The above 4-methylbenzenesulphonate (11.77 g, 34.8 mmole) was stirred under nitrogen with sodium azide (10 g; 150 mmole) in dry dimethylformamide (30 ml) for five days at 75°C. Most of the solvent was evaporated under vacuum keeping the temperature below 30°C. The residue was partitioned between ethyl acetate and water and the organic extract washed with water. Drying ($MgSO_4$) and evaporation of the solvent gave an oil which was chromatographed on silica. Elution with ethyl acetate, hexane (1:1) gave methyl-6-exo-azidobicyclo[2,2,2]octane-2-endo-carboxylate as an oil (4.28 g, 59%) contaminated with approximately 10% of methyl bicyclo[2,2,2]oct-5-ene-2-endo carboxylate.

(e) The azide of example 1(d) above (3.2 g) in methanol (30 ml) was hydrogenated over 10% palladium on charcoal catalyst (300 mg) at room temperature and 50 p.s.i. (3.45 bar). After five hours the mixture was filtered and evaporated to dryness. The residue was chromatographed on silica, eluting with a mixture of dichloromethane and methanol (98:2) followed by dichloromethane, methanol, 0.88 aqueous ammonia (94:5:1) to afford the required amine as an oil. An etherial solution of the product was treated with 4N HCl in dioxan to give the title hydrochloride which was isolated as a white solid (2.55 g) after recrystallisation from methanol-diethylether, m.p. 200-202°C. Found: C,54.13; H,8.47; N,6.17. $C_{10}H_{17}NO_2$.HCl, 0.1 H_2O requires C,54.21; H,8.28; N,6.32%.

EXAMPLE 2

Methyl-6-exo-aminobicyclo[2,2,2]octane-2-exo-carboxylate hydrochloride

(a) Diethyl diazocarboxylate (0.63 ml, 4 mmole) and diphenylphorylazide (0.86 ml; 4 mmole) were added simultaneously to an ice cold stirred solution of methyl 6-endo-hydroxybicyclo-[2,2,2]octane-2-exo-carboxylate (510 mg; 2.8 mmole) and triphenyl phosphine (1.05 g; 4 mmole) in dry tetrahydrofuran under nitrogen. After three hours the mixture was absorbed onto silica. Elution with a mixture of diethyl ether and hexane (2:8) gave crude product which was rechromatographed eluting with diethyl ether and hexane (1:9). The required methyl 6-exo-azidobicyclo[2,2,2]-octane- 2-exo-carboxylate was obtained as a clear liquid (400 mg, 69%). IR (film) 2100 cm^{-1}.

(b) The azide (390 mg, 1.87 mmole) from part (b) above was reduced following the procedure described in Example 1(e). The hydrochloride salt was recrystallised from a mixture of methylene chloride and diethyl ether to give methyl 6-exo-aminobicyclo-[2,2,2]octane-2-exo-carboxylate hydrochloride as a white solid (270 mg, 66%) m.p. 216-218°C. Found: C,54.44: H,8.63; N,6.32. $C_{10}H_{17}NO_2.HCl$ requires C,54.67; H,8.26; N,6.37%.

EXAMPLE 3

Methyl 5-endo-aminobicyclo[2,2,2]octane-2-endo-carboxylate hydrochloride

(a) Methyl 5-endo and 5-exo-hydroxybicyclo[2,2,2]octane-2-endo-carboxylate

Sodium borohydride (824 mg; 21.8 mmole) was added to an ice cold stirred solution of methyl 5-oxobicyclo[2,2,2]octane-2-endo-carboxylate (7.94 g; 43.6 mmole) in methanol (80 ml). After 2 hours the mixture was acidified to pH 4 with 2N hydrochloric acid and evaporated to a small volume under vacuum. The residue was partitioned between diethyl ether and water. The organic phase was washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation gave a crude mixture of isomers as a yellow oil (7.45 g). t.l.c. (silica; iso-propanol- methylene chloride (1:9)) Rf. 0.58 and 0.62. Chromatography on silica and eluting with diethyl ether and methylene chloride (1:9) gave an initial fraction (2.6 g), shown by g.l.c. to be 96% pure 5-endo isomer. ^{1}H-N.M.R. ($CDCl_3$) δ 3.80 (m H-C5), 3.72 (s CO_2CH_3). Following a

mixed fraction, a third fraction (1.64 g) was obtained which was shown by g.l.c. to be 94% pure 5-exo isomer. ^{1}H-N.M.R. ($CDCl_3$) δ 3.99 (m, H-C5) 3.68 (s, $-CO_2\underline{CH_3}$).

(b) The 5-exo-isomer from part (a) above (1.95 g; 10.58 mmole) was treated with 4-methylbenzenesulphonyl chloride in pyridine as described in Example 1(c). The crude product was chromatographed on silica, eluting with diethyl ether and hexane (4:6) to give methyl 5-exo-(4-methylbenzenesulphonyloxy)bicyclo-[2,2,2]octane-2-endo carboxylate as an oil (3.21 g, 90%). Found: C,60.29; H,6.53%. $C_{17}H_{22}O_5S$ requires C,60.33; H,6.55%.

(c) The above 5-exo-methylbenzenesulphonate (3.18 g, 9.4 mmole) was stirred under nitrogen with sodium azide (3.05 g; 47 mmole) in dry dimethylformamide (10 ml) at 55°C for eighteen hours and then at 75°C for forty-eight hours. Work up as described in Example 1(d) gave a pale yellow oil (1.95 g) which was chromatographed on silica. Elution with diethyl ether and hexane (5:95) gave methyl 5-endo-azidobicyclo[2,2,2]octane-2-endo carboxylate as a clear liquid (950 mg; 48%). Found: C,57.15; H,7.40; N,20.22. $C_{10}H_{15}N_3O_2$ requires C,57.40; H,7.23; N,20.08%.

(d) The above azide (940 mg; 4.49 mmole) was reduced as described in Example 1(e). The crude hydrochloride was recrystallised from methanol/diethyl ether to give the title amine as a white solid (430 mg, 44%), m.p. 156-7°C. Found: C,54.79; H,8.36; N,6.37. $C_{10}H_{17}NO_2$.HCl requires C,54.67; H,8.26; N,6.37%.

EXAMPLE 4

Methyl-5-exo-aminobicyclo[2,2,2]octane-2-endo-carboxylate hydrochloride

(a) The 5-endo-hydroxy compound from Example 3(a) (3.1 g; 16.82 mmole) was treated with 4-methylbenzenesulphonyl chloride (4.81 g; 25.2 mmole) in dry pyridine as described in Example 1(c). The crude product was chromatographed on silica, eluting with diethyl ether and hexane (4:6) to give methyl-5-endo-(4-methylbenzenesulphonyloxy)bicyclo[2,2,2]octane-2-endo-carboxylate as an oil (5.20 g, 91%). Found: C,60.29; H,6.54. $C_{17}H_{22}O_5S$ requires C,60.33; H,6.55%.

(b) The above 5-endo-methylbenzenesulphonate (5.15 g; 15.2 mmole) was stirred under nitrogen with sodium azide (4.94 g; 76 mmole) in dry dimethylformamide (15 ml) at 55°C for eighteen hours and then at 75°C for thirty hours. Work up as described in Example 1(d) gave a pale yellow liquid which was chromatographed on silica. Elution with diethyl ether and hexane (5:95) gave methyl-5-exo-azidobicyclo[2,2,2]octane-2-endo-carboxylate, as a clear liquid (1.9 g, 61%). Found: C,57.17; H,7.26; N,20.02. $C_{10}H_{15}N_3O_2$ requires C,57.40; H,7.23; N,20.08%.

(c) The above azide (1.9 g; 9.1 mmole) was reduced as described in Example 1(e). The crude hydrochloride was recrystallised from methanol/diethyl ether to give the title amine as a white solid (840 mg, 42%), m.p. 228-229°C. Found: C,54.64; H,8.45; N,6.31. $C_{10}H_{17}NO_2$.HCl requires C,54.67; H,8.26; N,6.37%.

EXAMPLE 5

1H-2β-Amino-2,3,3aα,4,5,6,7,7aα-octahydroindene-3aα-carboxylic acid ethyl ester

(a) 2H-2-Oxo-1,3,3aα,4,5,6,7,7aα-octahydroindene-3aα-carboxylic acid ethyl ester (2.9 g; 13.8 mmole) [W. Dauben et al., J. Org. Chem., 1961, 26, 297] in tetrahydrofuran (30 ml) was added dropwise under nitrogen to a stirred 1M solution of lithium trisiamylborohydride in tetrahydrofuran (15.2 ml; 15.2 mmole) at -70 to -60°C. After two hours the mixture was allowed to warm to ambient temperature and left to stand for eighteen hours. The mixture was then cooled to 10°C. Water (1 ml), ethanol (3.4 ml), 6N aqueous sodium hydroxide (2.3 ml) and 30% aqueous hydrogen peroxide (3.4 ml) were added in succession. After five minutes the aqueous phase was saturated with potassium carbonate, diethyl ether and saturated sodium chloride solution were added and the organic layer was separated off. The aqueous phase was re-extracted with diethyl ether and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give an oil which was chromatographed on silica. Gradient elution using hexane and ethyl acetate (3:7 to 1:1) gave 1H-2β-hydroxy-2,3,3aα-4,5,6,7,7aα-octahydro-indene-3aα-carbonyl acid ethyl ester as an oil (2.52 g; 86%). Found: C,67.70; H,9.67. $C_{12}H_{20}O_3$ requires C,67.89; H,9.50%.

(b) Diethyl azodicarboxylate (2.47 ml; 15.7 mmole) in tetrahydrofuran (15 ml) was added dropwise at 10°C to a stirred solution of the hydroxy acid from part (a) (2.22 g; 10.5 mmole), methyl 4-methylbenzenesulphonate (2.43; 13.1 mmole) and triphenyl

phosphine (3.43 g; 13.1 mmole) in tetrahydrofuran (25 ml). After stirring for 20 hours at ambient temperature, the mixture was evaporated to dryness, absorbed onto silica and chromatographed on silica. Gradient elution starting from hexane and methylene chloride (3:7) to neat methylene chloride gave 1H-2α-(4-methylbenzensulphonyloxy)-2,3,3aα,4,5,6,7,7aα-octahydroindene-3aα-carboxylic acid ethyl ester as a clear oil (2.01 g; 58%). Found: C,62.27; H,7.27. $C_{19}H_{26}O_5S$ requires C,62.27; H,7.15%.

(c) The product from part (b) above (1.99 g) was treated with sodium azide and reduced as described in Example 4 to give the crude amine which was chromatographed on silica. Gradient elution with increasing proportions of ethanol in methylene chloride (0 to 20%) gave pure title product as an oil (770 mg; 62% overall). Found: C,65.85; H,9.74; N,6.32. $C_{12}H_{21}NO_2$,0.5 H_2O requires C,65.42; H,10.07; N,6.36%.

EXAMPLE 6

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid benzyl ester

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (958 mg; 5 mmole) was added to an ice cold stirred mixture of 3-(1-carboxycyclopentyl)-2-(2-methoxyethyl)propanoic acid benzyl ester (836 mg; 2.5 mmole), methyl 6-exo-aminobicyclo[2,2,2]-octane-2-endo carboxylate hydrochloride (550 mg; 2.5 mmole), 1-hydroxybenzotriazole (337 mg; 2.5 mmole) and N-methylmorpholine (834 mg; 8.25 mmole) in dry methylene chloride (10 ml). After 0.5

hours the mixture was allowed to attain room temperature and stirred for a further eighteen hours. The mixture was diluted with methylene chloride, washed in succession with water, 1N hydrochloric acid, saturated aqueous sodium bicarbonate and water, and dried ($MgSO_4$). Evaporation gave an oil which was chromatographed on silica. Elution with ethyl acetate and hexane (3:7) gave the title diester as a gum (1.08 g; 85%). Found: C,69.42; H,8.29; N,2.75. $C_{29}H_{41}NO_6$, 0.11 $CH_3CO_2C_2H_5$ requires C,69.71; H,8.27; N,2.80%.

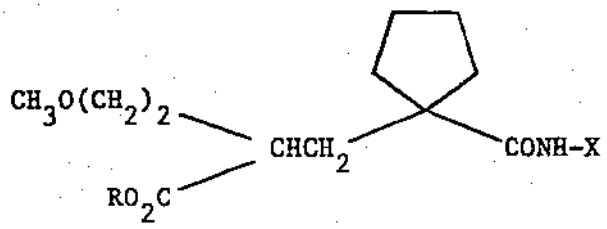
EXAMPLE 7

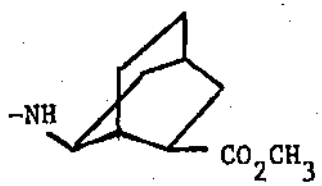
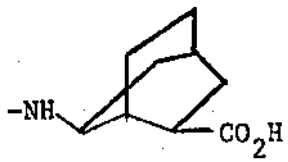
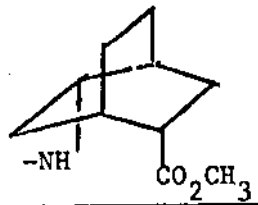
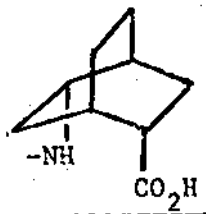
3-{1-[6-endo-carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl}-2-(2-methoxyethyl)propanoic acid

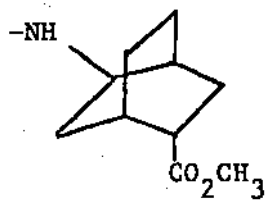
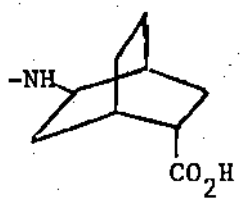
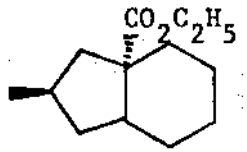
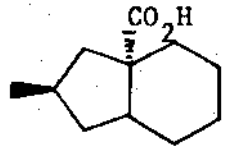
The diester from Example 6 (980 mg; 1.96 mmole) in methanol (18 ml) and water (12 ml) was hydrogenated over 5% palladium on charcoal catalyst (100 mg) at 50 p.s.i. (3.45 bar). After four hours the mixture was filtered through avicel, washing with methanol, and evaporated to dryness. The residue was partitioned between diethyl ether and 1N sodium hydroxide (4 ml). The aqueous phase was separated and the ether phase was again extracted with 1N sodium hydroxide (4 ml). The combined aqueous extracts were allowed to stand at room temperature for eighteen hours and then acidified with 2N hydrochloric acid. The suspension was extracted with methylene chloride, the extract washed with saturated aqueous sodium chloride solution and dried ($MgSO_4$). Evaporation of the solvent gave the required diacid as a white foam (705 mg, 91%). Found: C,63.50; H,8.61; N,3.31. $C_{21}H_{33}NO_6$ requires C,63.77; H,8.41; N,3.54%.

EXAMPLES 8 - 15

The following compounds were prepared from the appropriate amine of Examples 2 to 5 following the coupling and deprotection procedures of Examples 6 and 7.



Example	R	-NH-X	Form Isolated	Analysis % (Theoretical in brackets) C	H	N
8	$CH_2C_6H_5$		gum	69.42 (69.71	8.40 8.27	2.57 2.80)
9	H		foam ($0.5\ H_2O$)	62.51 (62.36	8.36 8.47	3.41 3.46)
10	$CH_2C_6H_5$		oil	69.36 (69.71	8.34 8.27	3.15 2.80)
11	H		foam ($0.4\ H_2O$)	62.58 (62.63	8.33 8.46	3.48 3.48)

Example	R	-NH-X	Form Isolated	Analysis % (Theoretical in brackets) C	H	N
12	$CH_2C_6H_5$		oil	69.70 (69.71	8.42 8.27	2.73 2.80)
13	H		foam (0.4 H_2O)	62.71 (62.63	8.49 8.46	3.47 3.48)
14	$CH_2C_6H_5$		oil	70.79 (70.56	8.79 8.60	2.66 2.66)
15	H		foam (0.33 H_2O)	63.48 (63.59	8.53 8.65	3.30 3.37)

EXAMPLE 16

6-endo-Hydroxymethylbicyclo[2,2,1]heptan-2-exo-amine hydrochloride

(a) A solution of 6-endo-hydroxybicyclo[2,2,1]heptane-2-endo-carboxylic acid lactone (11.0 g; 79.7 mmole) in diethyl ether (150 ml) was added dropwise over 0.5 hours under nitrogen to a stirred ice cooled suspension of lithium aluminium hydride (3.02 g; 79.7 mmole) in dry diethyl ether (50 ml), keeping the temperature between 10 and 20°C. The mixture was then stirred at room temperature for 2 hours, saturated aqueous ammonium chloride (20 ml) was carefully added followed by solid ammonium chloride (15 g) and magnesium sulphate to produce a granular suspension. The mixture was filtered, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a white solid (11.15 g). Chromatography on silica, eluting with diethyl ether and recrystallisation from ether and hexane gave 6-endo-hydroxy-methylbicyclo[2,2,1]heptan-2-endo-ol as a white solid (9.49; 84%). An analytical sample had m.p. 118-120°C. Found: C,67.87; H,10.24. $C_8H_{14}O_2$ requires C,67.57; H,9.93%.

(b) (1,1-Dimethylethyl)dimethylsilylchloride (10.98 g; 72.8 mmole) in dry methylene chloride (45 ml) was added with ice cooling to a stirred solution of the above diol (9.42 g; 66.2 mmole), triethylamine (7.37 g; 72.82 mmole) and 4-dimethylaminopyridine (325 mg, 2.65 mmole) in methylene chloride (55 ml). After stirring at room temperature for one and a half hours the solution was washed in succession with water, saturated aqueous ammonium chloride and water. Drying ($MgSO_4$) and evaporation under reduced pressure gave a pale yellow liquid.

Chromatography on silica eluting with diethyl ether and hexane (1:9 - 1:1) gave 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl]bicyclo[2,2,1]heptan-2-endo-ol as a clear liquid (16.2 g; 95%). Found C,65.05; H,10.98; $C_{14}H_{28}O_2Si$ requires C,65.57; H,11.00%.

(c) The carbinol from part (b) above (13.12 g; 51.6 mmole) was treated with sodium azide as described in Example 2(a) to give 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl]bicyclo[2,2,1]-heptane-2-exo-azide (5.83 g, 40%) as an oil. I.R. (film) ν max 2100 cm^{-1}. Found: C,60.25; H,9.83; N,14.11. $C_{14}H_{27}N_3OSi$ requires C,59.74; H,9.67; N,14.93%.

(d) A 1N solution of tetrabutylammonium fluoride in tetrahydrofuran (30 ml) was added to an ice cooled solution of the azide from part (c) above (5.8 g; 20.6 mmole) in dry tetrahydrofuran (30 ml). After two hours at 5°C the solution was diluted with diethyl ether and washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation gave a clear volatile liquid which was chromatographed on silica. Elution with diethyl ether and hexane (1:1) gave 6-endo-hydroxymethylbicyclo[2,2,1]-heptane-2-exo-azide as a liquid (2.95 g; 86%). I.R. (film) ν max 2100 cm^{-1}. Found: C,57.44; H,7.91; N,24.81. $C_8H_{13}N_3O$ requires C,57.46; H,7.84; N,25.13%.

(e) The azide from part (d) above was reduced as described in Example 1(e) but using ethanol as solvent. The crude hydrochloride was recrystallised from a mixture of methanol and diethyl ether to give the title amine as a white solid (3.24 g; 85%) m.p. 158-9°C. Found: C,53.91; H,9.23; N,7.70. $C_8H_{15}NO.HCl$ requires C,54.08; H,9.08; N,7.88%.

EXAMPLE 17

6-endo-Hydroxymethyl-7-oxabicyclo[2,2,1]heptan-2-exo-amine

(a) 6-endo-Hydroxy-5-exo-iodo-7-oxabicyclo[2,2,1]heptane-2-endo-carboxylic acid lactone (83.43 g; 0.316 mole) dissolved in tetrahydrofuran (250 ml) and ethyl acetate (500 ml) containing triethylamine (35.2 g; 0.35 mole) was hydrogenated over platinum (from platinum oxide, 4 g) at room temperature and 50 p.s.i. (3.45 bar). After six hours water was added and the mixture was filtered through avicel. The aqueous phase was extracted (x 2) with ethyl acetate, and the combined organic solutions were washed in succession with, 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate, sodium metabisulphite solution and water. Drying ($MgSO_4$) and evaporation gave a white solid (35.2 g). Recrystallisation from ethyl acetate and hexane gave 6-endo-hydroxy-7-oxabicyclo[2,2,1]heptane-2-endo-carboxylic acid lactone (28.18 g; 63%), m.p. 89.5-90°C. Found: C,60.11; H,5.83. $C_7H_8O_3$ requires C,59.99; H,5.75%.

(b) The lactone from part (a) above (14.1 g; 0.1 mole) was reduced with lithium aluminium hydride following the procedure in Example 16(a). The crude product was chromatographed on silica, eluting with ethyl acetate, to give 6-endo-hydroxymethyl-7-oxabicyclo[2,2,1]heptan-2-endo-ol as a hygroscopic waxy solid (11.7 g; 81%). Found: C,58.31; H,8.59. $C_7H_{12}O_3$ requires C,58.31; H,8.39%.

(c) The diol from part (b) above (11.63 g; 80.7 mmole) was treated with (1,1-dimethylethyl)dimethylsilylchloride as described in Example 16(b). Chromatography of the product on silica, eluting with diethyl ether and hexane (1:1 - 2:1), gave 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl]-7-oxabicyclo[2,2,1]-heptan-2-endo-ol as a clear liquid (18.58 g; 89%). Found: C,60.78; H,10.09. $C_{13}H_{26}O_3Si$ requires C; 60.42; H,10.14%.

(d) The carbinol from part (c) above (13.1 g; 50.69 mole) was treated with 4-methylbenzensulphonyl chloride as described in Example 1(c) except that the reaction mixture was allowed to stand at room temperature for five days. The crude product was chromatographed on silica, eluting with a gradient of diethyl ether and hexane (2:8 - 4:6), to give 6-endo-[(1,1-dimethyl-ethyl)dimethylsilyloxymethyl)]-7-oxabicyclo[2,2,1]heptan-2-endo-ol 4-methylbenzenesulphonate as a clear oil (15.84 g; 76%). Found: C,58.20; H,7.90. $C_{20}H_{32}O_5SiS$ requires C,58.22; H,7.82%.

(e) The 4-methylbenzenesulphonate from part (d) above (16.79 g; 40.67 mmole) and sodium azide (5.3; 81.3 mmole) in dry dimethylformamide (40 ml) were stirred under nitrogen for two days at 105°C.

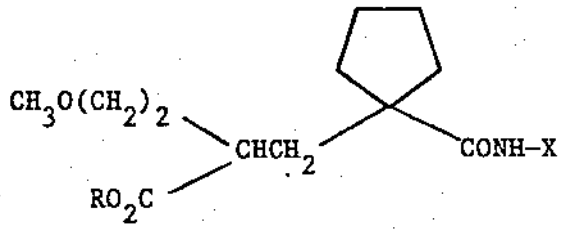
A further amount of sodium azide (2.65 g) was added, and stirring continued for six days at 105-110°C. The mixture was cooled, diluted with water and extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was chromatographed on silica. Gradient elution with diethyl ether and hexane (15:85 - 1:1) gave an initial fraction containing the required 6-endo-[(1,1-dimethylethyl)dimethylsilyloxymethyl)]-7-oxabicyclo-[2,2,1]heptan-2-exo-azide (2.54 g; 22%) as a clear liquid. Continued elution gave recovered starting material (10.7 g; 63%).

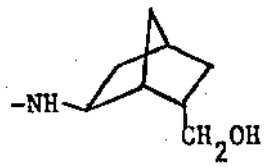
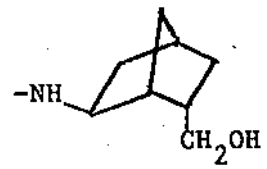
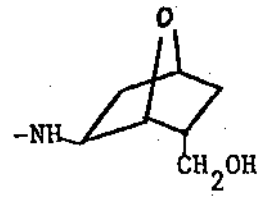
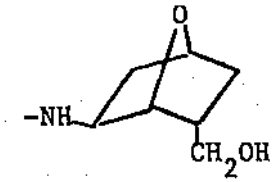
(f) The above azide (2.54 g; 8.96 mmole) was treated with tetrabutylammonium fluoride as described in Example 16(d) to yield 6-endo-hydroxymethyl-7-oxabicyclo[2,2,1]heptan-2-exo-azide as an oil (1.33 g; 88%). I.R. (film) ν max. 3400 and 2100 cm^{-1}. Found: C,49.53; H,6.63; N,24.60. $C_7H_{11}O_2N_3$ requires C,49.69; H,6.55; N,24.84%.

(g) The azide from part (f) above (1.3 g; 7.7 mmole) was hydrogenated in ethanol (25 ml) over 10% palladium on charcoal (100 mg) at 50 p.s.i. (3.46 bar). After three hours the suspension was filtered through avicel and the solvent evaporated to give a white solid which was recrystallised from a mixture of methylene chloride and diethyl ether to give the title amine (930 mg; 84%), m.p. 102-103.5°C. Found: C,58.43; H,9.53; N,9.72. $C_7H_{13}NO_2$ requires C,58.72; H,9.15; N,9.78%.

EXAMPLES 18 - 21

The amines of formula (VI) from Examples 16 and 17 were coupled to 3-(1-carboxycyclopentyl)-2-(2-methoxyethyl)propanoic acid benzyl ester and the products hydrogenated to remove the benzyl group following the procedures of Examples 6 and 7 to yield the following compounds:



Example	R	-NH-X	Form Isolated	Analysis % (Theoretical in brackets) C	H	N
18	$CH_2C_6H_5$		gum	70.64 (70.86	8.75 8.59	3.39 3.06)
19	H		foam (0.3 H_2O)	64.34 (64.42	9.00 9.08	3.79 3.76)
20	$CH_2C_6H_5$		oil	65.90 (66.03	7.93 7.91	2.92 2.94)
21	H		gum (0.6 H_2O)	59.98 (60.01	8.63 8.53	3.79 3.68)

EXAMPLE 22

3-{1-[6-endo-Carboxybicyclo[2,2,1]heptane-2-exo-carbamoyl]-cyclopentyl} -2-(2-methoxyethyl)propanoic acid

3-{1-[6-endo-Hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl} -2-(2-methoxyethyl)propanoic acid from Example 19 (350 mg; 0.95 mmole) dissolved in water (30 ml) containing sodium bicarbonate (240 mg; 2.8 mmole) was vigorously stirred over platinum (from platinum oxide 350 mg; 1.5 mmole) under oxygen at 40°C. After two hours the suspension was filtered through avicel. The filtrate was evaporated to a small volume under reduced pressure, saturated with salt and acidified with 2N hydrochloric acid. The suspension was extracted with ethyl acetate and the extract washed with saturated salt solution, dried ($MgSO_4$) and evaporated to give the title diacid as a white foam. (365 mg; 97%). Found: C,61.78; H,8.16; N,3.77. $C_{20}H_{31}NO_6$, 0.1 CH_2Cl_2, 0.1 $CH_3CO_2C_2H_5$ requires C,61.74; H,8.09; N,3.51%.

EXAMPLE 23

3-{1-[6-endo-Carboxy-7-oxabicyclo[2,2,1heptane-2-exo-carbamoyl]cyclopentyl} -2-(2-methoxyethyl)propanoic acid

The carbinol from Example 21 was oxidised following the procedure of Example 22 above to yield the title compound as a white foam. Found: C,58.32; H,7.82; N,3.39. $C_{19}H_{29}NO_7$, 0.1 CH_2CH_2 requires C,58.53; H,7.51; N,3.57%.

EXAMPLE 24

3-{1-[6-endo-Methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(2-methylthioethyl)propanoic acid benzyl ester

3-(1-Carboxycyclopentyl)-2-(2-methylthioethyl)propanoic acid benzyl ester was coupled to methyl 6-exo-aminobicyclo[2,2,2]-octane-2-endo-carboxylate (from Example 1) following the procedure of Example 6 to yield the title diester as an oil. Found: C,65.21; H,7.68; N,2.28. $C_{29}H_{41}NO_5S.H_2O$ requires C,65.27; H,8.12; N,2.62%.

EXAMPLE 25

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(2-methylsulphonylethyl)propanoic acid benzyl ester

The methylthio compound of Example 24 (220 mg; 0.43 mmole) was stirred with 3-chloroperbenzoic acid (184 mg) in methylene chloride for three hours at room temperature. The solvent was evaporated and the residue was partitioned between 5% aqueous sodium bicarbonate and diethyl ether. The ether extract was dried ($MgSO_4$) and the solvent evaporated. The crude product (220 mg) was chromatographed on silica, eluting with a gradient of ethyl acetate and hexane (1:4 — 1:2) to give the pure title product as a gum (75 mg; 33%). Found: C,63.89; H,7.96; N,2.48. $C_{29}H_{41}NO_7S$ requires C,63.60; H,7.55; N,2.56%.

EXAMPLE 26

3-{1-[6-endo-Carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl} -2-(2-methylsulphonylethyl)propanoic acid

Hydrogenation and hydrolysis of the product of Example 25 above following the procedure of Example 7 gave the title bis-acid as a white foam. Found: C,56.31; H,8.61; N,3.11. $C_{21}H_{33}NO_7S$ requires C,56.87; H,7.50; N,3.16%.

EXAMPLE 27

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl} -2-(4-bromobutyl)propanoic acid 1,1-dimethylethyl ester

3-(1-Carboxycyclopentyl)-2-(4-bromobutyl)propanoic acid 1,1-dimethylethyl ester was coupled to methyl 6-exo-amino-bicyclo[2,2,2]octane-2-endo-carboxylate (from Example 1) following the procedure of Example 6 to yield the title diester as an oil.

EXAMPLE 28

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl} -2-(4-azidobutyl)propanoic acid 1,1-dimethylethyl ester

The bromo compound from Example 27 above (780 mg, 1.44 mmole) and sodium azide (195 mg, 3 mmole) were stirred in dry dimethylformamilde (3 ml) at 50°C under nitrogen for two days. The mixture was diluted with water and extracted with diethyl

ether. The extract was washed with water, dried ($MgSO_4$) and evaporated to give a gum which was chromatographed on silica. Elution with diethyl ether and hexane gave the title azide as an oil (350 mg; 48%). Found: C,64.44; H,8.84; N,10.85. $C_{27}H_{44}N_4O_5$ requires C,64.24; H,8.79; N,11.10%.

EXAMPLE 29

3-{1-[6-endo-methoxycarbonylbicyclo[2,2,2]octane-2-exo-carbamoyl]cyclopentyl}-2-(4-aminobutyl)propanoic acid 1,1-dimethylethyl ester

The azide product from Example 28 above was reduced as described in Example 1(e). The crude product was chromatographed on silica by gradient elution using methanol and methylene chloride (1:99 - 7:93). The pure title product was obtained as a gum (208 mg; 64%).

EXAMPLE 30

3-{1-[6-endo-Carboxybicyclo[2,2,2]octane-2-exo-carbamoyl]-cyclopentyl}-2-(4-aminobutyl)propanoic acid

The diester product of Example 29 above (208 mg; 0.43 mmole) was allowed to stand at room temperature with trifluoroacetic acid (1 ml) in methylene chloride (1 ml) for four hours. The solvent was evaporated under vacuum, and the residue was triturated with warm diethyl ether. The insoluble salt was dissolved in 1N sodium hydroxide (3 ml), and allowed to stand at room temperature for four hours and at 0°C for eighteen hours. The solution was passed

through ion exchange resin (Bio-Rad AG 50W-X8, 4.0 g) and the column eluted with 2% aqueous pyridine to give the title diacid as a white foam (146 mg, 79%). Found: C,61.93; H,8.58; N,6.42. $C_{22}H_{36}N_2O_5$, 0.5 H_2O, 0.15 CH_2Cl_2 requires C,61.83; H,8.73; N,6.51%.

EXAMPLE 31

N-(1-Naphthoyl)-(S)-prolinol

1-Naphthoyl chloride (19.0 g; 0.1 mmole) was added dropwise over five minutes to a stirred ice cooled solution of (S)-prolinol (10.1 g; 0.1 mmole) and N-methylmorpholine (11.0 g; 0.1 mmole) in dry methelene chloride (100 ml). After stirring at room temperature for three hours, ice was added and the solvent was evaporated under reduced pressure. The residue was partitioned between diethyl ether and water and the organic phase was washed in succession with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying over $MgSO_4$ and evaporation gave a gum which was chromatographed on silica. Elution with ethyl acetate gave the title product (21.33 g; 84%). $[\alpha]_D^{25}$ -111.3°, $[\alpha]_{365}^{25}$ -405.0° (c. 1.15, CH_2Cl_2). Found: C,73.60; H,6.76; N,5.27. $C_{16}H_{17}NO_2.0.25\ H_2O$ requires C,73.96; H,6.79; N,5.39%.

EXAMPLE 32

1-(1-Naphthoyl)-2(S)-bromomethylpyrrolidine

Triphenylphosphine (26.3 g; 0.1 mole) was added to an ice cold stirred solution of N-(1-naphthoyl)-(S)-prolinol (21.33 g, 83.5 mmole) and carbon tetrabromide (33.1 g; 0.1 mole) in dry methelene chloride (220 ml). The mixture was allowed to warm to

room temperature over half an hour, stirred for a further hour, and the solvent was evaporated under reduced pressure. The residue was extracted (x 8) with diethyl ether. Direct application of the solutions to a silica column followed by elution with diethyl ether gave the title bromo derivative as gum (20.2 g; 72%). $[\alpha]_D^{25}$ - 126.6°, $[\alpha]_{365}^{25}$ -496.5° (c = 1.21; CH_2Cl_2). Found: C,57.11; H,4.76; N,4.15. $C_{16}H_{16}BrNO$ requires C,57.50; H,4.82; N,4.19%.

EXAMPLE 33

6(R and S)-endo-Hydroxybicyclo[2,2,2]octane-2(S and R)-endo-carboxylic acid. N-(1-naphthoyl)-2(S)-prolinol ester

6-endo-Hydroxybicyclo[2,2,2]octane-2-endo-carboxylic acid lactone (5.02 g; 33 mmole) was heated at 100°C with 1.02 N cesium hydroxide (32.3 ml; 33 mmole) and dioxan (15 ml). After three hours the solution was allowed to cool to room temperature and, after standing overnight, the solvent was evaporated under reduced pressure. The residue was dried azeotropically with toluene (x 2) and triturated with hot diethyl ether. The resulting cesium salt (3.93 g; 13 mmole) and 1-(1-naphthoyl)-2(S)-bromomethylpyrrolidine (4.34 g; 13 mmole) were stirred for two days at room temperature in dry dimethylformamide (10 ml). The mixture was diluted with water, extracted with ethyl acetate, and the organic extract was washed in succession with saturated aqueous sodium bicarbonate, and water. Drying ($MgSO_4$) and evaporation under reduced pressure gave a yellow gum which was chromatographed on silica. Elution with acetone and toluene (3:7) allowed the diastereoisomers to be separated as gums.

Isomer I t.l.c. (acetone, toluene, 3:7) Rf. 0.32. $[\alpha]_D^{25}$ - 78.6°, $[\alpha]_{365}^{25}$ -336.0° (c = 1.06, CH_2Cl_2). Found: C,73.98; H,7.31; N,3.39. $C_{25}H_{29}NO_4.0.1\ CH_3C_6H_5$ requires C,74.08; H,7.21; N,3.36%.

Isomer II t.l.c. Rf. 0.29 $[\alpha]_D^{25}$ - 58.8°, $[\alpha]_{365}^{25}$ -258.7° (c = 1.03, CH_2Cl_2). Found: C,73.75; H,7.31; N,3.35. $C_{25}H_{29}NO_4$. 0.1 $CH_3C_6H_5$ requires C,74.08; H,7.21; N,3.36%.

EXAMPLE 34

6-(S or R)-exo-Aminobicyclo[2,2,2]octane-2(R or S)-endo-carboxylic acid N-(1-naphthoyl)-2(S)-prolinol ester hydrochloride

Isomer II from Example 33 above (1.16 g; 2.85 mmole) was treated with 4-methylbenzenesulphonyl chloride followed by reaction of the product with sodium azide and reduction of the azide product following the procedures of Example 1(c) to (e), to yield the title amine as an amorphous solid which failed to crystallise. T.l.c. (dichloromethane, methanol, acetic acid, 90:10:1) Rf 0.3. $[\alpha]_D^{25}$ -12.9°, $[\alpha]_{365}^{25}$ -93.9° (c = 0.026, methanol).

EXAMPLE 35

(+)-3-{1-[6(S or R)-endo-Carboxybicyclo[2,2,2]octane-2(R or S)-exo-carbamoyl]cyclopentyl}-2(R,S)-(methoxyethoxymethyl)propanoic acid

The product from Example 34 above was coupled to 3-(1-carboxycyclopentyl)-2-(2-methoxyethoxymethyl)propanoic acid 1,1-dimethylethyl ester following the procedure of Example 6. The coupled diester was obtained as a foam. Found: C,69.91; H,8.11;

Treatment of the product with trifluoroacetic acid followed by sodium hydroxide according to the procedure of Example 30 to remove the 1,1-dimethylethyl and N-(1-naphthoyl)-2(S) prolinol ester groups gave the title dicarboxylic acid as its dextrorotatory diastereoisomer. $[\alpha]_D^{25}$ +53.9°, $[\alpha]_{365}^{25}$ + 180.60° (c = 1.2, CH_2Cl_2). Found: C,61.59; H,8.58; N,3.16. $C_{22}H_{35}NO_7$, 0.2 H_2O requires C,61.58; H,8.31; N,3.26%.

It will be appreciated from the foregoing that what we will claim may include the following:-

(1) The compounds of the formula (I) and pharmaceutically acceptable salts thereof and bioprecursors therefor.

(2) Processes as described herein for preparing the compounds of the formula (I) and their salts;

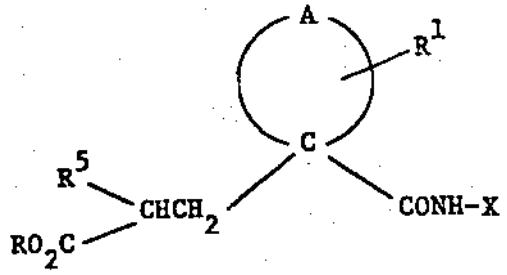
(3) Pharmaceutical compositions comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof of bioprecursor therefor, and a pharmaceutically acceptable diluent or carrier;

(4) A compound of the formula (I), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for use as a diuretic agent for the treatment of hypertension, heart failure and renal insufficiency.

(5) Use of a compound for the formula (I) for the manufacture of a medicament for the treatment of hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menières disease, hyperaldosteronism, pulmonary oedema, ascites, hypercalciuria, glaucoma, asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders, hyperreninaemia and the modulation of gastric acid secretion.

CLAIMS

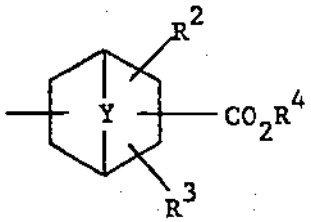
1. A compound having the formula:



(I)

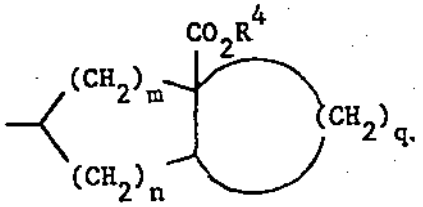
wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

X is a bridged cyclic group of the formula:-



wherein Y is O, CH_2 or $(CH_2)_2$,

or a bicyclic group of the formula:-



wherein each of n and m is independently 1 or 2 and q is an integer of from 3 to 5;

each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

R^2 and R^3 are each independently H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, C_1-C_6 alkoxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$ or a saturated heterocyclic group;

or C_1-C_6 alkyl substituted by one or more substituents chosen from halo, hydroxy, C_1-C_6 alkoxy, C_2-C_6 hydroxyalkoxy, C_1-C_6 alkoxy(C_1-C_6 alkoxy), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, aryloxy(C_1-C_4 alkoxy), heterocyclyl, heterocyclyloxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$, $-CONR^6R^7$, $-SH$, $-S(O)_pR^{10}$, $-COR^{11}$ or $-CO_2R^{12}$;

wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl (optionally substituted by hydroxy or C_1-C_4 alkoxy), aryl, aryl(C_1-C_4 alkyl), C_2-C_6 alkoxyalkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4 alkyl)-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4 alkyl), aryl(C_1-C_4 alkoxy), heterocycyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, aryl, heterocyclyl or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{11} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{12} is H or C_1-C_4 alkyl;

and p is 0, 1 or 2;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

2. A pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof of bioprecursor therefor, and a pharmaceutically acceptable diluent or carrier;

3. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for use as a diuretic agent for the treatment of hypertension, heart failure and renal insufficiency.

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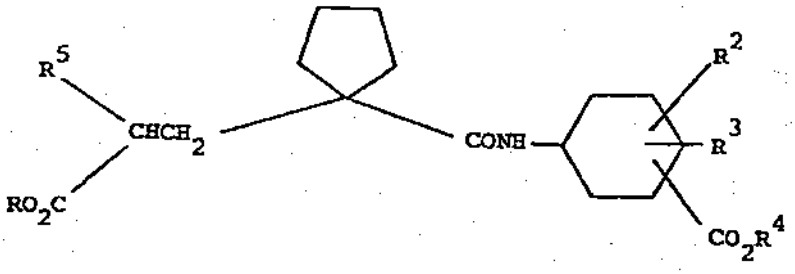

(II)

(57) Abstract

Compounds of formula (II), wherein each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group; R^2 is a C_4 alkyl group; R^3 is H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy; and R^5 is defined to include a range of alkyl, alkenyl, alkynyl, arylalkynyl, cycloalkyl, cycloalkenyl, alkoxy, amino, substituted amino, amido, sulphonamido and substituted alkyl groups; and phamaceutically acceptable salts thereof, are diuretic agents of utility in the treatment of hypertension, heart failure, renal insufficiency and other disorders.

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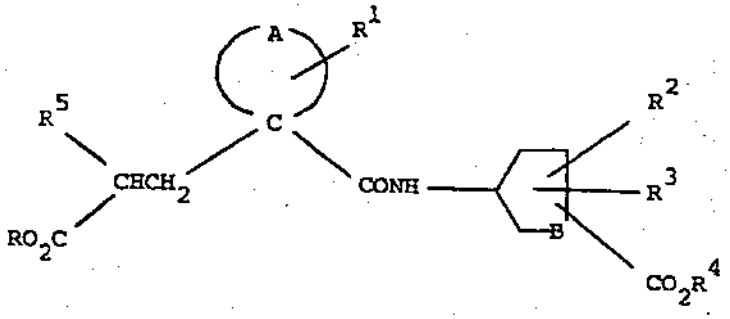
CYCLOALKYL-SUBSTITUTED GLUTARAMIDE DIURETIC AGENTS

This invention relates to a series of cycloalkyl-substituted glutaramide derivatives which are diuretic agents having utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as hypertension and heart failure.

According to the specification of our European patent application 0274234 we describe and claim a series of cycloalkyl-substituted glutaramide derivatives having the formula:



(I)

wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

B is $(CH_2)_m$ wherein m is an integer of from 1 to 3;

each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

R^2 and R^3 are each independently H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, C_1-C_6 alkoxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$ or a saturated heterocyclic group;

or C_1-C_6 alkyl substituted by one or more substituents chosen from halo, hydroxy, C_1-C_6 alkoxy, C_2-C_6 hydroxyalkoxy, C_1-C_6 alkoxy(C_1-C_6 alkoxy), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, aryloxy(C_1-C_4 alkoxy), heterocyclyl, heterocyclyloxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$, $-CONR^6R^7$, $-SH$, $-S(O)_pR^{10}$, $-COR^{11}$ or $-CO_2R^{12}$;

wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl (optionally substituted by hydroxy or C_1-C_4 alkoxy), aryl, aryl(C_1-C_4 alkyl), C_2-C_6 alkoxyalkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4 alkyl)-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4 alkyl), aryl(C_1-C_4 alkoxy), heterocycyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, aryl, heterocyclyl or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{11} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

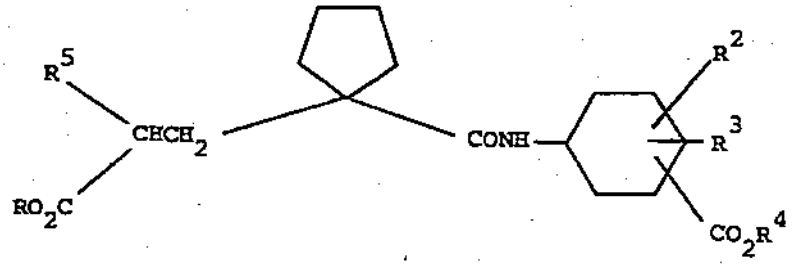
R^{12} is H or C_1-C_4 alkyl;

and p is 0, 1 or 2;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

The compounds are inhibitors of the zinc-dependent, neutral endopeptidase E.C.3.4.24.11. This enzyme is involved in the breakdown of several peptide hormones, including artrial natriuretic factor (ANF), which is secreted by the heart and which has potent vasodilatory, diuretic and natriuretic activity. Thus, by inhibiting the neutral endopeptidase E.C.3.4.24.11, the compounds can potentiate the biological effects of ANF and, in particular, the compounds are diuretic agents having utitility in the treatment of a number of disorders, including hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical odema, Menières disease, hyperaldosteroneism (primary and secondary) and hypercalciura.

A particularly preferred group of compounds of the formula (I) identified in EP-A-0274234 are those wherein A is $(CH_2)_4$, R^1 is H and B is $(CH_2)_2$, i.e. compounds of the formula (II) wherein R, R^2, R^3, R^4 and R^5 are as previously defined for formula(I):



(II)

We have now surprisingly discovered that compounds of the formula (II) in which R^2 is a C_4-alkyl group have significantly increased potency over compounds wherein R^2 is H, CH_3 or C_2H_5 as exemplified in EP-A-0274234.

Thus, according the present invention there are provided compounds having the formula II wherein R, R^3, R^4 and R^5 are as previously defined and R^2 is a C_4-alkyl group.

In the above definitions, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched-chain. The term aryl as used herein means an aromatic hydrocarbon group such as phenyl or naphthyl which may optionally be substituted with, for example, one or more OH, CN, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, carbamoyl, aminosulphonyl, amino, mono or di(C_1-C_4 alkyl) amino or (C_1-C_4 alkanoyl)amino groups. Halo means fluoro, chloro, bromo or iodo.

The term heterocyclyl means a 5 or 6 membered nitrogen, oxygen or sulphur containing heterocyclic group which, unless otherwise stated, may be saturated or unsaturated and which may optionally include a further oxygen or one to three nitrogen atoms in the ring and which may optionally be benzofused or substituted with for example, one or more halo, C_1-C_4 alkyl, hydroxy, carbamoyl, benzyl, oxo, amino or mono or di-(C_1-C_4 alkyl)amino or (C_1-C_4 alkanoyl)amino groups. Particular examples of heterocycles include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, isoindolinyl, quinolyl, quinoxalinyl, quinazolinyl and benzimidazolyl, each being optionally substituted as previously defined.

The compounds of formula (II) may contain several asymmetric centres and thus they can exist as enantiomers and diastereomers. The invention includes both the separated individual isomers as well as mixtures of isomers.

The pharmaceutically acceptable salts of the compounds of formula (II) containing an acidic centre are those formed with bases which form non-toxic salts. Examples include metal salts such as the sodium, potassium or calcium salts or salts with amines such as diethylamine. Compounds having a basic centre can also form acid addition salts with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate and tartrate salts.

The term bioprecursor in the above definition means a pharmaceutically acceptable biologically degradable derivative of the compound of formula (I) which, upon administration to an animal or human being, is converted in the body to produce a compound of the formula (I).

The term biolabile ester-forming group is well understood in the art as meaning a group which provides an ester which can be readily cleaved in the body to liberate the corresponding diacid of formula (II) wherein R and R^4 are both H. A number of such ester groups are described in EP-A-0274234 and include for example 5-indanyl in addition to ethyl and benzyl.

Preferred compounds of the invention are those compounds of the formula (II) wherein R and R^4 are both H (diacids) as well as biolabile mono and diester derivatives thereof wherein one or both of R and R^4 is a biolabile ester group.

The group R^5 is preferably n-propyl, 2-methoxyethoxymethyl, 2-methoxyethyl, methoxymethyl or allyl. In a further group of preferred compounds the group CO_2R^4 is attached at the 4-position of the cyclohexane ring and is of cis-stereochemistry relative to the 1-position.

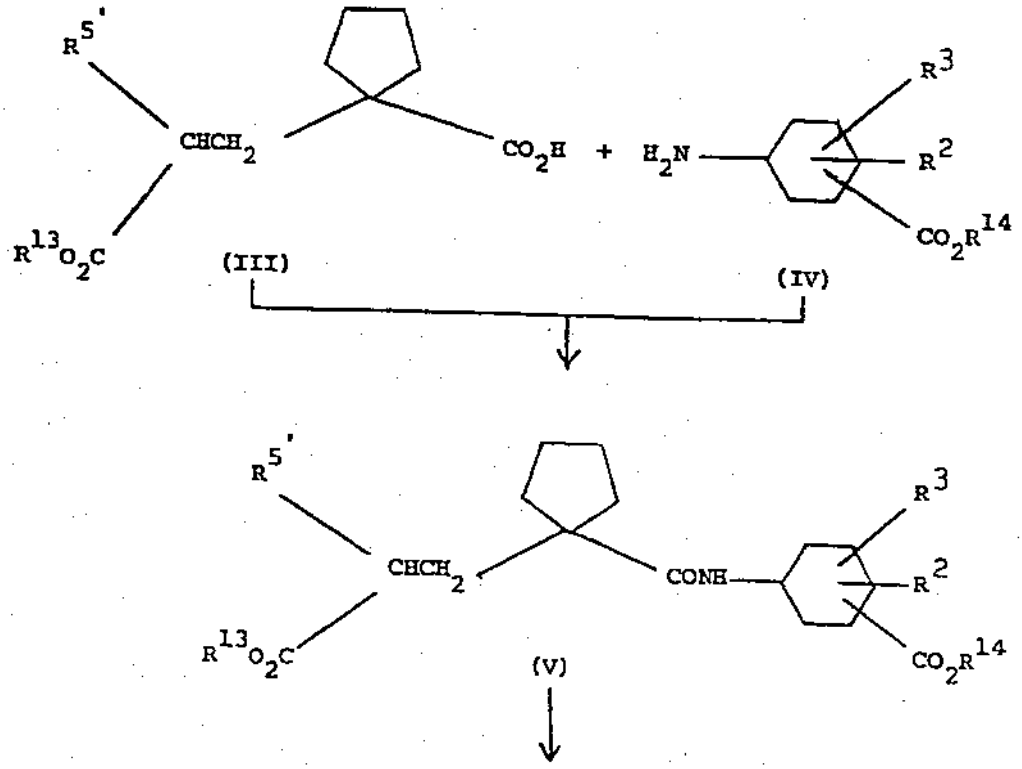
Particularly preferred individual compounds of the invention include-:

3-[1-(c-4-carboxycarbonyl-c-3-butylcyclohexyl-r-1-carbamoyl) cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid;

3-[1-(c-4-carboxycarbonyl-t-3-butylcyclohexyl-r-1-carbamoyl)cyclo-pentyl]-2S-(2-methoxyethoxymethyl)propanoic acid;
and
3-[1-(c-4-carboxycarbonyl-c-3-butylcyclohexyl-r-1-carbamoyl)cyclo-pentyl-2-(2-methoxyethyl)propanoic acid.

The compounds of formula (II) are prepared following the synthetic procedures outlined in EP-A-0274234. The basic procedure involves the synthesis of a partially protected cyclopentyl-substituted glutaric acid derivative (III) which is coupled to cyclohexylamine derivative (IV). The carboxylic acid in the amine, if free, or any reactive groups in R^5, may require protection during the coupling step and such protecting groups are removed in the final stage of the process. The route is illustrated below wherein $R^{5'}$ is as defined for R^5 with any reactive group therein protected if necessary and R^{13} and R^{14} are as defined for R and R^4 excluding H, or they are conventional caboxylic acid protecting groups.

Scheme 1



(II)

Preparation of the starting cyclopentyl-substituted glutaric acid derivatives of formula (III) is described in EP-A-0274234, and in our UK patent application no 8811873.2. The amines of formula (IV) are prepared by conventional methods from known starting materials. Thus, for example, in one procedure 2-butyl-4-oxocyclohex-2-ene carboxylic acid ethyl ester is reduced and the keto group converted to an amine group by way of the oxime. The product in this case is converted to the N-t-butyloxycarbonyl derivative to enable separation of the cis and trans isomers by chromatography. The major product, the all cis isomer, was deprotected and used in the coupling reaction. Alternatively the ketal derivative of the ketone is isomerised by treatment with a strong base to give the trans isomer and the keto group again converted to the amine by, in this case, reaction with methoxylamine followed by reduction. Again chromatography of the N-t-butyloxycarbonyl derivative enabled the cis isomer to be separated from the trans isomer for use in the subsequent coupling steps.

The coupling is achieved using conventional amide coupling techniques. Thus in one process, the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a diimide condensing agent, for example 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as N-methylmorpholine. The reaction is generally complete after a period of from 12 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water or filtration

to remove the urea biproduct and evaporation of the solvent. The product may be further purified by crystallisation or chromatography as necessary.

The diesters of formula (V) may be further reacted to give the monoester or diacid derivatives of formula (II) wherein one or both of R and R^4 are H. The conditions used will depend on the precise nature of the groups R^{13} and R^{14} present in the compound of formula (V) and a number of variations are possible. Thus for example when both of R^{13} and R^{14} are benzyl, hydrogenation of the product will yield the diacid of formula (I) wherein R and R^4 are both H. Alternatively if R^{13} is benzyl and R^{14} is alkyl, hydrogenation will yield a monoester product. This can then be hydrolysed, if desired, again to yield the diacid product. When one of R^{13} and R^{14} is t-butyl, treatment of the compound of formula (V) with trifluoroacetic acid yields the corresponding acid.

In each case the product may be obtained as the free carboxylic acid or it may be neutralised with an appropriate base and isolated in salt form.

In the case where the compounds of formula (II) contain one or more optically active centres, the product may be obtained as a mixture of isomers or diastereoisomers and these may be separated by conventional methods.

Appropriate coupling, protecting and deprotecting methods for all of the above steps and alternative variations and procedures will be well known to those skilled in the art by reference to standard text books and to the examples provided hereafter.

As previously mentioned, the compounds of the invention are potent inhibitors of the neutral endopeptidase (E.C.3.4.24.11). This enzyme is involved in the breakdown of a number of peptide hormones and, in particular we have discovered that it is involved in the breakdown of atrial natriuretic factor (ANF).

By preventing the degradation of ANF, by endopeptidase E.C.3.4.24.11, the compounds of the invention, can potentiate its biological effects and the compounds are thus diuretic and natriuretic agents of utility in a number of disorders as previously described.

Activity against neutral endopeptidase E.C.3.4.24.11 is assessed using a procedure based on the assay described by J. T. Cafford, R. A. Skidgel, E. G. Erdos and L. B. Hersh, Biochemistry, 1983, 32, 3265-3271. The method involves determining the concentration of compound required to reduce by 50% the rate of release of radiolabelled hippuric acid from hippuryl-L-phenylalanyl-L-arginine by a neutral endopeptidase preparation from rat kidney.

The activity of the compounds as diuretic agents is determined by measuring their ability to increase urine output and sodium ion excretion in saline loaded conscious mice. In this test, male mice (Charles River CD1, 22-28 g) are acclimatised and starved overnight in metabowls. The mice are dosed intravenously via the tail vein, with the test compound dissolved in a volume of saline solution equivalent to 2.5% of body weight. Urine samples are collected each hour for two hours in pre-weighed tubes and analysed for electrolyte concentration. Urine volume and sodium ion concentration from the test animals are compared to a control group which received only saline.

For administration to man in the curative or prophylactic treatment of hypertension, congestive heart failure or renal insufficiency, oral dosages of the compounds will generally be in the range of from 3-700 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 1 to 150 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range 5 to 500 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

The compounds may be administered alone but may also be administered together with such other agents as the physician shall direct to optimise control of blood pressure or to treat congestive heart failure, renal insufficiency or other disorders in any particular patient in accordance with established medical practice.

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compound of the formula (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, in particular in the treatment of hypertension, congestive heart failure or renal insufficiency in a human being.

The preparation of the compounds of the invention is illustrated by the following Examples in which Examples 1 and 2 describe preparation of amines of the formula (IV) and Examples 3 to 8 describe preparation of the compounds of the formula (II).

EXAMPLE 1

c-4-Amino-c-2-butyl-r-1-cyclohexanecarboxylic acid ethyl ester hydrochloride

(1) cis-2-Butyl-4-oxocyclohexane carboxylic acid ethyl ester

2-Butyl-4-oxocyclohex-2-ene carboxylic acid ethyl ester [Tetrahedron 37 1033 (1981)] (4.48 g; 20 mmole) dissolved in absolute ethanol (15 ml) containing 2N hydrochloric acid (1 ml) was reduced at room temperature over 5% palladium on carbon (150 mg) at 50 p.s.i. (3.45 bar). After one hour the mixture was filtered through avicel and the solvent was evaporated under reduced pressure. The residue was taken up in diethyl ether and washed successively with water, saturated aqueous sodium bicarbonate and water. Drying over $MgSO_4$ and evaporation gave an oil (4.2g) which was chromatographed on silica. Elution with diethyl ether:hexane (2:8) gave the pure title ester (3.6 g, 80%) as a clear liquid. Found: C,68.86; H,9.84. $C_{13}H_{22}O_3$ requires C,68.99; H,9.80%.

(2) cis-2-Butyl-4-hydroximinocyclohexanecaboxylic acid ethyl ester

Sodium acetate (1.56 g; 19 mmole) and hydroxylamine hydrochloride (1.32 g; 19 mmole) were dissolved in water (5 ml). Ethanol (50 ml) was added and the mixture was filtered. The above ester (3.57 g; 15.8 mmole) was added and the solution was refluxed for two hours. The solvent was evaporated under reduced pressure and the residue partitioned between diethyl ether and water. The ether extract was washed in turn with saturated aqueous sodium bicarbonate and water, dried ($MgSO_4$) and the solvent evaporated to give the required oxime as an oil (3.8 g; 100%). Found: C,64.64, H,9.48, N,5.91. $C_{13}H_{23}NO_3$ requires C,64.70; H,9.61; N,5.80%.

(3) c-2-Butyl-c-4-(1,1-dimethylethoxycarbonylamino-r-1-cyclohexane carboxylic acid ethyl ester

An aqueous solution of titanium trichloride (37 ml, 15% w/v; 36.5 mmole) was added dropwise at room temperature under nitrogen over 1.5 hours to a stirred solution of the above oxime (4.0 g; 16.57 mmole), ammonium acetate (16 g) and sodium cyanoborohydride (3.12 g; 49.7 mmole) in absolute ethanol (200 ml). After stirring for 14 hours the solvent was evaporated, water was added and the mixture was basified to pH8 with 1N sodium hydroxide. The product was stirred in air to oxidize unreacted reagent, and the suspension was then extracted with ethyl acetate. The organic extract was washed with saturated salt solution, dried ($MgSO_4$) and evaporated to give the crude amine as a clear gum (4.3 g). This product was

dissolved in dry methylene chloride (80 ml) containing N-methylmorpholine (1.68 g; 16.6 mmole), di-tert-butyldicarbonate (7.23 g; 33.14 mmole) added and the solution allowed to stand at room temperature for 48 hours. The solvent was evaporated and the residue partitioned between diethyl ether and water. The ether extract was washed succesively with 0.5N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying over $MgSO_4$ and evaporation gave an oil (5.8 g) which was chromotographed on silica (600 g). Elution with diethyl ether:hexane (2:8) gave the required cis compound as an oil (2.72 g; 50%). Rf 0.38 (silica; ether:hexane 3:7). NMR: δ = 2.66 (HC-CO_2Et), δ =3.45 (HC-NH-). Found: C,66.06; H,10.17; N,4.19. $C_{18}H_{33}NO_4$ requires C,66.02; H,10.16; N,4.28%. Continued elution then gave the more polar trans-isomer as an oil which solidified on standing (860 mg; 16%) Rf0.27. NMR: δ =2.45 (HC-CO_2Et), δ =3.68 (HC-NH-). Found: C,65.75; H, 10.13; N, 4.17. $C_{18}H_{33}NO_4$ requires C, 66.02; H, 10.16; N,4.28%.

(4) c-4-Amino-c-2-butyl-r-1-cyclohexane carboxylic acid ethyl ester hydrochloride

An ice cold solution of the above cis-isomer (3.2 g; 9.8 mmole) in diethyl ether (100 ml) was saturated with HCl. After 3 hours the solvent was evaporated under a stream of nitrogen and the residue triturated with diethyl ether. Filtration gave a white solid (2.43 g; 94%) m.p. 249-250°C. Found: C,59.16; H,9.83; N,5.38. $C_{13}H_{26}ClNO_2$ requires C,59.19; H,9.93; N,5.31%.

EXAMPLE 2

c-4-Amino-t-2-butyl-r-1-cyclohexane carboxylic acid ethyl ester hydrochloride

(1) cis-7-Butyl-1,4-dioxaspiro[4,5]decane-8-carboxylic acid ethyl ester

cis-2-Butyl-4-oxocyclohexane carboxylic acid ethyl ester (9.05g; 40 mmole), ethyleneglycol (2.73 g; 44 mmole) and p-toluene-sulphonic acid (100 mg) were refluxed in benzene (80 ml) using a Dean-Stark water trap. After 12 hours the mixture was cooled, diluted with diethyl ether and washed with saturated aqueous sodium bicarbonate followed by water. Drying over $MgSO_4$ and evaporation gave a liquid (10.80 g 100%) which was pure enough to use directly. Found: C,66.71; H,9.79, $C_{15}H_{26}O_4$ requires C,66.64; H,9.69%.

(2) trans-7-Butyl-1,4-dioxaspiro[4,5]decane-8-carboxylic acid ethyl ester

Potassium-tert-butoxide (1.9 g; 17 mmole) was added to a solution of the above ester (10.75 g; 39.7 mmole) in tert-butanol (90 ml), which had been dried over 3A seive, and the mixture was refluxed under nitrogen for 24 hours. The solution was then neutralised with 2N HCl and evaporated to a small volume under reduced pressure. The residue was taken up in diethyl ether washed with water, dried over $MgSO_4$ and evaporated to give a yellow liquid (10.0 g) which was chromotographed on silica (300 g). Elution with diethyl ether:hexane (2:8) gave the required trans-isomer as a clear liquid (8.80 g, 82%). Found: C,66.58; H,9.67. $C_{15}H_{26}O_4$ requires C,66.64; H,9.69%.

(3) trans-2-butyl-4-oxocyclohexanecarboxylic acid ethyl ester

The above ester (8.75 g; 32.4 mmole) in absolute ethanol (70 ml) was added to 1N sulphuric acid (50 ml) and the mixture was refluxed for 3 hours. Half the solvent was evaporated and the residual suspension was extracted with diethyl ether. The extract was washed with saturated aqueous sodium bicarbonate followed by water, dried ($MgSO_4$) and evaporated to give a clear liquid (6.85 g). Chromatography on silica (500 g) eluting with diethyl ether:hexane (2:8) gave the required ketone (6.05 g; 83%) as a clear liquid. Found: C,68.73; H,9.85. $C_{13}H_{22}O_3$ requires C,68.99; H,9.80%.

(4) trans-2-butyl-4-methoximinocyclohexane carboxylic acid ethyl ester

The above ketone (6.02 g, 26.6 mmole), methoxylamine hydrochloride (2.89 g; 34.6 mmole), sodium acetate (2.84 g; 34.6 mmole) were refluxed in absolute ethanol (100 ml) for 3 hours. After standing overnight at room temperature, most of the solvent was evaporated under reduced pressure and the residue was partitioned between diethyl ether and water. The ether extract was washed with saturated aqueous sodium bicarbonate followed by water, dried ($MgSO_4$) and evaporated to give a clear oil (6.77 g, 100%) which was pure enough to use directly. Found: C,65.78; H,9.71; N,5.43. $C_{14}H_{25}NO_3$ requires C,65.85; H,9.87; N,5.49%.

(5) t-2-Butyl-c-4-(1,1-dimethylethoxycarbonylamino)-1-r-cyclohexane carboxylic acid ethyl ester

Trifluoroacetic acid (10.2 ml, 0.13 mmole) in dry tetrahydrofuran (20 ml) was added dropwise under nitrogen to a stirred suspension of sodium borohydride (5.0g; 0.13 mmole) in dry tetrahydrofuran (120 ml). The temperature was kept between 10-20°C with ice cooling and after 15 minutes a solution of the above ester (6.75 g; 26.4 mmole) in tetrahydrofuran (20 ml) was added. The temperature rose to 33°C and brief cooling was required to return the temperature to 20°C. After 4 hours water was carefully added, with ice cooling, followed by diethyl ether. The organic phase was washed with saturated salt solution, dried ($MgSO_4$) and evaporated to give crude amine (8.2 g). This product was dissolved in dry methylene chloride (100 ml) containing N-methyl morpholine (2.67 g; 26.4 mmole), di-tert-butyldicarbonate (11.52 g; 52.8 mmole) was added and the solution allowed to stand at room temperature for 48 hours. The solvent was evaporated and the residue partitioned between diethyl ether and water. The ether extract was washed successively with 0.5N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying over $MgSO_4$ and evaporation gave an oil (8.86 g). Chromatography on silica eluting with diethyl ether:hexane (2:8) gave the required cis-isomer as an oil (1.61 g; 19%). Rf 0.35 (silica, ether:hexane 3:7). NMR: δ=2.13 (HC-CO_2Et), δ=3.88 (HC-NH-).

Found: C,65.96; H,10.14; N,4.20. $C_{18}H_{33}NO_4$ requires C,66.02; H,10.16; N,4.28%. Continued elution then gave the more polar trans-isomer as a white solid (1.53 g; 18%). Recrystallisation from hexane gave a white solid m.p. 78-9°C. Rf = 0.3. NMR: δ = 2.1 (HC-CO_2Et), δ=3.49 (HC-NH-). Found: C,66.08; H,10.24; N,4.17. $C_{18}H_{33}NO_4$ requires C,66.02; H,10.66; N,4.28%.

(6) c-4-Amino-t-2-butyl-r-1-cyclohexane carboxylic acid ethyl ester hydrochloride

An ice cold solution of the above cis-isomer (1.58 g; 4.83 mmole) in diethyl ether (50 ml) was saturated with HCl. After 3 hours the solvent was evaporated under a stream of nitrogen and the residue was triturated with diethyl ether. Filtration gave the required amine salt as a white solid (1.17 g; 92%), m.p. 166-7°C. Found: C,59.18; H,10.27; N,5.19. $C_{13}H_{26}ClNO_2$ requires C,59.19; H,9.93; N,5.31%.

EXAMPLE 3

3-[1-(c-4-Ethoxycarbonyl-c-3-butylcyclohexyl-r-1-carbamoyl) cyclopentyl]-2S-2-methoxyethoxymethyl)propanoic acid 1,1-dimethyl-ethyl ester, (diastereoisomers).

1-Ethyl-3-(3-dimethylamimopropyl)carbodiimide (575 mg; 3 mmole) was added to an ice cold stirred solution of 3-(1-carboxy-cyclopentyl)-2S-(2-methoxyethoxymethyl)propanoic acid 1,1-dimethyl ethyl ester (495 mg; 1.5 mmole), 1-hydroxybenzotriazole (202 mg; 1.5 mmole) N-methylmorpholine (455 mg; 4.5 mmole) and c-4-amino-c-2-butyl-r-1-cyclohexane carboxylic acid ethyl ester hydrochloride (396 mg; 1.5 mmole) in dry methylene chloride (15 ml). After half an hour the mixture was allowed to attain room temperature, and after five hours the solvent was evaporated under reduced pressure. The residue on standing for 20 hours was taken up in diethyl ether and washed successively with 0.5N hydrochloric acid, water, aqueous sodium bicarbonate solution and water. Drying over $MgSO_4$ and evaporation gave a gum (770mg).

The crude product was chromotographed on silica and the two diastereoisomers were separated by elution with a mixture of diethyl ether:hexane:toluene (10:7:3).

Isomer I was obtained as a gum Rf=0.25 (silica, diethyl ether, hexane, toluene 10:7:3). Found: C,66.90; H,9.89; N,2.53. $C_{30}H_{53}NO_7$ requires C,66.76; H,9.90; N,2.60%.

Isomer II also obtained as a gum Rf=0.22. Found: C,66.93, H,9.90; N,2.41. $C_{30}H_{53}NO_7$ required as above.

EXAMPLE 4

3-[1-(c-4-Carboxy-c-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid, (diastereoisomers)

Isomer A Trifluoroacetic acid (5 ml) was added to an ice cold solution of isomer I from Example 3 above (350 mg) in dry methylene chloride. After standing at room temperature for 2.5 hours, the solvent was evaporated under reduced pressure and the residue dried azeotropically with toluene. The residue was dissolved in diethyl ether and washed twice with water, 5% aqueous ammonium carbonate being added dropwise to the first washing until the pH of the aqueous phase remained at about 5. The ether solution was then extracted with 1N sodium hydroxide (10 ml x 2) and the combined aqueous extracts maintained at 65°C for two days. The solution was acidified with concentrated hydrochloric acid and extracted with diethyl ether. The ether extract was washed with saturated salt solution, dried ($MgSO_4$) and evaporated to give the title product as a gummy foam (264 mg; 89%). $[\alpha]_D^{25}$ + 22.1 (c = 0.95, CH_2Cl_2). Found: C,62.93; H,8.87; N 2.90. $C_{24}H_{41}NO_5$ requires C,63.27; H,9.07; N,3.07%.

Isomer B Prepared similarly from isomer II of Example 3 (330 mg), and was also obtained as a gummy foam (241 mg; 87%). $[\alpha]_D^{25}$-21.9° (c = 0.95, CH_2Cl_2). Found: C,63.58; H,9.18; N,2.89 $C_{24}H_{41}NO_7$ requires C,63.27; H,9.07; N,3.07%.

EXAMPLE 5

3-[1-(c-4-Ethoxycarbonyl-t-3-butyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid 1,1-dimethylethyl ester

The procedure of Example 3 was followed but using the trans-isomer of the amine from Example 2. The diester product, a diastereoisomer mixture, was obtained as a gum (83%). Found: C,66.85; H,9.80; N,2.92. $C_{30}H_{53}NO_7$ requires C,66.76; H,9.90; N,2.60%.

EXAMPLE 6

3-[1-(c-4-Carboxy-t-3-butyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid

The product of Example 5 was deprotected following the procedure of Example 4 to yield the title diacid product, a mixture of diastereoisomers, as a gum (99%). Found: C,63.28; H,9.15; N,3.07. $C_{24}H_{41}NO_7$ requires C,63.27; H,9.07; N,3.07%.

EXAMPLE 7

3-[1-(c-4-Ethoxycarbonyl-c-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2-(2-methoxyethyl)propanoic acid benzyl ester

Oxalyl chloride (1.55 g; 12.2 mmole) was added to a stirred solution of 3-(1-carboxycyclopentyl)-2-(2-methoxyethyl)propanoic acid benzyl ester(2.04 g; 6.1 mmole) in dry methylene chloride containing two drops of dimethylformide. After 2 hours the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in dry methylene chloride (10 ml) and 5.7 ml of this solution was added to an ice cold stirred solution of c-4-amino-c-2-butyl-r-1-cyclohexane carboxylic acid ethyl ester hydrochloride (605 mg 2.3 mmole) and N-methylmorpholine (607 mg; 6 mmole) in dry methylene chloride (5 ml). After 0.5 hours the ice bath was removed and after a further 1 hour the solvent was evaporated under reduced pressure. The residue was suspended in water, extracted with diethyl ether and the organic extract washed successively with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation gave an oil (1.64 g) which was chromotographed on silica. Elution with diethyl ether:hexane (1:1) gave the required diester as an oil. (1.07 g; 86%). Found: C,70.83;H,9.11; N,2.44. $C_{32}H_{49}NO_6$ requires C,70.69; H,9.08; N 2.58%.

EXAMPLE 8

3-[1-(c-4-Carboxy-c-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2-(2-methoxyethyl)propanoic acid

The above diester from Example 7 (1.03g; 1.89 mmole) was dissolved in a mixture of ethanol (25 ml) and water (10 ml) and hydrogenated over 10% palladium on carbon (200 mg) at room temperature and 50 psi (3.4 bar). After 1.5 hours the mixture was filtered through avicel and evaporated to dryness. The residual gum was dissolved in 1N sodium hydroxide and the solution was kept under nitrogen at 50°C for two days. Further 1N sodium hydroxide (10 ml) was added and hydrolysis continued for 24 hours. On cooling the solution was acidified with 2N hydrochloric acid and extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$) and evaporated to give the title product as a white foam (660 mg; 82%). Found: C,63.80; H,9.34; N,3.39. $C_{23}H_{39}NO_6 . 0.4H_2O$ requires C,63.83; H,9.27, N,3.27%.

TEST DATA

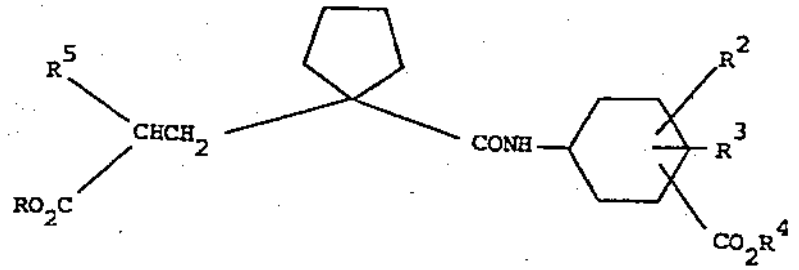
The compounds were assessed for their ability to inhibit the neutral endopeptidase E.C.3.4.24.11 following the procedure described herein. IC_{50} data in comparison with compounds from EP-A-0274234 are given below:

Compound	IC_{50}
Example 4 isomer A	3.6×10^{-9}
Example 4 isomer B	5.6×10^{-9}
Example 6	7.9×10^{-9}
Example 8	8.0×10^{-9}
EP-A-274234	
Example 325 (2S isomer)*	3.9×10^{-8}
Example 217	5.0×10^{-8}

* (EP-A-0342850, Example 4)

CLAIMS

1. A compound having the formula-:



wherein each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

R^2 is a C_4 alkyl group;

R^3 is H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, C_1-C_6 alkoxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$ or a saturated heterocyclic group;

or C_1-C_6 alkyl substituted by one or more substituents chosen from halo, hydroxy, C_1-C_6 alkoxy, C_2-C_6 hydroxyalkoxy, C_1-C_6 alkoxy(C_1-C_6 alkoxy), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy,

aryloxy(C_1-C_4 alkoxy), heterocyclyl, heterocyclyloxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$, $-CONR^6R^7$, -SH, $-S(O)_pR^{10}$, $-COR^{11}$ or $-CO_2R^{12}$; wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl (optionally substituted by hydroxy or C_1-C_4 alkoxy), aryl, aryl(C_1-C_4 alkyl), C_2-C_6 alkoxy- alkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4 alkyl)-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4 alkyl), aryl(C_1-C_4 alkoxy), heterocycyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, aryl, heterocyclyl or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{11} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{12} is H or C_1-C_4 alkyl;

and p is 0, 1 or 2;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

2. A compound as claimed in claim 1 wherein R^5 is n-propyl, 2-methoxyethoxymethyl, 2-methoxyethyl, methoxymethyl or allyl.

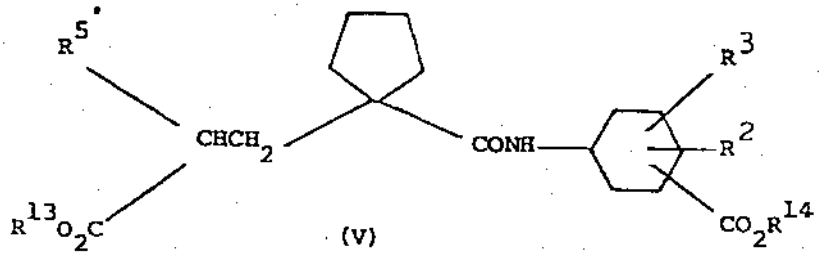
3. A compound as claimed in claim 1 or claim 2 wherein R and R^4 are both H.

4. A compound as claimed in claim 1 or claim 2 wherein one of R and R^4 is a biolabile ester group and the other is H.

5. A compound as claimed in claim 4 wherein said biolabile ester group is 5-indanyl.

6. A compound as claimed in claim 1 wherein said compound is 3-[1-(c-4-carboxycarbonyl-c-3-butylcyclohexyl-r-1-carbamoyl) cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid;
3-[1-(c-4-carboxycarbonyl-t-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; or
3-[1-(c-4-carboxycarbonyl-c-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl-2-(2-methoxyethyl)propanoic acid.

7. A process for preparing a compound of the formula (II) as claimed in claim 1 which comprises subjecting a compound of the formula-:



(V)

wherein R^{13} and R^{14} are as defined for R and R^4 excluding H, or they are conventional carboxylic acid protecting groups and $R^{5'}$ is as defined for R^5 with any reactive groups therein optionally protected;

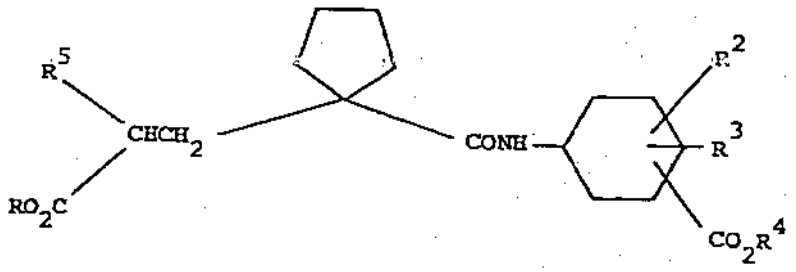
to a hydrolysis and/or hydrogenation and/or other deprotection reaction to remove any protective group present in $R^{5'}$ and to remove one or both of R^{13} and R^{14} to yield the corresponding dicarboxylic acid of formula (II) wherein R and R^4 are both H, or to yield the corresponding mono-ester product wherein one of R and R^4 is H and the other is a biolabile ester-forming group; and optionally forming a pharmaceutically acceptable salt of the product.

8. A process as claimed in claim 7 wherein R^{13} and R^{14} are selected from t-butyl, ethyl and benzyl and said groups are removed by treatment with trifluoroacetic acid, aqueous alkali or catalytic hydrogenation respectively, to yield the compound of formula (II) wherein R and R^4 are both H.

9. A pharmaceutical composition comprising a compound of the formula (II) as claimed in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

10. A compound of the formula (II) as claimed in any of claims 1 to 6 or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for the treatment of hypertension, heart failure or renal insufficiency.

11. A process for preparing a compound having the formula-:



(II)

wherein each of R and R^4 is independently H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

R^2 is a C_4 alkyl group;

R^3 is H, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl(C_2-C_6 alkynyl), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, C_1-C_6 alkoxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$ or a saturated heterocyclic group;

or C_1-C_6 alkyl substituted by one or more substituents chosen from halo, hydroxy, C_1-C_6 alkoxy, C_2-C_6 hydroxyalkoxy, C_1-C_6 alkoxy(C_1-C_6 alkoxy), C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy,

aryloxy(C_1-C_4 alkoxy), heterocyclyl, heterocyclyloxy, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^9$, $-CONR^6R^7$, -SH, $-S(O)_pR^{10}$, $-COR^{11}$ or $-CO_2R^{12}$;

wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl (optionally substituted by hydroxy or C_1-C_4 alkoxy), aryl, aryl(C_1-C_4 alkyl), C_2-C_6 alkoxy-alkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4 alkyl)-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4 alkyl), aryl(C_1-C_4 alkoxy), heterocycyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, aryl, heterocyclyl or NR^6R^7 wherein R^6 and R^7 are as previously defined;

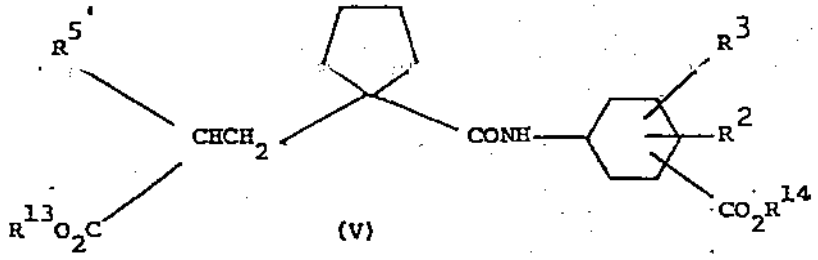
R^{11} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{12} is H or C_1-C_4 alkyl;

and p is 0, 1 or 2;

and pharmaceutically acceptable salts thereof, which comprises

subjecting a compound of the formula-:



(V)

wherein R^{13} and R^{14} are as defined for R and R^4 excluding H, or they are conventional carboxylic acid protecting groups and $R^{5'}$ is as defined for R^5 with any reactive groups therein optionally protected;

to a hydrolysis and/or hydrogenation and/or other deprotection reaction to remove any protective group present in $R^{5'}$ and to remove one or both of R^{13} and R^{14} to yield the corresponding dicarboxylic acid of formula (II) wherein R and R^4 are both H, or to yield the corresponding mono-ester product wherein one of R and R^4 is H and the other is a biolabile ester-forming group; and optionally forming a pharmaceutically acceptable salt of the product.

12. A process as claimed in claim 1 wherein R^5 is n-propyl, 2-methoxyethoxymethyl, 2-methoxyethyl, methoxymethyl or allyl.

13. A process as claimed in claim 1 or claim 2 wherein R and R^4 are both H.

14. A process as claimed in claim 1 or claim 2 wherein one of R and R^4 is a biolabile ester group and the other is H.

15. A process as claimed in claim 4 wherein said biolabile ester group is 5-indanyl.

16. A process as claimed in claim 1 wherein said compound of formula (II) produced is-:

3-[1-(c-4-carboxycaronyl-c-3-butylcyclohexyl-r-1-carbamoyl) cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid;

3-[1-(c-4-carboxycarbonyl-t-3-butylcyclohexyl-r-1-carbamoyl)cyclo-pentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; or

3-[1-(c-4-carboxycarbonyl-c-3-butylcyclohexyl-r-1-carbamoyl)cyclo-pentyl-2-(2-methoxyethyl)propanoic acid.

17. A process as claimed in claim 1 wherein R^{13} and R^{14} are selected from t-butyl, ethyl and benzyl and said groups are removed by treatment with trifluoroacetic acid, aqueous alkali or catalytic hydrogenation respectively, to yield the compound of formula II wherein R and R^4 are both H.

18. A process as claimed in claim 7 wherein R^{13} is t-butyl and R^{14} is ethyl and the compound of formula V is treated with trifluoroacetic acid followed by aqueous alkali to yield the compound of formula II wherein R and R^4 are both H.

19. A process as claimed in claim 7 wherein R^{13} is benzyl and R^{14} is ethyl and the compound of formula V is subjected to catalytic hydrogenation followed by treatment with aqueous alkali to yield the compound of formula II wherein R and R^4 are both H.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/00220

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 C 235/82, A 61 K 31/16

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System [8]	Classification Symbols
IPC[5]	C 07 C 235/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [9]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [10]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0274234 (PFIZER) 13 July 1988 see claims 1-14,16-21 (cited in the application)	1-19

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* Special categories of cited documents: [14]

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th June 1990	28. 06. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS T. TAZELAAR

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9000220 SA 34940

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/06/90
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0274234	13-07-88	AU-A- 8240787	07-07-88
		JP-A- 63165353	08-07-88

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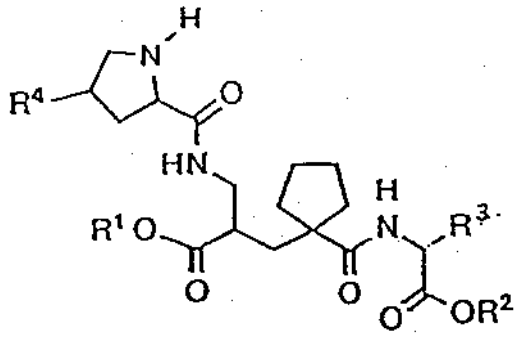
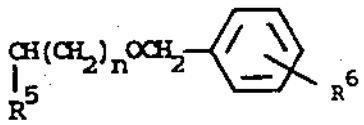
(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

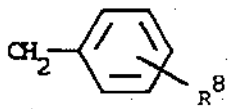
Published
With international search report.

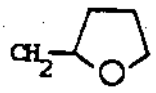
(54) Title: CYCLOPENTANE-DERIVED GLUTARAMIDE ANTIHYPERTENSIVE AGENTS



(I)

(a) 

(c) 

(d) 

(57) Abstract

Compounds of formula (I), wherein R^1 and R^2 are each independently H or a biolabile ester-forming group, and either or both of OR^1 and OR^2 may optionally be replaced by NH_2; R^3 is (a), wherein R^5 is H or methyl, R^6 is H or halo, and n is 0 or 1; (b) CH_2OR^7, wherein R^7 is C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, (C_1-C_4 alkoxy)C_1-C_6 alkyl, (C_1-C_4 alkoxy)C_3-C_6 alkenyl, (halo)C_3-C_6 alkenyl, (C_3-C_7 cycloalkyl)C_1-C_6 alkyl or (CF_3)C_1-C_6 alkyl; (c) wherein, R^8 is CH_2OH, CH_2OCH_3, $OCH(R^5)CH_2OH$ or $OCH_2CH_2OCH_3$ and R^5 is a previously defined; (d) or (e) (C_1-C_4 alkoxy)C_3-C_6 alkenyl or (C_1-C_4 alkoxy)-C_2-C_6 alkyl; and R^4 is H or hydroxy; and pharmaceutically acceptable salts thereof, are diuretic and natriuretic agents having utility in the treatment of hypertension, heart failure, renal insufficiency and other disorders.

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CYCLOPENTANE-DERIVED GLUTARAMIDE ANTIHYPERTENSIVE AGENTS

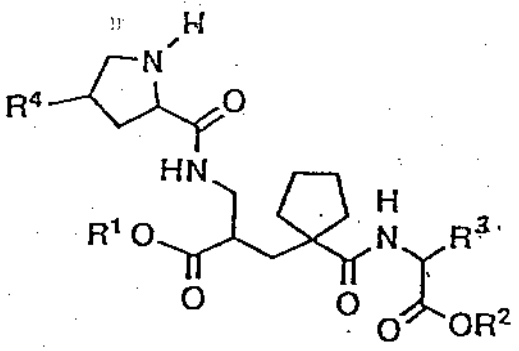
This invention relates to a series of cyclopentyl-substituted glutaramide derivatives which are antihypertensive agents having utility in the treatment of various cardiovascular disorders, including hypertension and heart failure.

According to the specification of our European patent application 0358398, we disclose certain cycloalkyl-substituted glutaramide derivatives which are inhibitors of the zinc dependent enzymes neutral metalloendopeptidase (E.C. 3.4.24.11) and angiotensin converting enzyme. Thus these compounds have a dual pharmacological action by inhibiting two key enzymes involved in blood pressure control, which makes them particularly useful in the treatment of various forms of hypertension and associated cardiovascular disorders, e.g. congestive heart failure and glaucoma.

The present invention includes further novel cyclopentyl-substituted glutaramide diacids which also possess said dual enzyme inhibitory activity. More specifically the invention provides biolabile (and thus prodrug) monoester, diester, monoamide, diamide and monoester-monoamide derivatives of the compounds, which have improved oral bioavailability profiles over those of the bioprecursors disclosed in EP-A-0358398. That is, after oral administration of the prodrugs disclosed herein, significantly enhanced systemic levels of the derived diacids are achieved. Without wishing to be bound by any particular mechanism of action, this is thought, at least in part, to be due to their improved resistance to breakdown by gastrointestinal enzymes, which allows the compounds to be more fully absorbed before

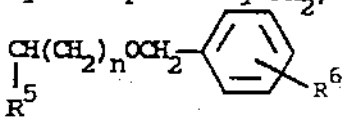
conversion to the active diacid species takes place.

The compounds are of the formula:



(I)

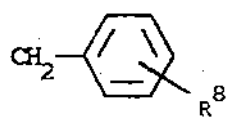
wherein R^1 and R^2 are each independently H or a biolabile ester-forming group, and either or both of OR^1 and OR^2 may optionally be replaced by NH_2;

R^3 is (a) 

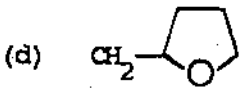
wherein R^5 is H or methyl, R^6 is H or halo, and n is 0 or 1;

(b) CH_2OR^7

wherein R^7 is C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, (C_1-C_4 alkoxy)C_1-C_6 alkyl, (C_1-C_4 alkoxy)C_3-C_6 alkenyl, (halo)C_3-C_6 alkenyl, (C_3-C_7 cycloalkyl)C_1-C_6 alkyl or (CF_3)C_1-C_6 alkyl;

(c) 

wherein R^8 is CH_2OH, CH_2OCH_3, $OCH(R^5)CH_2OH$ or $OCH_2CH_2OCH_3$ and R^5 is as previously defined;

(d)  or

(e) (C_1-C_4 alkoxy)C_3-C_6 alkenyl or (C_1-C_4 alkoxy)C_2-C_6 alkyl;

and R^4 is H or hydroxy;

and include pharmaceutically acceptable salts thereof.

In the above definitions halo means fluoro, chloro, bromo or iodo. Alkyl groups having three or more carbon atoms, and alkenyl or alkynyl groups having four or more carbon atoms, may be straight or branched-chain.

The term biolabile ester-forming group is well understood in the art as meaning a group which provides an ester which can be readily cleaved in vivo to liberate the corresponding acid.

In the case of the compounds of formula (I), such biolabile mono- or diester prodrugs are particularly advantageous in providing compounds of the formula (I) suitable for oral administration. The suitability of any particular ester-forming group can be assessed by conventional in vivo animal or in vitro enzyme hydrolysis studies. Thus desirably, for optimum effect, the ester should only be hydrolysed after absorption is complete. Accordingly, the ester should be resistant to premature hydrolysis by digestive enzymes before absorption, but should be productively hydrolysed by, for example, gut-wall, plasma or liver enzymes. In this way, the active diacid is released into the bloodstream following oral absorption of the prodrug.

Suitable biolabile esters include alkyl, alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl and alkoxycarbonyloxyalkyl esters, including cycloalkyl and aryl substituted derivatives thereof, aryl esters, cycloalkyl esters, haloalkyl esters, oxoalkyl esters, dihydroxyalkyl esters including ketal derivatives thereof, pyridyl esters and [4-(5-alkyl or 5-aryl-1,3-dioxolen-2-onyl]methyl esters, wherein said alkanoyl or alkyl groups may contain from 1 to 8 carbon atoms and be branched or straight chain, said cycloalkyl groups may contain from 3-8 carbon atoms and said cycloalkanoyl groups from 4-8 carbon atoms wherein both are optionally benzo-fused, and said aryl groups are phenyl, naphthyl or indanyl optionally substituted with one or more C_1-C_4 alkyl, C_1-C_4 alkoxy or C_1-C_4 alkoxycarbonyl groups or with halo atoms.

Thus examples of R^1 and R^2 when they are biolabile ester-forming groups include C_1-C_5 alkyl, C_5-C_7 cycloalkyl, (cyclohexyl)C_1-C_3 alkyl, (phenyl)C_1-C_3 alkyl, 1-(C_2-C_5 alkanoyloxy)C_1-C_4 alkyl, 1-(C_5-C_6 cycloalkylacetoxy)C_1-C_4 alkyl, 1-(C_5-C_7 cycloalkylcarboxy)C_1-C_4 alkyl, 1-(2-indanylcarboxy)C_1-C_4 alkyl, 1-(benzoyloxy)C_1-C_4 alkyl, 3-phthalidyl, 1-(C_1-C_4 alkoxy-carbonyloxy)C_1-C_4 alkyl, [4-(5-[C_1-C_4 alkyl]-1,3-dioxolen-2-onyl)]methyl, acetonyl, indanyl and pyridyl.

Preferred biolabile ester-forming groups are methyl, ethyl, (3-cyclohexyl)propyl, (3-phenyl)propyl, pivaloyloxymethyl, 1-(cyclohexylacetoxy)ethyl, 1-(cyclohexylcarboxy)ethyl, 1-(2-indanylcarboxy)ethyl, 1-(benzoyloxy)ethyl, 1-(ethoxycarbonyloxy)-ethyl and [4-(5-methyl-1,3-dioxolen-2-onyl)]methyl.

The invention also includes amide derivatives (wherein either

or both of OR^1 and OR^2 are replaced by NH_2). Such compounds are also bioprecursors to the dicarboxylic acids and their suitability too may be assessed as indicated above.

The compounds of the formula (I) contain three or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. The invention includes both the separated individual isomers as well as mixtures of isomers. The preferred stereoisomers are those derived from either (S)-proline or 4(R)-hydroxy-(S)-proline, in which each of the terminal carboxylic acid/ester/amide groups is attached to an asymmetric carbon atom of (S)-configuration.

Also included in the invention are radiolabelled derivatives of compounds of the formula (I) which are suitable for biological studies.

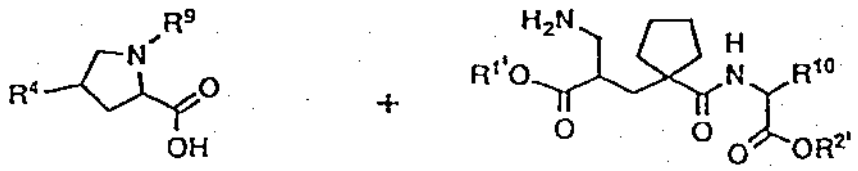
The pharmaceutically acceptable salts of the compounds of formula (I) containing an acidic centre are those formed with bases which form non-toxic salts. Examples include the alkali or alkaline earth metal salts such as the sodium, potassium or calcium salts, or salts with amines such as diethylamine. Compounds having a basic centre can also form acid addition salts with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, citrate, tartrate, lactate, fumarate, maleate, succinate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

Preferred compounds are prodrug mono or diesters of compounds of the formula (I) wherein R^3 is benzyloxymethyl (O-benzyl serine

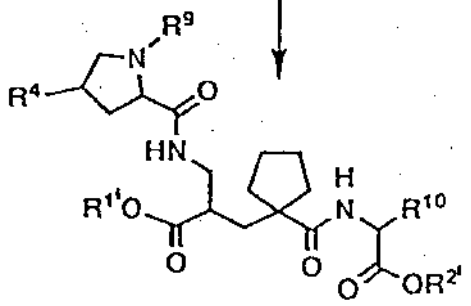
derivates), 1-(2-butenyl)oxymethyl, 1-(4-methoxy-2-butenyl)oxymethyl or 2-chloro-2-propenyloxymethyl. R^4 is preferably H. Preferred mono-esters are those wherein R^1 is H and R^2 is methyl, (3-phenyl)propyl or (3-cyclohexyl)propyl, and preferred diesters are those wherein R^1 is pivaloyloxymethyl, 1-(cyclohexylacetoxy)ethyl, 1-(cyclohexylcarboxy)ethyl, 1-(2-indanylcarboxy)ethyl, 1-(benzoyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl or [4-(5-methyl-1,3-dioxolen-2-onyl]methyl, and R^2 is ethyl.

It will be appreciated from the foregoing discussion that the biologically active species in vivo are the diacids, that is compounds of the formula (I) wherein both R^1 and R^2 are H, and R^3 and R^4 are as previously defined for the formula (I). Thus these diacids form a further preferred aspect of the invention.

The compounds of the formula (I) can be prepared by a number of methods using the coupling and protective procedures of amino-acid chemistry. One procedure involves coupling of a suitably N-protected proline or 4-hydroxyproline derivative of the formula (II), wherein R^4 is as previously defined and R^9 is a conventional amino acid N-protecting group such as t-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl or benzyloxycarbonyl, with an amine of the formula (III), wherein $R^{1'}$ and $R^{2'}$ are as previously defined for R^1 and R^2 respectively but are not H, and R^{10} is as defined for R^3 with any reactive groups therein optionally protected, to provide a compound of the formula (IV) as shown in the following reaction scheme:



(II) (III)



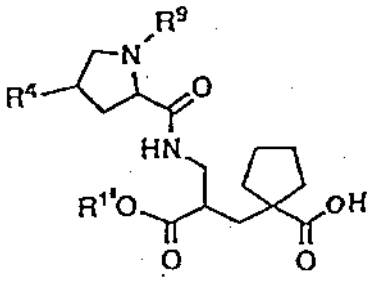
(IV)

(I)

The reaction of the compounds of formula (II) and (III) is achieved using conventional amide coupling techniques. Thus in one process the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a diimide condensing agent, for example 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as N-methylmorpholine. The reaction is generally complete after a period of from 12 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water, or filtration, to remove the urea by-product and

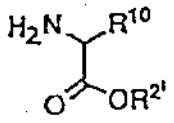
evaporation of the solvent. The product may be further purified by crystallisation or chromatography if necessary.

In an alternative analogous procedure, the diester products of formula (IV) may be obtained by coupling compounds of formulae:



(V)

+



(VI)

and the reaction is achieved following similar procedures to those described above.

The diesters of formula (IV) are subsequently deprotected to give the diester, monoester or diacid derivatives of formula (I). The conditions used will depend on the precise nature of the groups $R^{1'}$ and $R^{2'}$ in the compound of formula (IV) and a number of variations is possible. Thus, for example, when one of $R^{1'}$ and $R^{2'}$ is t-butyl and the other is alkyl, treatment of the compound of formula (IV) with hydrogen chloride or trifluoroacetic acid yields a monoalkyl ester of formula (I) wherein one of $R^{1'}$ and $R^{2'}$ is H and the other is alkyl. Alternatively, when both of $R^{1'}$ and $R^{2'}$ are t-butyl, said acid deprotection affords a diacid of formula (I) wherein R^1 and R^2 are both H. As an alternative carboxylic acid protecting group, benzyl may be employed instead of t-butyl. In such cases, catalytic hydrogenation removes the benzyl groups(s) to furnish either the monoester or diacid as

required.

A further variation is that in which a monoester of formula (I), wherein R^1 is H and R^2 is a biolabile ester-forming group, is converted to a diacid of formula (I), wherein both R^1 and R^2 are H, by base hydrolysis, e.g. using an aqueous sodium or potassium hydroxide medium.

Amides wherein either or both of OR^1 and OR^2 are replaced by NH_2 are obtained by starting with the appropriate amide derivative corresponding with formula (III), (V) or (VI) in the coupling step, that is wherein either of $OR^{1'}$ or $OR^{2'}$ is NH_2 or both of $OR^{1'}$ and $OR^{2'}$ are NH_2.

Depending on the protection/deprotection strategy employed, further conventional deprotection steps may be required to remove R^9 and/or any protecting groups present in R^{10}.

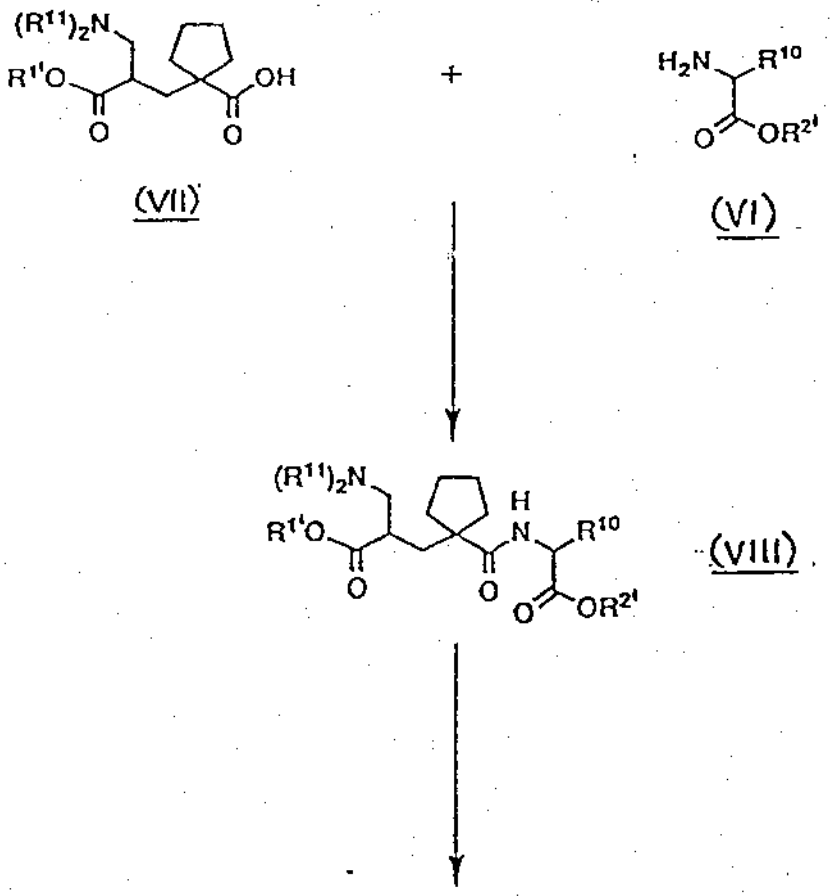
Required diester prodrugs which are not directly accessible from compounds of formula (IV) may be obtained from monoesters of formula (IV) wherein either $R^{1'}$ or $R^{2'}$ is H. This may be achieved for example by alkylation of an alkali metal, preferably caesium, salt of the monoacid with the required alkyl halide, preferably bromide or iodide, or by coupling of the monoacid with an alcohol or phenol by conventional techniques as described above. Further deprotection steps, e.g. to remove R^9 and/or any protecting group contained in R^{10}, are carried out as appropriate to afford compounds of formula (I) wherein neither R^1 nor R^2 is H.

Thus certain novel compounds of the formula (IV), wherein $R^{1'}$ and $R^{2'}$ are each independently selected from t-butyl or benzyl, are useful intermediates for the preparation of compounds of the formula (I) and also form part of the invention.

The compounds of formula (I) may be isolated as, for example, hydrochloride or sodium salts directly from the previous deprotection step. Alternatively, they may be converted to other pharmaceutically acceptable acid addition, alkali metal or alkaline earth metal salts by routine procedures.

Appropriate coupling, protection and deprotection methods for all of the above steps and alternative variations and procedures will be well known to those skilled in the art by reference to relevant text-books and to the examples provided hereafter.

The proline derivatives of formula (II) are either commercially available or preparable by standard methods in accordance with literature precedent. The amines of formula (III) may be prepared by analogy with processes described in EP-A-0358398 using the aminomethylglutaric acid derivative of formula (VII), wherein R^{11} is benzyl or 1(S)-phenylethyl and $R^{1'}$ is as previously defined, and the appropriate α-amino ester of formula (VI) , wherein R^{10} and $R^{2'}$ are as previously defined, to afford the coupled product of the formula (VIII), followed by catalytic hydrogenolytic removal of the R^{11} groups as shown in the following reaction scheme:



(VII) (VI) (VIII) (III)

The compounds of formula (V) are preparable according to processes described in EP-A-0358398, by coupling the sodium salt of 1-(2-t-butoxycarbonyl-3-aminopropyl)cyclopentane carboxylic acid with the proline fragment (II).

The novel α-amino esters of formula (VI) may be prepared from commercially available N-protected α-amino acid derivatives such as those of glycine, serine or tyrosine by established methods in accordance with literature precedent. For example, standard alkylation of the serine alcoholic hydroxyl group provides ether derivatives, whilst Mitsunobu or Heck modification of the tyrosine phenolic hydroxyl group or its trifluoromethanesulphonyl

derivative respectively leads to a variety of 4-alkoxy or 4-alkyl phenylalanine derivatives, which are also obtainable by C-benzylation of glycine derivatives using the asymmetric alkylation procedure developed by O'Donnell et al. Subsequent N-deprotection then affords the compounds of formula (VI).

As previously mentioned, the prodrugs of the invention offer an oral bioavailability advantage in the systemic delivery of the potent, dual inhibitor diacids of the formula (I) derived therefrom wherein R^1 and R^2 are H. These diacids are potent inhibitors of the neutral endopeptidase (E.C.3.4.24.11). This enzyme is involved in the breakdown of a number of peptide hormones including, in particular, the breakdown of atrial natriuretic factor (ANF). Thus the diacids of the invention, by preventing the degradation of ANF by endopeptidase E.C.3.4.24.11, can potentiate its biological effects and the compounds are thus diuretic, natriuretic and antihypertensive agents of utility in a number of disorders including hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menieres disease, hyperaldosteronism (primary and secondary) and hypercalciuria. In addition, because of their ability to potentiate the effects of ANF, the compounds have utility in the treatment of glaucoma. As a further result of their ability to inhibit the neutral endopeptidase E.C.3.4.24.11 the compounds of the invention may have activity in other therapeutic areas including for example the treatment of asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity, gastrointestinal disorders (especially diarrhoea and

irritable bowel syndrome), the modulation of gastric acid secretion and the treatment of hyperreninaemia.

Activity against neutral endopeptidase E.C.3.4.24.11 is assessed using a procedure based on the assay described by J. T. Gafford, R. A. Skidgel, E. G. Erdos and L. B. Hersh, Biochemistry, 1983, 32, 3265-3271. The method involves determining the concentration of compound required to reduce by 50% the extent of release of radiolabelled hippuric acid from hippuryl-L-phenyl-alanyl-L-arginine by a neutral endopeptidase preparation from rat kidney.

The diacids of the invention are also inhibitors of angiotensin converting enzyme. As such they are useful in treating a further variety of conditions for which ACE inhibitors are known to be useful including limitation of ischaemic damage to the myocardium, protection of the kidney against hyperfiltration damage, prevention or reversal of left ventricular hypertrophy, memory enhancement, control of cognitive function, dementia, and preventing reocclusion following coronary angioplasty or coronary artery bypass surgery. Their activity against this enzyme is assessed using a modified procedure based on the assay described by M.S. Rohrbach, Anal. Biochem., 1978, 84, 272. The method involves determining the concentration of compound required to reduce by 50% the extent of release of radiolabelled hippuric acid from hippuryl-L-histidyl-L-leucine by angiotensin converting enzyme isolated from rat kidney.

Inhibitory activity is also measured in vivo following intravenous injection to anaesthetised rats using the methods described by I. L. Natoff et al., Journal of Pharmacological

Methods, 1981, 5, 305 and by D. M. Gross et al., J. Pharmacol. Exp. Ther., 1981, 216, 552. The dose of inhibitor required to reduce the pressor response produced by intravenous injection of angiotensin I (50 ng bolus) by 50% is determined.

The activity of the diacids as diuretic agents is determined by measuring their ability to increase urine output and sodium ion excretion in saline loaded conscious mice. In this test, male mice (Charles River CD1, 22-28 g) are acclimatised and starved overnight in bowls. The mice are dosed intravenously via the tail vein, with the test compound dissolved in a volume of saline solution equivalent to 2.5% of body weight. Urine samples are collected each hour for two hours in pre-weighed tubes and analysed for electrolyte concentration. Urine volumes and sodium ion concentrations from the test animals are compared with those of a control group which received only saline.

The antihypertensive activity of the prodrugs of the invention and the diacids derived therefrom is evaluated by measuring the fall in blood pressure, following oral or intravenous administration respectively, to salt-depleted, diuretic primed, spontaneously hypertensive rats, salt-depleted renally hypertensive dogs, or DOCA/salt hypertensive rats.

The systemic bioavailability of diacid obtained after oral administration of a prodrug of the invention is determined, e.g. in rat, by measuring the fraction of the biologically active dose recovered via the urine (measured by in vitro assay of neutral endopeptidase activity as previously described) and comparing it with the corresponding fraction after an equivalent dose of the corresponding diacid, when administered by the intravenous route.

Alternatively plasma concentrations of diacid are measured in dog following oral administration of the prodrug and again compared with the corresponding values obtained after the intravenous administration of an equivalent dose of the corresponding diacid.

For administration to man in the curative or propylactic treatment of hypertension, congestive heart failure or renal insufficiency, oral dosages of the compounds of the invention will generally be in the range of from 3-1500 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 1 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range 1 to 500 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose,

or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood.

The compounds may be co-administered with other agents as may be beneficial for the control of blood pressure or the treatment of cardiac conditions or renal insufficiency. Thus, for example, they may be co-administered with digitalis or another cardiac stimulant drug, an alpha-blocker, a beta-blocker, exogenous ANF, a potassium channel activator or another diuretic agent, as shall be determined by the physician as appropriate to the particular patient or disease state.

Thus, in a further aspect, the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compound of formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either, for use in medicine.

The invention further includes the use of a compound of formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either, for the manufacture of a medicament for the treatment of hypertension, heart failure or renal insufficiency.

The invention yet further includes a method for the propylactic or curative treatment of hypertension, heart failure or renal insufficiency in a human being, which comprises administering to said human being an effective amount of a compound of formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either.

The preparation of the compounds of the invention and of the intermediates for use in their preparation are illustrated by the following Examples and Preparations. The purity of the compounds was routinely monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} plates and the following solvent systems (SS):

1 hexane/ethyl acetate, 4:1

2 hexane/diethyl ether, 1:1

3 hexane/ethyl acetate, 1:1

4 hexane/diethyl ether, 6:4

5 hexane/diethyl ether, 1:4

6 hexane/diethyl ether, 3:7

7 ethyl acetate/ethanol, 9:1

8 ethyl acetate

9 dichloromethane/methanol/acetic acid, 80:20:1

10 isobutyl methyl ketone/acetic acid/water, 2:1:1 (upper phase)

11 hexane/ethyl acetate, 1:4

12 ethyl acetate/ethanol, 19:1

13 hexane/diethyl ether, 4:1

14 dichloromethane/methanol, 9:1

15 diethyl ether/dichloromethane, 1:1

16 diethyl ether

17 hexane/ethyl acetate, 6:4

18 hexane/diethyl ether, 4:6

19 dichloromethane/methanol/ammonia, 90:10:1

20 hexane/2-propanol/ammonia, 90:10:0.5

21 dichloromethane/ethanol/acetic acid, 90:10:1

22 dichloromethane/methanol/acetic acid, 90:10:1

23 n-butanol/water/acetic acid, 12/5/3

24 dichloromethane/methanol/acetic acid, 40:10:1

25 ethyl acetate/toluene, 1:1

26 dichloromethane/methanol/acetic acid/hexane, 90:10:1:150

^{1}H-Nuclear magnetic resonance (nmr) spectra were recorded using a Nicolet QE-300 or Brucker AC-300 spectrometer and were in all cases consistent with the structures of the compounds described hereinafter.

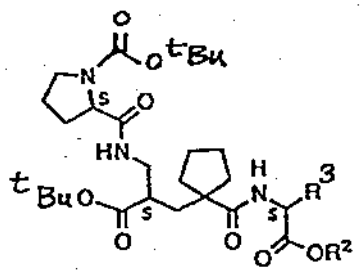
EXAMPLE 1

N-[1-{3-[N-t-Butoxycarbonyl-(S)-prolylamino]-2(S)-t-butoxycarbonylpropyl}cyclopentanecarbonyl]-O-benzyl-(S)-serine methyl ester

To a stirred, ice-cold solution of 1-{3-[N-t-butoxycarbonyl-(S)-prolylamino]-2(S)-t-butoxycarbonylpropyl}cyclopentane carboxylic acid (Preparation 80, 351 mg, 0.75 mmol) in dichloromethane (15 ml) were added, sequentially, 1-hydroxybenzotriazole (122 mg, 0.90 mmol), N-methylmorpholine (265 mg, 2.62 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (287 mg, 1.50 mmol) and, 0.25 hour later, O-benzyl-(S)-serine methyl ester hydrochloride (202 mg, 0.82 mmol). The ice bath was removed, stirring continued for 24 hours, then the reaction mixture was evaporated under vacuum. The residue was partitioned between ethyl acetate (100 ml) and 2M hydrochloric acid (50 ml), then the organic phase separated, washed successively with 2M hydrochloric acid (2 x 30 ml), saturated aqueous sodium bicarbonate solution (30 ml) and saturated brine (30 ml), dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate provided a foam (546 mg) which was purified by chromatography on silica gel, using 30% ethyl acetate in hexane as eluent, to afford the title compound as a white foam (409 mg, 83%). Rf 0.54 (SS 15) and 0.24 (SS 3), $[\alpha]_D^{25}$ -18° (c = 0.1, MeOH). Found: C,63.35; H,8.12; N,6.23. $C_{35}H_{53}N_3O_9$ requires C,63.71; H,8.10; N,6.37%.

EXAMPLES 2-40

The following Examples were obtained according to the method of Example 1 using 1-(3-[N-t-butoxycarbonyl-(S)-prolylamino-2(S)-t-butoxycarbonylpropyl]cyclopentane carboxylic acid and the appropriate α-amino ester of formula (VI) from the Preparations section.



Example No.	R^3	R^2	Rf	Analysis % C (theoretical in brackets)	H	N
2	$-CH_2OCH_2Ph$	$-CH(CH_2CH_3)_2$	0.45 (SS 3)	65.28 (65.43	8.59 8.59	5.86 5.87)
3	$-CH(CH_3)OCH_2Ph$ (R)	$-CH_3$	0.57 (SS 16)			
4	$-CH_2OCH_2Ph$		0.38 (SS 16)	65.78 (65.99	8.30 8.45	5.59 5.77)
5	$-CH_2OCH_2Ph$		0.66 (SS 8)	67.26 (67.77	7.96 7.80	5.47 5.51)
6	$-CH_2OCH_2Ph$		0.44 (SS 3)	67.58 (67.77	7.83 7.80	5.47 5.51)
7	$-CH_2OCH_2Ph$		0.67 (SS 16)	67.37 (67.07	8.62 8.77	5.26 5.46)

8	$-CH_2OCH_2Ph$	$-(CH_2)_3Ph$	0.64 (SS 16)	67.64 (67.60	8.06 8.05 5.50 5.50)
9		t_{Bu}	0.40 (SS 17)	62.43 (62.80	8.39 8.69 5.72 5.49)a
10		t_{Bu}	0.56 (SS 3)	67.51 (67.21	7.89 8.21 4.84 5.11)
11	(S)	t_{Bu}	0.22 (SS 18)	67.53 (67.52	8.59 8.32 4.87 5.03)
12		t_{Bu}	0.22 (SS 6)	64.86 (65.03	8.41 8.47 5.92 5.99)
13		$-(CH_2)_3Ph$		66.92 (66.82	7.90 8.08 5.45 5.44)b
14		$-(CH_2)_3Ph$	0.54 (SS 3)	65.84 (66.05	7.80 7.73 5.31 5.37)

15	$-CH_2OCH_2\underset{Cl}{\underset{\vert}{C}}=CH_2$	$-(CH_2)_3Ph$	0.65 (SS 3)		
16	$-CH_2CH_2OCH_2Ph$	$-(CH_2)_3Ph$	0.65 (SS 3)		
17		t_{Bu}	0.65 (SS 5)	65.24 (65.43	8.59 8.59	5.72 5.87)
18	$-CH_2OCH_2\underset{E}{CH}=CHCH_2OCH_3$	$-(CH_2)_3Ph$	0.79 (SS 16)	64.94 (64.97	8.25 8.38	5.41 5.54)
19	$-CH_2OCH_2\underset{E}{CH}=CHCH_3$	$-(CH_2)_3Ph$	0.45 (SS 3)	66.22 (66.00	8.34 8.45	5.58 5.77)
20	$-CH_2OCH_2CH=CH_2$	$-(CH_2)_3Ph$	0.39 (SS 3)	61.59 (61.61	8.69 8.56	6.86 6.74)
21	$-CH_2O(CH_2)_3CH_3$	$-CH_2Ph$	-	-		

22	$-CH_2CH_2O(CH_2)_2CH_3$	$-C_2H_5$	0.6 (SS 5)	62.19 (61.95	8.89 8.98	6.46 6.57)
23	$-CH_2O(CH_2)_2CH_3$	$-C_2H_5$	0.38 (SS 3)	61.97 (61.41	8.62 8.86	6.67 6.71)
24	$-CH_2CH=CHCH_2OCH_2CH_3$ (E)	$-CH_3$	0.26 (SS 3)	61.99 (62.14	8.48 8.69	6.45 6.59)
25	$-CH_2OCH_2C\equiv CH_3$	$-CH_2Ph$	0.79 (SS 16)			
26	$-CH_2O(CH_2)_3OCH_3$	$-(CH_2)_3Ph$	0.34 (SS 3)	64.37 (64.40	8.27 8.51	5.58 5.63)
27	$-CH_2OCH_2C(=CH_2)CH_2OCH_3$	$-(CH_2)_3Ph$	0.65 (SS 3)	64.36 (64.41	7.97 8.31	5.42 5.48)c
28	$-CH_2OCH_2C\equiv CH$	$-(CH_2)_3Ph$	0.46 (SS 3)	66.04 (65.80	8.14 8.07	5.96 5.90)

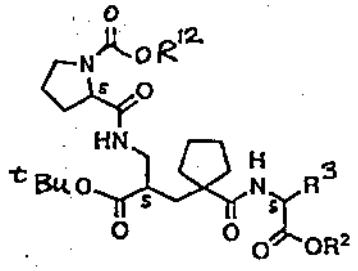
29		$-CH_2Ph$	0.09 (SS 26)	-		
30	$-CH_2OCH_2CF_3$	$-CH_2Ph$	0.09 (SS 26)	-		
31	$-CH_2OCH(CH_3)_2$	$-CH_2Ph$	0.09 (SS 26)	-		
32	$-CH_2OCHCF_3$ (CH$_3$)	$-CH_2Ph$	0.09 (SS 26)	55.44 (55.29	7.03 7.42	6.31 6.45)
33		$-CH_2Ph$	0.10 (SS 26)	-		
34	$-CH_2OCH_2C(CH_3)=CH_2$	$-(CH_2)_3Ph$	0.74 (16)	65.32 (65.40	8.42 8.38	5.63 5.71)c
35		$-C_2H_5$	0.41 (SS 3)	62.91 (63.13	8.95 8.93	6.28 6.31)

36	$-CH_2OCH_2CH_2CH(CH_3)_2$	$-C_2H_5$	0.46 (SS 3)	62.31 (62.46	8.89 9.09	6.35 6.43)
37	$-CH_2OCH_2CH=CHCH_2OCH_3$ (E)	$-C_2H_5$	0.50 (SS 16)	61.04 (61.15	8.47 8.60	6.25 6.29)
38	$-CH_2OCH_2CH=CHCH_3$ (E)	$-C_2H_5$	0.80 (SS 16)	62.11 (62.14	8.42 8.69	6.60 6.59)
39	$-CH_2OCH_2Ph$	$-C_2H_5$	0.36 (SS 3)	64.16 (64.02	8.23 8.00	6.24 6.15)
40	$-(CH_2)_4OCH_3$	$-CH_3$	0.35 (SS 3)	61.19 (61.42	8.78 8.86	6.67 6.71)

a. H_2O
b. 0.50 H_2O
c. 0.1 CH_2Cl_2

EXAMPLES 41-45

The following compounds were prepared following the coupling procedure of Example 1 but using the appropriate N-protected proline derivative of formula (V) (see Preparations 81 and 82) and coupling to the appropriate α-amino ester or amide derivative of formula (VI).



Example No.	R^3	OR^2	R^{12}	Rf	Analysis % C (theoretical in brackets)	H	N
41	$-CH_2OCH_3$	$-O(CH_2)_3Ph$	$PhCH_2-$	0.28 (SS 20)	66.83 (66.55	7.74 7.68	5.76 5.82)
42		$-O(CH_2)_3Ph$	$PhCH_2-$	0.3 (SS 20)	67.62 (67.78	7.78 7.80	5.39 5.31)
43	$-CH_2OCH_2Ph$	$-OC_2H_5$	$PhCH_2-$	0.51 (SS 16)	65.56 (65.50	7.34 7.58	5.86 5.87)d
44	$-CH_2OCH_2Ph$	$-OC_2H_5$	Cl_3CCH_2-	0.28 (SS 3)	54.13 (54.51	6.48 6.46	5.73 5.61)
45	$-CH_2OCH_2Ph$	$-NH_2$	Cl_3CCH_2-	0.58 (SS 8)	52.03 (52.18	6.21 6.43	7.57 7.77)e

d. 0.40 H_2O
e. 0.25 CH_2Cl_2

EXAMPLE 46

N-{1-[3-Benzyloxycarbonylamino-2(S)-t-butoxycarbonylpropyl]-cyclopentanecarbonyl}-O-benzyl-(S)-serine (3-phenyl)propyl ester

This was obtained by the procedure of Example 1 using 1-[3-benzyloxycarbonylamino-2(S)-t-butoxycarbonylpropyl]cyclopentane carboxylic acid (Preparation 83) and the product of Preparation 38 to provide the title compound, Rf 0.52 (SS 3). Found: C,67.25; H,7.44; N,3.89. $C_{41}H_{52}N_2O_8$; 1.50 H_2O requires C,67.65; H,7.61; N,3.85%.

EXAMPLE 47

N-{1-[3-Amino-2(S)-t-butoxycarbonylpropyl]cyclopentanecarbonyl}-O-benzyl-(S)-serine (3-phenyl)propyl ester

This was obtained from Example 46 by Method C (catalytic hydrogenation - see Preparation 37) to provide the title compound, Rf 0.67 (SS 10). Found: C,69.54; H,8.45; N,4.66. $C_{33}H_{46}N_2O_6$ requires C,69.93; H,8.18; N,4.94%.

EXAMPLE 48

N-[1-{2(S)-t-Butoxycarbonyl-3-[N-t-butoxycarbonyl-4(R)-hydroxy-(S)-prolylamino]propyl}cyclopentanecarbonyl]-O-benzyl-(S)-serine (3-phenyl)propyl ester

This was obtained from N-t-butoxycarbonyl-4(R)-hydroxy-(S)-proline and Example 47 using the coupling methodology of Example 1, Rf 0.61 (SS 8), Found: C,65.91; H,7.73; N,5.31. $C_{43}H_{61}N_3O_{10}$ requires C,66.22; H,7.88; N,5.39%.

EXAMPLE 49

N-[1-{3-(N-Benzyloxycarbonyl-(S)-prolylamino)-2(S)-carboxy-propyl}-1-cyclopentanecarbonyl]-O-benzyl-(S)-serine ethyl ester

The title compound was prepared from Example 43, by trifluoroacetic acid deprotection (see deprotection Method A, Example 76) and was obtained as a white foam, Rf 0.68 (SS 10). Found: C,64.92; H,6.90; N,6.13. $C_{35}H_{45}N_3O_9$ requires C,64.49; H,6.96; N,6.45%.

EXAMPLE 50

N-[1-{3-(N-(2,2,2-Trichloroethoxycarbonyl-(S)-prolylamino)-2-(S)-carboxypropyl}-1-cyclopentanecarbonyl]-O-benzyl-(S)-serine ethyl ester

Prepared from Example 44 as described above to give the title product as a white foam, Rf 0.39 (SS 14). Found C,51.31; H,5.61; N,5.86. $C_{30}H_{40}N_3Cl_3O_9$; 0.5 H_2O requires C,51.33; H,5.89; N,5.98%.

EXAMPLE 51

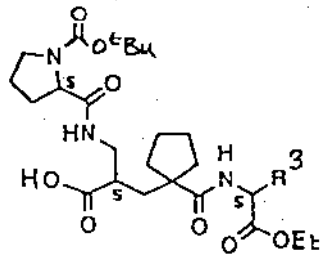
N-[1-{3-(N-t-Butoxycarbonyl-(S)-prolylamino)-2(S)-carboxy-propyl}-1-cyclopentanecarbonyl]-O-[trans-4-methoxybut-2-enyl]-(S)-serine ethyl ester

A stirred solution of N-[1-{3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxycarbonylpropyl}-1-cyclopentane-carbonyl}-O-[trans-4-methoxybut-2-enyl]-(S)-serine ethyl ester (1.13 g, 1.69 mmol) in dry dichloromethane (20 ml) at -5°C was saturated with anhydrous hydrogen chloride. After five hours the reaction was degassed with nitrogen, the solvent evaporated under

vacuum and the residual foam dried azeotropically with dichloromethane. This crude product was dissolved in a solution of sodium bicarbonate (0.427 g, 5.076 mmole) in water (20 ml) and the resulting solution cooled to 15°C. A solution of di-t-butyldicarbonate (0.739 g, 3.384 mmol) in dioxan (20 ml) was added dropwise with stirring and the resulting mixture allowed to warm to room temperature. After eighteen hours the reaction was evaporated under vacuum to low volume, diethyl ether (20 ml) and water (20 ml) were added and the aqueous layer separated, washed with diethyl ether and then acidified to pH 2 with 2N hydrochloric acid. The crude product was extracted with ethyl acetate (3 x 30 ml) and the combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under vacuum. Azeotropic treatment of the residue with dichloromethane gave the required product as a colourless foam (960 mg, 92%), Rf 0.55 (SS 22). Found: C,58.62; H,7.97; N,7.04. $C_{30}H_{49}N_3O_{10}$ requires C,58.90; H,8.07; N,6.87%.

EXAMPLES 52-53

The following compounds were prepared from Examples 38 and 39 using the procedure described above for Example 51.



Example No.	R^3	Rf	Analysis % (theoretical in brackets) C	H	N
52	$-CH_2OCH_2CH=CHCH_3$ (E)	0.56 (SS 22)	59.24 (59.41	8.16 8.17	7.35 7.17)a
53	$-CH_2OCH_2Ph$	0.53 (SS 22)	51.31 (51.33	5.61 5.89	5.86 5.98)b

a. 0.25 H_2O b. 0.50 H_2O

EXAMPLE 54

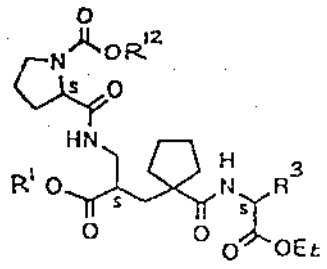
N-[1-(3-(N-Benzyloxycarbonyl-(S)-prolylamino)-2(S)-pivaloyloxy-methoxycarbonylpropyl)-1-cyclopentanecarbonyl]-O-benzyl-(S)-serine ethyl ester

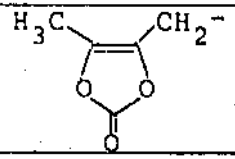
N-[1-(3-(N-Benzyloxycarbonyl-(S)-prolylamino)-2(S)-carboxy-propyl)-1-cyclopentanecarbonyl]-O-benzyl-(S)-serine ethyl ester (Example 49, 0.648 g, 0.99 mmol) was dissolved in acetonitrile (10 ml) and water (5 ml) added. Aqueous caesium carbonate (12%) was added until the pH was 8, the resulting solution evaporated under vacuum and then the residue azeotroped with toluene (4 x 10 ml). The resulting foam was dissolved in N,N-dimethylacetamide (5 ml)

and pivaloyloxymethylchloride (0.298 g, 1.98 mmol) added to the stirred solution. After 16 hours at room temperature the solvent was removed under vacuum and the residue partitioned between diethyl ether (100 ml) and 2M hydrochloric acid (50 ml). The ether layer was separated, washed successively with 2M hydrochloric acid (2 x 25 ml) and saturated brine (25 ml), dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate afforded the crude product which was purified by column chromatography (40 g silica, eluent 30% ethyl acetate in hexane) to give the title compound as a white foam, Rf 0.61 (SS 15). Found C,64.50; H,7.33; N,5.43. $C_{41}H_{55}N_3O_{11}$ requires C,64.29; H,7.24; N,5.49%.

EXAMPLES 55-71

The following Examples were prepared using the procedure described above by reaction of the caesium salt of the appropriate monoester with the appropriate chloride of formula R^1-Cl, except that for Example 67 the corresponding alkyl iodide was used and for Examples 59, 61 and 68 the corresponding alkyl bromides were used.



Example No.	R^3	R^1	R^{12}	Rf	Analysis % C H N (theoretical in brackets)
55	$-CH_2OCH_2Ph$	$(CH_3)_2CHCO_2CH(CH_3)-$	Cl_3CCH_2-	0.68 (SS 8)	53.77 6.23 5.22 (53.57 6.24 5.20)
56	$-CH_2OCH_2Ph$	$CH_3(CH_2)_2CO_2CH(CH_3)-$	Cl_3CCH_2-	0.66 (SS 8)	53.75 6.35 5.18 (53.57 6.24 5.20)
57	$-CH_2OCH_2Ph$	$CH_3CH_2OCO_2CH(CH_3)-$	Cl_3CCH_2-	0.19 (SS 3)	52.50 6.04 5.13 (51.95 5.97 5.19)
58	$-CH_2OCH_2Ph$	CH_3COCH_2	Cl_3CCH_2-	0.51 (SS 8)	-
59	$-CH_2OCH_2Ph$		^tBu	0.48 (SS 8)	60.39 7.06 5.65 (60.55 7.01 5.71)a
60	$-CH_2OCH_2Ph$	$CH_3CH_2CO_2C(CH_3)_2-$	Cl_3CCH_2-	0.36 (SS 25)	-

61	$-CH_2OCH_2Ph$		Cl_3CCH_2-	0.22 (SS 16)	54.72 (54.54	5.13 5.29 4.45 4.96)b
62	$-CH_2OCH_2CH=CHCH_2OCH_3$ E	$(CH_3)_3CCO_2CH_2-$	t_{Bu}	0.55 (SS 16)	60.09 (59.57	8.28 8.19 5.71 5.79)
63	$-CH_2OCH_2CH=CHCH_2OCH_3$ E		t_{Bu}	0.35, 0.40 (SS 16)	61.33 (61.64	7.23 7.56 5.19 5.53)
64	$-CH_2OCH_2CH=CHCH_2OCH_3$ E		t_{Bu}	0.60, 0.65 (SS 16)	61.50 (61.60	8.53 8.40 5.03 5.39)
65	$-CH_2OCH_2CH=CHCH_3$ E		t_{Bu}	0.57, 0.51 (SS 16)	61.87 (62.02	8.15 8.35 5.70 5.71)
66	$-CH_2OCH_2CH=CHCH_3$ E		t_{Bu}	0.55, 0.65 (SS 16)	62.37 (62.36	7.33 7.55 5.09 5.28)c
67	$-CH_2OCH_2CH=CHCH_3$ E		n_{Bu}	0.40 (SS 3)	62.66 (62.14	8.33 8.69 6.78 6.59)

68	$-CH_2OCH_2CH{=}CHCH_3$ (E)		t_{Bu}	0.30 (SS 16)	58.98 (58.86	7.38 7.41 6.08 6.06)
69	$-CH_2OCH_2CH{=}CHCH_3$ (E)	$(CH_3)_3CCO_2CH_2-$	t_{Bu}	0.57 (SS 16)	60.69 (60.41	8.15 8.26 5.89 6.04)
70	$-CH_2OCH_2CH{=}CHCH_3$ (E)		t_{Bu}	0.51, 0.62 (SS 16)	62.36 (62.46	8.20 8.47 5.58 5.60)
71	$-CH_2OCH_2CH{=}CHCH_3$ (E)		t_{Bu}	0.43, 0.51 (SS 16)	62.35 (62.53	7.64 7.60 5.71 5.76)

a. 0.0625 CH_2Cl_2
b. 0.22 CH_2Cl_2
c. 0.3 CH_2Cl_2

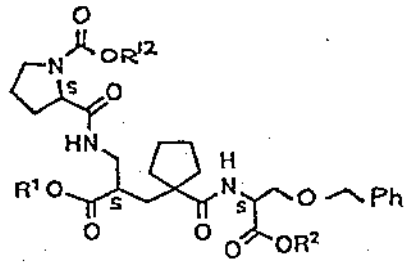
EXAMPLE 72

N-[1-(3-[N-(2,2,2-Trichloroethoxycarbonyl)-(S)-prolylamino]-2-(S)-(1-isobutyryloxy)ethoxycarbonyl)-1-cyclopentanecarbonyl]-O-benzyl-(S)-serine amide

Deprotection of Example 45 with trifluoroacetic acid according to Method A (Example 76), followed by conversion of the monocarboxylic acid product to its caesium salt and reaction with (1-isobutyryloxy)ethyl chloride following the procedures described above, gave the title compound as a white foam, Rf 0.44, 0.51 (SS 8). Found: C,52.63; H,6.21; N,7.15. $C_{34}H_{47}N_4O_{10}Cl_3$ requires C,52.48; H,6.09; N,7.20%.

EXAMPLES 73-75

The following esters were prepared from the appropriate acid and amine starting materials using the carbodiimide coupling described in Example 1.



Example No.	R^1	OR^2	R^{12}	Rf	Analysis % C (theoretical in brackets)	H	N
73		OEt	$PhCH_2-$	0.41 (SS 16)	68.85 (68.81	6.99 6.96	5.44 5.47)
74		NH_2	Cl_3CCH_2	0.60 (SS 8)	56.93 (56.89	5.64 5.94	7.04 7.17)
75		OEt	Cl_3CCH_2	0.28 (SS 8)	54.69 (54.59	5.45 5.63	6.97 7.27)

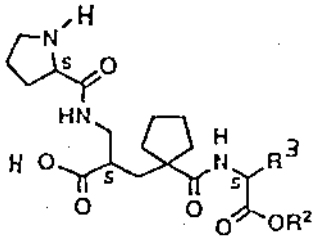
EXAMPLE 76 (DEPROTECTION METHOD A)

N-(1-[2(S)-Carboxy-3(S)-prolylaminopropyl]cyclopentanecarbonyl)-4-hydroxymethyl-(S)-phenylalanine-(3-phenyl)propyl ester

Trifluoroacetic acid (6 ml, 78 mmol) was added to a stirred, ice-cold solution of Example 13 (458 mg, 0.6 mmol) and anisole (973 mg, 9 mmol) in dichloromethane (6 ml). After 14 hours at 0°C, the reaction mixture was evaporated under vacuum and the residue azeotroped with toluene (3 x 20 ml) then dissolved in water (5 ml). The aqueous solution was washed with diethyl ether (2 x 50 ml), then subjected to ion-exchange chromatography (AG50W-X8 resin) using water and then 8% aqueous pyridine as eluents. Evaporation under vacuum of the appropriate (ninhydrin positive) fractions afforded the title compound as a white powder (210 mg, 55%), Rf 0.40 (SS 10). Found: C,66.26; H,7.46; N,6.85. $C_{34}H_{45}N_3O_7$; 0.50 H_2O requires C,66.21; H,7.52; N,6.81%.

EXAMPLES 77-104

The following Examples were obtained from the corresponding diester using the appropriate deprotection Method A, (trifluoroacetic acid, see above), B, (hydrogen chloride, described under Preparation 36), C, (catalytic hydrogenation, described under Preparation 37), D (formic acid, described under Preparation 24) or E (zinc in acetic acid, described under Preparation 66) to give the monoester products.



Example No.	Method	R^3	R^2	Rf	Analysis % C (theoretical in brackets) H N
77	B	$-CH_2OCH_2Ph$	$-CH_3$	0.30 (SS 10)	
78	B	$-CH_2OCH_2Ph$	$-CH(CH_2CH_3)_2$	0.31 (SS 10)	62.31 (62.36) 8.07 8.19 7.20 7.27)a
79	B	$-CH(CH_3)OCH_2Ph$ (R)	$-CH_3$	0.28 (SS 10)	56.12 (55.80) 7.03 7.45 6.95 7.23)b
80	B	$-CH_2OCH_2Ph$		0.37 (SS 10)	60.54 (60.50) 7.75 7.67 6.72 6.83)c
81	B	$-CH_2OCH_2Ph$		0.58 (SS 10)	62.24 (62.27) 6.98 6.99 6.29 6.40)d
82	B	$-CH_2OCH_2Ph$		0.30 (SS 10)	64.67 (64.53) 7.35 7.33 6.52 6.64)e

83	B	$-CH_2OCH_2Ph$	$-CH_2CH_2CH_2$-	0.26 (SS 10)	65.44 (65.56	8.10 8.42 6.55 6.75) f
84	B	$-CH_2OCH_2Ph$	$-(CH_2)_3Ph$	0.31 (SS 10)	61.81 (61.81	7.18 7.04 6.15 6.31) g
85	A		H	0.15 (SS 10)	60.08 (59.65	7.28 7.23 7.66 7.73)
86	C then A		H	0.18 (SS 9)	58.13 (58.09	7.27 7.31 7.58 7.82) a
87	C then A		H	0.24 (SS 9)	59.57 (59.76	7.28 7.43 7.60 7.74)
88	A		H	0.18 (SS 10)	61.19 (61.33	7.14 7.21 8.69 8.58)
89	B		$-(CH_2)_3Ph$	0.19 (SS 9)	61.60 (61.67	6.62 6.85 6.09 6.35) h

90	A	$-CH_2OCH_2C(Cl)=CH_2$	$-(CH_2)_3Ph$	0.20 (SS 9)	50.66 (51.11	5.57 5.67 5.18 5.39) i
91	B	$-CH_2CH_2OCH_2Ph$	$-(CH_2)_3Ph$	0.25 (SS 9)	63.34 (63.43	7.44 7.38 6.11 6.34) j
92	A		H	0.25 (SS 9)	62.04 (62.01	7.57 7.41 8.05 8.34)
93	A	$-CH_2OCH_2CH=CHCH_2OCH_3$ E	$-(CH_2)_3Ph$	0.21 (SS 22)	59.63 (59.38	7.33 7.48 6.32 6.49) k
94	A	$-CH_2OCH_2CH=CHCH_3$ E	$-(CH_2)_3Ph$	0.15 (SS 22)	60.65 (60.33	7.62 7.67 6.63 6.81) k
95	B	$-CH_2OCH_2CH=CH_2$	$-CH_2CH_3$	0.29 (SS 22)		
96	B	$-CH_2O(CH_2)_3CH_3$	$-CH_2Ph$	0.53 (SS 23)	59.90 (59.83	7.46 7.62 7.06 7.22)

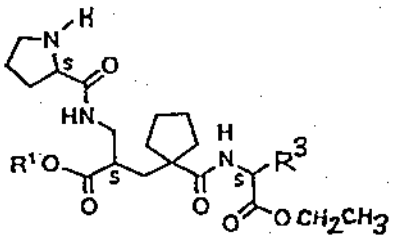
97	B	$-CH_2CH_2O(CH_2)_2CH_3$	$-CH_2CH_3$	0.45 (SS 10)	
98	B	$-CH_2O(CH_2)_2CH_3$	$-CH_2CH_3$	0.29 (SS 29)	
99	B	$-CH_2CH=CHCH_2OCH_2CH_3$ (E)	$-CH_3$	0.15 (SS 22)	
100	A	$-CH_2OCH_2C\equiv CH_3$	$-CH_2Ph$	0.40 (SS 23)	62.08 (64.30) 7.12 7.26 7.66 7.76)
101	A	$-CH_2O(CH_2)_3OCH_3$	$-(CH_2)_3Ph$	0.24 (SS 22)	59.55 (59.46 7.66 7.73 6.60 6.71)h
102	B	$-CH_2OCH_2C(=CH_2)CH_2OCH_3$	$-(CH_2)_3Ph$	0.40 (SS 22)	54.28 (54.36 6.36 6.64 5.39 5.51)1

103	B	$-CH_2OCH_2C\equiv CH$	$-(CH_2)_3Ph$	0.05 (SS 22)	54.61 (54.63	6.28 6.26 5.75 5.93)g
104	E	$-CH_2OCH_2CCH_3$ $\|$ CH_2	$-(CH_2)_3Ph$	0.09 (SS 22)	60.29 (60.45	7.93 7.77 6.40 6.61)m

a. H_2O
b. HCl; 1.50 H_2O
c. HCl; 0.40 H_2O
d. HCl; 0.75 H_2O
e. 1.50 H_2O
f. 0.50 H_2O
g. HCl; 0.25 CH_2Cl_2
h. HCl
i. 1.5 CF_3CO_2H; 0.2 CH_2Cl_2
j. HCl; 0.25 H_2O
k. HCl; 0.5 H_2O
l. 1.25 CF_3CO_2H; H_2O
m. H_2O; HCO_2H

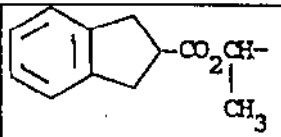
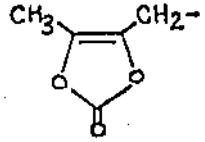
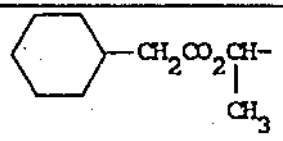
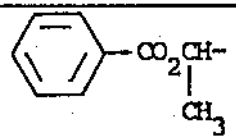
EXAMPLES 105-123

The following compounds were prepared by deprotection of the corresponding N-protected proline diester compound to give the following diester products. N-Trichloroethoxycarbonyl derivatives were deprotected following deprotection method E (zinc in acetic acid) and N-t-butyloxycarbonyl derivative were deprotected using deprotection method B (hydrogen chloride).



Example No.	Method	R^3	R^1	Rf	Analysis % C H N (theoretical in brackets)
105	E	$-CH_2OCH_2Ph$	$(CH_3)_2CHCO_2CH(CH_3)-$	0.45 (SS 10)	
106	E	$-CH_2OCH_2Ph$	$CH_3(CH_2)_2CO_2CH(CH_3)-$	0.43 (SS 10)	
107	E	$-CH_2OCH_2Ph$	$CH_3CH_2OCO_2CH(CH_3)-$	0.40 (SS 10)	57.92 (57.35) 7.45 7.22 6.35 6.26)a
108	E	$-CH_2OCH_2Ph$	CH_3COCH_2-	0.34 (SS 10)	57.14 (57.08) 7.30 7.05 6.30 6.58)b
109	B	$-CH_2OCH_2Ph$		0.29 (SS 10)	56.61 (56.77) 6.43 6.73 6.06 6.20)c
110	E	$-CH_2OCH_2Ph$	$CH_3CH_2CO_2C(CH_3)_2-$	0.28 (SS 22)	

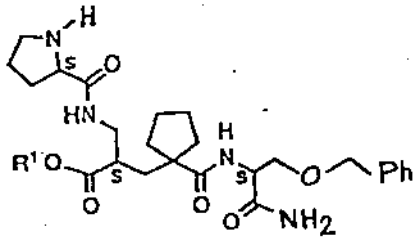
111	E	$-CH_2OCH_2Ph$		0.32 (SS 10)			
112	E	$-CH_2OCH_2Ph$		0.37 (SS 10)			
113	E	$-CH_2OCH_2Ph$		0.26 (SS 10)			
114	B	$-CH_2OCH_2CH=\underset{E}{CHCH_2OCH_3}$	$(CH_3)_3CCO_2CH_2-$	0.30 (SS 22)	55.58 (55.47	7.90 7.96	6.05 6.26)d
115	B	$-CH_2OCH_2CH=\underset{E}{CHCH_2OCH_3}$		0.30 (SS 22)	57.91 (57.90	7.11 7.29	5.61 5.96)d
116	B	$-CH_2OCH_2CH=\underset{E}{CHCH_2OCH_3}$		0.30 (SS 22)	58.40 (58.69	8.04 8.16	5.78 5.89)a
117	B	$-CH_2OCH_2CH=\underset{E}{CHCH_3}$		0.30 (SS 22)	58.72 (58.33	7.28 8.13	6.05 6.18)e

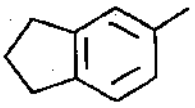
118	B	$-CH_2OCH_2CH=CHCH_3$ E		0.30 (SS 22)	55.97 (56.17	6.38 6.88	4.93 5.31) f
119	B	$-CH_2OCH_2CH=CHCH_3$ E	^nBu	0.25 (SS 22)	58.48 (58.57	8.18 8.43	7.18 7.32) a
120	B	$-CH_2OCH_2CH=CHCH_3$ E		0.20 (SS 22)	54.65 (54.50	6.95 7.10	6.39 6.57) d
121	B	$-CH_2OCH_2CH=CHCH_3$ E	$(CH_3)_3CCO_2CH_2-$	0.35 (SS 22)	56.88 (57.00	7.71 7.97	6.49 6.65) a
122	B	$-CH_2OCH_2CH=CHCH_3$ E		0.39 (SS 22)	59.22 (59.50	8.12 8.22	5.91 6.12) a
123	B	$-CH_2OCH_2CH=CHCH_3$ E		0.36 (SS 22)	59.29 (59.49	7.14 7.26	6.07 6.31) a

a. HCl
b. HCl; 0.33 CH_2Cl_2
c. HCl; 0.6 H_2O
d. HCl; 0.5 H_2O
e. HCl; 0.4 H_2O
f. HCl; CH_2Cl_2

EXAMPLES 124-126

These amides were obtained directly, in the case of Examples 124 and 125, by N-deprotection of the corresponding trichloroethoxycarbonyl proline precursors (Examples 74 and 72 respectively) using zinc and acetic acid (Method E). Example 126 was obtained from Example 45 in two stages, whereby Method E was followed by trifluoroacetic acid deprotection of the t-butyl ester (Method A).



Example No.	R^1	Rf	Analysis % (Theoretical in brackets) C	H	N
124		0.56 (SS 23)	60.85 (60.60	6.93 6.78	7.38 8.19)a
125	$(CH_3)_2CHCO_2CH(CH_3)-$	0.53 (SS 23)	47.85 (48.45	5.90 6.56	7.06 7.29)b
126	H	0.38 (SS 23)	58.29 (58.24	7.48 7.62	10.66 10.87)c

a. 0.5 CH_2Cl_2
b. 0.75 $ZnCl_2$; $2H_2O$
c. 1.5 H_2O

EXAMPLE 127

N-[1-{2(S)-Carboxy-3-[4(R)-hydroxy-(S)-prolylamino]propyl}cyclopentanecarbonyl]-O-benzyl-(S)-serine (3-phenyl)propyl ester

This was obtained from Example 48 by reaction with hydrogen chloride in dichloromethane (deprotection Method B) to furnish the title compound, Rf 0.45 (SS 10). Found: C,60.78; H,6.88; N,6.22. $C_{34}H_{45}N_3O_{10}$; HCl; H_2O requires C,60.21; H,7.13; N,6.20%.

EXAMPLE 128

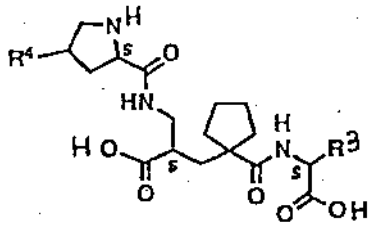
N-{1[2(S)-Carboxy-3-(S)-prolylaminopropyl]cyclopentanecarbonyl}-O-benzyl-(S)-serine

1M Aqueous sodium hydroxide solution (1.5 ml, 1.5 mmol) was added to a stirred solution of Example 77 (171 mg, 0.30 mmol) in 1,4-dioxan (2 ml). After 48 hours the pH of the solution was adjusted to 8 using dilute hydrochloric acid, then the solution subjected to ion-exchange chromatography (AG50 resin) using water and then a 1-10% aqueous pyridine gradient as eluents. Evaporation under vacuum of the appropriate (ninhydrin positive) fractions, followed by freeze drying of an aqueous solution of the residue, furnished the title compound as a white powder (108 mg, 70%), Rf (SS 10). Found: C,59.52; H,7.19; N,8.28. $C_{25}H_{35}N_3O_7$; H_2O requires C,59.15; H,7.35; N,8.28%.

EXAMPLES 129-148

The following Examples were obtained by hydrolysis of the appropriate ester following the procedure of Example 128.

Examples 129-147 are unsubstituted (S)-proline derivatives (R^4 = H) while Example 148 is the 4(R)-hydroxy-(S)-proline derivative (R^4 = OH) derived from Example 127.



Example No.	R^3	Rf	Analysis % C (theoretical in brackets)	H	N
129	$-CH(CH_3)OCH_2Ph$ (R)	0.16 (SS 10)	58.99 (58.84	7.48 7.60	7.61 7.91)a
130		0.06 (SS 9)	57.51 (57.73	6.63 6.86	8.09 8.08)
131		0.20 (SS 10)	53.11 (53.22	6.90 6.80	8.87 8.87)
132	$-CH_2CH_2OCH_2Ph$	0.20 (SS 10)	60.79 (60.92	7.66 7.47	8.20 8.20)

Example No.	R^3	Rf	Analysis % C (theoretical in brackets)	H	N
133	$-CH_2OCH_2CH=CHCH_2OCH_3$ (E)	0.08 (SS 22)	56.18 (56.08	7.60 7.78	8.52 8.53)b
134	$-CH_2OCH_2CH=CHCH_3$ (E)	0.03 (SS 22)	57.27 (57.13	7.49 7.84	9.31 9.08)b
135	$-CH_2OCH_2CH=CH_2$	0.08 (SS 22)	56.62 (56.92	8.05 7.59	9.37 9.48)c
136	$-CH_2O(CH_2)_3CH_3$	0.27 (SS 10)	52.47 (51.80	7.62 7.90	8.07 8.24)d
137	$-CH_2CH_2O(CH_2)_2CH_3$	0.27 (SS 10)	57.48 (57.54	8.13 8.20	9.15 9.15)

138	$-CH_2O(CH_2)_2CH_3$	0.09 (SS 22)	55.93 (55.53	7.67 7.78	9.13 9.16)e
139	$-CH_2CH=CHCH_2OCH_2CH_3$ (E)	0.07 (SS 22)	59.14 (59.08	7.56 7.98	8.81 8.99)
140	$-CH_2OCH_2C=CCH_3$	0.23 (SS 10)	56.13 (56.27	7.37 7.51	8.86 8.95)d
141	$-CH_2O(CH_2)_3OCH_3$	0.07 (SS 22)	55.70 (56.03	7.77 7.91	8.65 8.91)
142	$-CH_2OCH_2\underset{\|}{C}CH_2OCH_3$ ($\underset{\|}{C}$ = CH_2)	0.03 (SS 22)	55.98 (56.08	7.76 7.78	8.50 8.53)b
143	$-CH_2OCH_2C\equiv CH$	0.08 (SS 22)	57.11 (57.06	7.13 7.18	9.37 9.51)f

144	$-CH_2O(CH_2)_2CH(CH_3)_2$	0.10 (SS 22)	59.13 (58.83	8.21 8.37	8.90 8.95)
145		0.09 (SS 22)	59.44 (59.86	8.27 8.16	8.58 8.73)
146	$-(CH_2)_4OCH_3$	0.10 (SS 22)	57.81 (58.00	8.05 8.19	9.28 9.22)
147		0.26 (SS 22)	57.15 (57.13	7.69 7.85	9.16 9.09)a
148	$-CH_2OCH_2Ph$	0.24 (SS 10)	54.67 (54.64	6.96 7.07	8.16 7.96)g

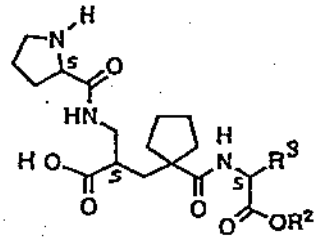
a. 1.5 H_2O
b. 0.5 H_2O
c. 0.2 H_2O
d. H_2O
e. 0.2 CH_2Cl_2
f. 0.25 H_2O
g. $2H_2O$

EXAMPLES 149-158

Examples 149-153 were obtained from the appropriate precursor N-protected proline diester derivatives (Examples 29-33 respectively) by catalytic hydrogenation (deprotection Method C) followed by treatment of the resulting monoacids with hydrogen chloride (deprotection Method B).

Examples 154-156 were obtained from similar precursors (Examples 36, 35 and 40 respectively) using hydrogen chloride treatment only (deprotection Method B).

Examples 157-158 are the result of three successive deprotection steps from their analogous precursors (Examples 41 and 42 respectively): base hydrolysis of the (3-phenyl)propyl ester group according to the method of Example 128, but using routine extraction procedures rather than ion-exchange chromatography to isolate the monoacid, followed by Method B and finally Method C.



Example No.	R^3	R^2	Rf	Analysis % C (theoretical in brackets)	H	N
149	$-CH_2OCH_2$-	H	0.13 (SS 24)			
150	$-CH_2OCH_2CF_3$	H	0.13 (SS 24)			
151	$-CH_2OCH(CH_3)_2$	H	0.13 (SS 24)	51.85 (51.79	7.78 7.66	8.03 8.63)a
152	$-CH_2OCHCF_3$ (CH3 branch)	H	0.13 (SS 24)	47.08 (47.41	6.33 6.25	7.35 7.90)b
153	$-CH_2O$-	H	0.13 (SS 24)	53.88 (53.84	7.63 7.66	7.80 8.19)a

154	$-CH_2O(CH_2)_2CH(CH_3)_2$	$-CH_2CH_3$	0.26 (SS 22)		
155	$-CH_2OCH_2$	$-CH_2CH_3$	0.26 (SS 22)		
156	$-(CH_2)_4OCH_3$	CH_3	0.18 (SS 22)		
157	$-CH_2OCH_3$	H	0.10 (SS 10)		
158	$-CH_2$	H	0.13 (SS 10)		

a. HCl, 0.5 H_2O
b. HCl

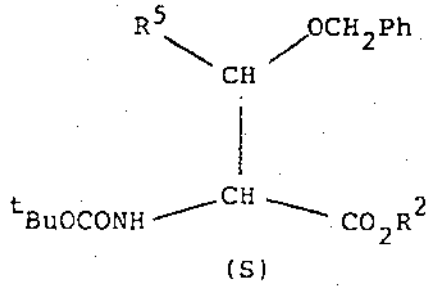
PREPARATION 1

N-t-Butoxycarbonyl-O-benzyl-(S)-serine methyl ester

N-t-Butoxycarbonyl-O-benzyl-(S)-serine (2.34 g, 7.9 mmol) was added to a stirred suspension of anhydrous potassium carbonate (2.19 g, 15.8 mmol) in dimethylformamide (25 ml), followed by iodomethane (1.34 g, 9.4 mmol). After 48 hours at room temperature, the reaction mixture was evaporated under vacuum and the residue partitioned between ethyl acetate (100 ml) and 2M hydrochloric acid (50 ml). The organic phase was separated, washed successively with 2M hydrochloric acid (50 ml), saturated aqueous sodium bicarbonate solution (50 ml) and saturated brine (50 ml), then dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave the required product as a colourless oil (2.40 g, 97%), Rf 0.57 (silica; SS 1). Found: C,62.18; H,7.48; N,4.63. $C_{16}H_{23}NO_5$ requires C,62.11; H,7.49; N,4.53%.

PREPARATIONS 2-5

The following Preparations were effected according to the procedure of Preparation 1 using the appropriate α-amino acid derivative and alkyl halide.



Preparation No.	R^2	R^5	Rf	Analysis % C H N (theoretical in brackets)
2	$-CH_2CH_2CH_2Ph$	H	0.65 (SS 2)	69.68 7.48 3.55 (69.70 7.56 3.39)
3	$-CH(CH_2CH_3)_2$	H	0.62 (SS 3)	
4	$-CH_3$	(R)CH_3	0.59 (SS 3)	
5	$-CH_2CH_3$	H	0.60 (SS 3)	62.45 7.79 4.10 (62.27 7.84 4.27)a

a. 0.25 H_2O

PREPARATION 6

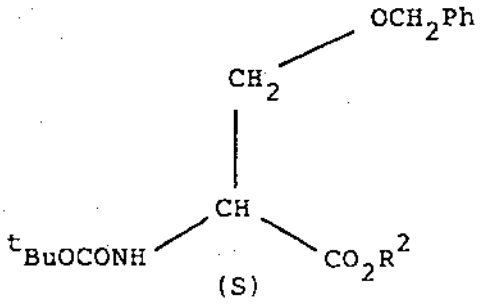
N-t-Butoxycarbonyl-O-benzyl-(S)-serine cyclohexyl ester

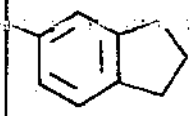
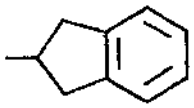
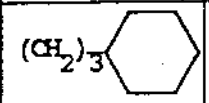
To a stirred solution of N-t-butoxycarbonyl-O-benzyl-(S)-serine (5.00 g, 16.9 mmol) and cyclohexanol (3.39 g, 33.8 mmol) in dichloromethane (50 ml) at 0°C were added, sequentially, 1-hydroxybenzotriazole (2.75 g, 20.3 mmol), N-methylmorpholine (4.27 g, 42.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.22 g, 22.0 mmol) and 4-dimethylaminopyridine (0.21 g, 1.7 mmol). The ice bath was removed, then the reaction mixture was stirred for 24 hours at room temperature and evaporated under vacuum. The residue was partitioned between ethyl acetate (200 ml) and 2M hydrochloric acid (100 ml), then the

organic phase was separated, washed successively with 2M hydrochloric acid (2 x 100 ml), saturated aqueous sodium bicarbonate solution (2 x 100 ml) and saturated brine (100 ml), dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate provided an oil (5.47 g), which was purified chromatographically using silica gel (200 g) and an 8:2 mixture of hexane:ether as eluent. Evaporation under vacuum of the appropriate fractions afforded the title compound as a colourless oil (1.74 g, 27%), Rf 0.62 (silica; SS 2), $[\alpha]_D^{25}$ -63.0° (c = 0.1, MeOH). Found: C,66.61; H,8.34; N,3.71. $C_{21}H_{31}NO_5$ requires C,66.81; H,8.28; N,3.71%.

PREPARATIONS 7-9

The following Preparations were effected according to the procedure of Preparation 6 using N-t-butoxycarbonyl-O-benzyl-(S)-serine and the appropriate alcohol or phenol.



Preparation No.	R^2	Rf	Analysis % C H N (theoretical in brackets)
7			69.72 7.11 3.35 (70.05 7.10 3.40)
8		0.66 (SS 3)	69.70 7.16 3.49 (70.05 7.10 3.40)
9		0.53 (SS 2)	68.69 8.92 3.70 (68.70 8.89 3.34)

PREPARATION 10

N-t-Butoxycarbonyl-O-benzyl-(S)-serine amide

N-t-Butoxycarbonyl-O-benzyl-(S)-serine (10.0 g, 34 mmol) was added to a stirred suspension of ammonium bicarbonate (8.0 g, 102 mmol) and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (10.05 g, 41 mmol) in chloroform (80 ml). After 48 hours at room temperature the solvent was removed under vacuum and the residue partitioned between ethyl acetate (200 ml) and 2N hydrochloric acid (50 ml). The ethyl acetate phase was separated, washed with saturated sodium bicarbonate (50 ml) then brine (20 ml), dried ($MgSO_4$), then filtered. Evaporation under vacuum of the filtrate followed by crystallisation of the residue from ethyl acetate/hexane gave the title compound as a crystalline white solid. Found: C,61.38; H,7.35; N,9.48. $C_{15}H_{22}N_2O_4$ requires C,61.20; H,7.53; N,9.51%.

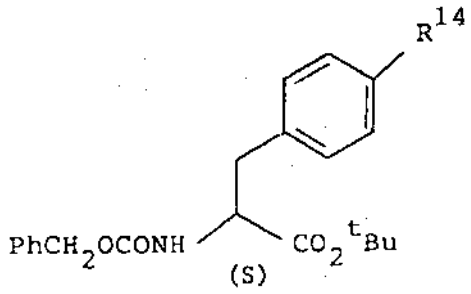
PREPARATION 11

N-Benzyloxycarbonyl-O-(2-methoxyethyl)-(S)-tyrosine t-butyl ester

Diethyl azodicarboxylate (4.4 ml, 28 mmol) was added under nitrogen to a stirred, ice-cold solution of N-benzyloxycarbonyl-(S)-tyrosine t-butyl ester (5.2 g, 14 mmol), triphenylphosphine (7.34 g, 28 mmol) and 2-methoxyethanol (3.3 ml, 42 mmol) in dry tetrahydrofuran (30 ml). The ice bath was removed, then the reaction mixture was stirred for 24 hours at room temperature and evaporated under vacuum. The residue was digested with a hot 1:1 mixture of ether and hexane, then the supernatant solution was chromatographed on silica gel (500 g) using a 1:1 mixture of ether and hexane as eluent. Evaporation under vacuum of the required fractions furnished the title compound as an oil (5.8 g, 95%), Rf 0.30 (silica; SS 2).

PREPARATIONS 12-13

The following Preparations were effected according to the procedure of Preparation 11 using N-benzyloxycarbonyl-(S)-tyrosine and the appropriate alcohol.



Preparation No.	R^{14}	Rf	Analysis % C H N (theoretical in brackets)
12	$-OCH_2CH_2OCH_2Ph$	0.25 (SS 4)	71.21 6.92 2.82 (71.27 6.98 2.77)
13	$-OCH(CH_3)CH_2OCH_2Ph$ (S)	0.42 (SS 2)	71.74 7.15 2.75 (71.65 7.18 2.70)

PREPARATION 14

N-Benzyloxycarbonyl-O-trifluoromethanesulphonyl-(S)-tyrosine t-butyl ester

To a stirred solution of N-benzyloxycarbonyl-(S)-tyrosine t-butyl ester (2.22 g, 5.97 mmol) in dichloromethane (20 ml) at -78°C were added, sequentially , triethylamine (1.21 g, 11.94 mmol) and N-phenyl trifluoromethanesulphonimide (2.13 g, 5.97 mmol). The cooling bath was removed, then the reaction mixture was stirred for 24 hours at room temperature and evaporated under vacuum. The residue was partitioned between ethyl acetate (200 ml) and saturated aqueous sodium bicarbonate solution (100 ml), then the organic phase separated, washed with saturated aqueous sodium bicarbonate solution (50 ml) and saturated brine (50 ml), dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave an oil, which was purified by chromatography on silica gel (100 g) using an elution gradient of hexane:ether: diethylamine (90:10:1 to 50:50:1). Evaporation under vacuum of the required fractions provided the title compound as a white

crystalline solid (2.45 g, 82%), m.p. 48-49°C, $[\alpha]_D^{25}$ -33° (c = 0.1, MeOH). Found: C,52.51; H,4.76; N,2.76. $C_{22}H_{24}F_3NO_7S$ requires C,52.47; H,4.80; N,2.78%.

PREPARATION 15

N-Benzyloxycarbonyl-4-hydroxymethyl-(S)-phenylalanine t-butyl ester

(i) N-Benzyloxycarbonyl-4-(2-ethoxycarbonyl-1-ethenyl-(S)-phenylalanine t-butyl ester

A solution of the product of Preparation 14 (12.99 g, 25.8 mmol), ethyl acrylate (5.6 ml, 51.6 mmol), triethylamine (16 ml) and bis(triphenylphosphine)palladium (II) chloride (1.05 g, 1.5 mmol) was stirred under nitrogen at 100-110°C for 18 hours. Evaporation under vacuum followed by dilution of the residue with water gave a suspension which was extracted with a 1:1 mixture of hexane and ether. The organic extract was washed successively with 1M hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and saturated brine, then dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave a yellow oil (11.5 g) which was chromatographed on silica gel (600 g) using a 3:2 mixture of hexane and ether as eluent. Evaporation under vacuum of the appropriate fractions afforded the required olefin as a viscous oil (8.42 g, 72%), Rf 0.42 (SS 2). Found: C, 69.10; H,6.99; N,3.07. $C_{26}H_{31}NO_6$ requires C,68.86; H,6.89; N,3.09%.

(ii) N-Benzyloxycarbonyl-4-(2-ethoxycarbonyl-1,2-dihydroxyethyl)-(S)-phenylalanine t-butyl ester

To a stirred solution of the previous product (8.42 g, 18.56 mmol) in a mixture of acetone (30 ml) and water (8 ml) were added, sequentially, N-methylmorpholine-N-oxide (3.78 g, 28 mmol) and a 2.5% solution of osmium tetroxide in t-butanol (1.5 ml). After 18 hours acetone (50 ml) was added, the reaction mixture evaporated under vacuum then the residue chromatographed on silica gel (500 g) using a 4:1 mixture of ether and hexane as eluent. Evaporation under vacuum of the appropriate fractions furnished the required diol as a gum (8.62 g, 95%), Rf 0.25 (SS 5). Found: C,64.33; H,6.72; N,3.00. $C_{26}H_{33}NO_8$ requires C,64.05; H,6.82; N,2.87%.

(iii) N-Benzyloxycarbonyl-4-formyl-(S)-phenylalanine t-butyl ester

A solution of the previous product (8.61 g, 17.7 mmol) in ether (200 ml) was vigorously stirred with a solution of sodium periodate (7.55 g, 35.3 mmol) in water (150 ml) for 20 hours. The ether phase was separated, washed with water, dried ($MgSO_4$) and evaporated under vacuum to provide an oil (7.03 g) which, after chromatography on silica gel using a 1:1 mixture of hexane and ether as eluent, gave the required aldehyde as a clear oil (6.68 g, 99%), Rf 0.30 (SS 2). Found: C,68.80; H,6.54; N,3.68. $C_{22}H_{25}NO_5$ requires C,68.91; H,6.57; N,3.65%.

(iv) Title compound

Sodium borohydride (330 mg, 8.7 mmol) was added to a stirred, ice-cold solution of the previous product (6.67g, 17.4 mmol) in ethanol (60 ml). After 10 minutes the reaction solution was

acidified to pH 6 with 1M hydrochloric acid, then evaporated under vacuum. The residue was partitioned between ether and water, then the organic phase separated, washed successively with 1M hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and saturated brine, dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate provided an oil which was chromatographed on silica gel using a 7:3 mixture of ether and hexane as eluent. Evaporation under vacuum of the appropriate fractions afforded the required alcohol as an oil (6.6 g, 98%), which solidified on chilling. Rf 0.33 (SS 6), $[\alpha]_D^{25}$ +47.8° (c = 1.04, CH_2Cl_2). Found: C,68.21; H,7.09; N,3.66. $C_{22}H_{27}NO_5$ requires C,68.55; H,7.06; N,3.63%.

PREPARATION 16

N-Benzyloxycarbonyl-4-hydroxymethyl-(S)-phenylalanine (3-phenyl)-propyl ester

The t-butyl ester group of the product of Preparation 15 was dealkylated by Method B described in Preparation 36, then the resulting acid was realkylated using (3-phenyl)propyl bromide according to the method of Example 54 to give the title compound as an oil, Rf 0.25 (SS 6). Found: C,72.35; H,6.42; N,3.12. $C_{27}H_{29}NO_5$ requires C,72.46; H,6.53; N,3.13%.

PREPARATION 17

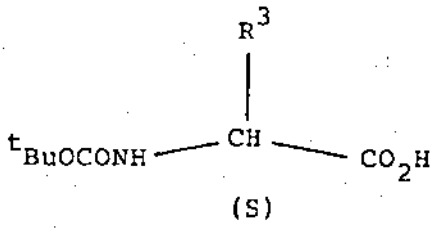
N-t-Butoxycarbonyl-O-(4-fluorobenzyl)-(S)-serine

Sodium hydride (80% dispersion in oil; 2.25 g, 75.05 mmol)

was added under nitrogen to a stirred solution of N-t-butoxy-carbonyl-(S)-serine (7.0 g, 34.11 mmol) in dry tetrahydrofuran (150 ml) at 0°C. The ice-bath was removed, stirring continued for 4 hours, then a solution of 4-fluorobenzyl chloride (5.42 g, 37.5 mmol) in dry tetrahydrofuran (50 ml) was added dropwise. After a further 15 hours more sodium hydride (0.51 g, 17.0 mmol) was added followed, 4 hours later, by more 4-fluorobenzyl chloride (2.47 g, 17.0 mmol). The reaction mixture was stirred for a further 20 hours and then, after destruction of excess sodium hydride using 2-propanol, evaporated under vacuum. The residue was dissolved in water (70 ml), then the solution washed with ether and acidified to pH 3.5 with 2M hydrochloric acid. Exhaustive extraction with ethyl acetate, washing of the combined extracts with water, followed by evaporation under vacuum of the dried ($MgSO_4$) extracts, provided an oil (6.3 g). Purification of the oil by chromatography on silica gel using an elution gradient of ethyl acetate:hexane (from 50:50 to 100:0), followed by elution with ethanol:ethyl acetate (10:90), furnished the required product as a colourless solid (1.95 g, 18%), Rf 0.40 (SS 7). Found: C,55.16; H,5.74; N,4.06. $C_{15}H_{20}FNOS$; 0.20 CH_2Cl_2 requires C,55.27; H,6.22; N,4.24%.

PREPARATIONS 18-22

The following Preparations were effected according to the procedure of Preparation 17 using the appropriate alkylating agents. For Preparations 19 and 20, N-t-butoxycarbonyl-(S)-homoserine was the starting material.



Preparation No.	R^3	Rf
18	$-CH_2OCH_2C(Cl)=CH_2$	0.30 (SS 8)
19	$-CH_2CH_2OCH_2Ph$	0.40 (SS 8)
20	$-(CH_2)_2O(CH_2)_2CH_3$	0.25 (SS 6)
21	$-CH_2OCH_2C\equiv CH$	0.3 (SS 7)
22	$-CH_2OCH_2C(=CH_2)-CH_3$	0.48 (SS 7)

PREPARATION 23

N-Triphenylmethyl-O-2-propenyl-(S)-serine ethyl ester

40% Aqueous sodium hydroxide solution (0.87 ml, 8.66 mmol) was added at 10°C to a stirred solution of N-triphenylmethyl-S-serine ethyl ester (2.5 g, 6.66 mmol), allyl bromide (886 mg, 7.32 mmol) and benzyltriethylammonium chloride (1.51 g, 6.66 mmol) in dichloromethane (10 ml). The mixture was allowed to warm to room temperature and stirred overnight. Dichloromethane was added, then the solution washed with water, dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave an oil which was chromatographed on silica, eluting with a 4:1 mixture of hexane and ethyl acetate, to give the pure product as a colourless oil (2.14 g, 77%), Rf 0.52 (SS 1), $[\alpha]_D^{25}$ + 52.3 (c = 0.99, CH_2Cl_2).

Found: C,76.94; H,7.10; N,3.25. $C_{27}H_{29}NO_3$; 0.1 CH_2Cl_2 requires C,76.76; H,6.94; N,3.30%.

PREPARATION 24 (DEPROTECTION METHOD D)

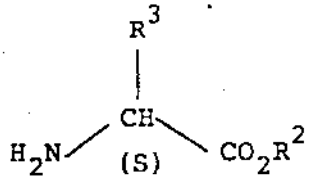
O-(2-Propenyl)-(S)-serine ethyl ester

A solution of the above product (1.0 g, 2.4 mmole) in formic acid (15 ml) was allowed to stand at room temperature for 5 hours. The solvent was then evaporated under vacuum and the residue dried azeotropically with acetonitrile. The resulting white solid was dissolved in water (15 ml) and the solution extracted with diethyl ether. The aqueous phase was basified to pH 9 with sodium carbonate, extracted with ethyl acetate (x 3) and dichloromethane (x 2), and then the combined organic extracts dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave the pure

product as an oil (319 mg, 76%), Rf 0.29 (SS 21). Found: C,55.98; H,8.80; N7.99. $C_8H_{15}NO_3$ requires C,55.47; H,8.73; N,8.09%.

PREPARATIONS 25-29

The following compounds were prepared from the corresponding N-trityl-(S)-serine ester by alkylation under phase transfer conditions followed by formic acid deprotection as described in the above Preparations. Preparations 25 to 28 are (3-phenyl)propyl esters (R^2=$(CH_2)_3Ph$), Preparation 29 is the ethyl ester ($R^2 = CH_2CH_3$).

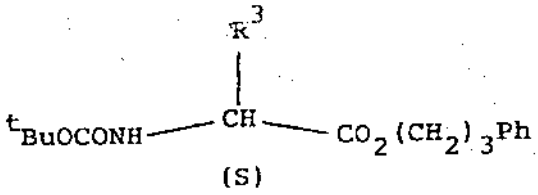


Example No.	R^3	Rf	Analysis % (Theoretical in brackets) C	H	N
25	$-CH_2OCH_2CH{=}CHCH_2OCH_3$ E	0.54 (SS 22)	66.06 (66.42	7.89 8.20	4.47 4.56)
26	$-CH_2OCH_2CH{=}CHCH_3$ E	0.45 (SS 22)	61.34 (61.24	7.80 7.71	4.46 4.46)a
27	$-CH_2O(CH_2)_3OCH_3$	0.42 (SS 22)	64.84 (65.06	8.49 8.53	4.80 4.74)
28	$-CH_2OCH_2\underset{\underset{CH_2}{\|}}{C}CH_2OCH_3$	0.35 (SS 8)	66.39 (66.43	7.92 8.20	4.57 4.56)
29	$-CH_2O(CH_2)_2CH(CH_3)_2$	0.35 (SS 22)			

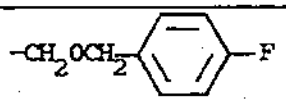
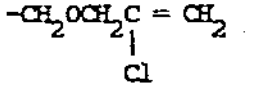
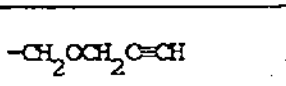
a. HCl

PREPARATIONS 30-35

The following Preparations were effected according to the procedure of Example 54 using (3-phenyl)propyl bromide with the respective products of Preparations 17-22.



(S)

Prep. No.	R^3	Rf	Analysis % C (theoretical in brackets)	H	N
30		0.35 (SS 1)	66.64 (66.80	7.09 7.01	3.23 3.25)
31		0.30 (SS 1)			
32	$-(CH_2)_2OCH_2Ph$	0.40 (SS 1)			
33	$-(CH_2)_2O(CH_2)_2CH_3$	0.25 (SS 6)	58.07 (58.11	9.26 9.40	4.89 4.84)
34	$-CH_2OCH_2C{\equiv}CH$	0.38 (SS 1)	66.56 (66.46	7.56 7.53	3.92 3.83)
35		0.51 (SS 1)	66.50 (66.82	8.30 8.28	3.81 3.71)

PREPARATION 36 (DEPROTECTION METHOD B)

O-Benzyl-(S)-serine methyl ester hydrochloride

A stirred, ice-cold solution of the product of Preparation 1 (2.05g, 66.3 mmol) in dichloromethane (50 ml) was saturated with hydrogen chloride. After a further 3 hours at 0°C, the reaction mixture was evaporated under vacuum and the residual solid azeotroped with dichloromethane (3 x 30 ml) to afford the title compound as a white powder (1.67 g, 97%), Rf 0.60 (SS 9), $[\alpha]_D^{25}$ +21° (c = 0.1, MeOH). Found: C,54.14; H,6.54; N,5.75. $C_{11}H_{15}NO_3$; HCl requires C,53.77; H,6.56; N,5.70%.

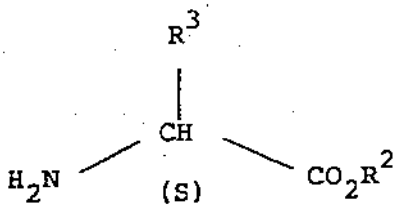
PREPARATION 37 (DEPROTECTION METHOD C)

O-(2-Methoxyethyl)-(S)-tyrosine t-butyl ester

A solution of the product of Preparation 11 (5.4 g) in a mixture of ethanol (40 ml) and water (10 ml) was hydrogenated over 5% palladium on charcoal at 50 psi (3.45 bar) for 2 hours. The reaction mixture was filtered, the filtrate evaporated under vacuum and the residual oil chromatographed on silica gel (300 g) using a 1:39 mixture of ethanol and ethyl acetate as eluent.. Evaporation under vacuum of the required fractions afforded the title compound as a clear oil (3.07 g, 82%), Rf 0.30 (SS 8), $[\alpha]_D^{25}$ + 10.1° (c = 1.63, CH_2Cl_2). Found: C,64.67; H,8.54; N,4.63. $C_{16}H_{25}NO_4$ requires C,65.06; H,8.53; N,4.74%.

PREPARATIONS 38-55

The following Preparations were effected using deprotection Methods A, B or C, with the corresponding N-protected amino acid ester starting material. Method A is described under Example 76 (trifluoroacetic acid), Method B is described under Preparation 36 (hydrogen chloride) and Method C is described under Preparation 37 (hydrogenation).



Preparation No.	Method	R^3	R^2	Rf	Analysis % C (theoretical in brackets)	H	N
38	B	$-CH_2OCH_2Ph$	$CH_2CH_2CH_2Ph$	0.83 (SS 9)	64.59 (64.89	5.95 5.95	3.95 3.98) a
39	B	$-CH_2OCH_2Ph$	$CH(CH_2CH_3)_2$	0.59 (SS 10)	59.89 (59.69	7.90 8.01	4.49 4.64) b
40	B	$-CH(CH_3)OCH_2Ph$ (R)	CH_3	0.43 (SS 10)			
41	B	$-CH_2OCH_2Ph$		0.55 (SS 10)	61.10 (61.23	7.75 7.71	4.39 4.46) b
42	B	$-CH_2OCH_2Ph$			62.70 (62.64	6.70 6.14	3.79 3.79) c
43	B	$-CH_2OCH_2Ph$		0.50 (SS 10)	65.45 (65.60	6.49 6.37	4.04 4.03) b

Preparation No.	Method	R^3	R^2	Rf	Analysis % C (theoretical in brackets) H N
44	B	$-CH_2OCH_2Ph$	$-CH_2CH_2CH_2-$	0.57 (SS 10)	63.46 (63.47 8.31 8.52 4.33 3.90) d
45	C		t_{Bu}	0.30 (SS 11)	70.97 (71.13 7.72 7.87 3.81 3.77)
46	C		t_{Bu}	0.37 (SS 12)	
47	C		t_{Bu}	0.70 (SS 9)	
48	C		$-CH_2CH_2CH_2Ph$	0.25 (SS 9)	

Preparation No.	Method	R^3	R^2	Rf	Analysis % C H N (theoretical in brackets)
49	B		$-CH_2CH_2CH_2Ph$		62.00 6.30 3.69 (62.04 6.30 3.81) b
50	A	$-CH_2OCH_2C(Cl)=CH_2$	$-CH_2CH_2CH_2Ph$	0.30 (SS 9)	59.71 6.78 4.45 (59.78 6.82 4.65) e
51	B	$-CH_2CH_2OCH_2Ph$	$-CH_2CH_2CH_2Ph$	0.35 (SS 9)	64.07 7.09 3.59 (64.42 7.30 3.76) f
52	B	$-CH_2OCH_2Ph$	$-CH_2CH_3$	0.53 (SS 10)	55.28 7.06 5.31 (55.49 6.98 5.39)b
53	B	$-CH_2CH_2O(CH_2)_2CH_3$	$-CH_2CH_3$	0.40 (SS 22)	

54	B	$-CH_2OCH_2C{\equiv}CH$	$-(CH_2)_3Ph$	0.46 (SS 22)	68.28 (68.46	7.27 7.28 5.33 5.32)g
55	B	$-CH_2OCH_2C(=CH_2)CH_3$	$-(CH_2)_3Ph$	0.44 (SS 22)	68.49 (68.39	8.73 8.39 4.95 4.99)e

a. HCl; 0.10 H_2O
b. HCl
c. HCl; 0.25 CH_2Cl_2
d. HCl; 0.20 H_2O
e. 0.20 H_2O
f. HCl; 0.50 H_2O
g. 0.1 H_2O

PREPARATION 56

O-Benzyl-(S)-serine amide

This was obtained in 97% yield as the hydrochloride salt by subjecting N-t-butoxycarbonyl-O-benzyl-(S)-serine amide (Preparation 10) to deprotection Method B; Rf 0.40 (SS 10). Found: C,52.10; H,6.45; N,11.89. $C_{10}H_{14}N_2O_2$; HCl requires C,52.06; H,6.55; N,12.14%.

PREPARATION 57

N-(2,2,2-Trichloroethoxycarbonyl)-aziridine-2(S)-carboxylic acid benzyl ester

a) Trifluoroacetic acid (40 ml) was added dropwise over 10 minutes to a stirred, ice-cooled solution of N-trityl-aziridine-2-carboxylic acid benzyl ester (10 g, 1.0 eq) in methanol/chloroform (1:1, 40 ml) and the reaction mixture stirred for 1.5 hours, when the reaction was complete (by TLC). The reaction mixture was evaporated under vacuum to yield a crystalline residue which was partitioned between diethyl ether (100 ml) and water (50 ml). The aqueous phase was extracted with diethyl ether (2 x) and the organic phases combined. The aqueous phase was neutralised with sodium bicarbonate and reextracted with ether. The combined ether extracts were dried ($MgSO_4$), filtered and evaporated to yield an oil (3.93 g).

b) A solution of the oil from part (a) (3.39 g) in dichloromethane (30 ml) was treated with 2,2,2-trichloroethyl-chloroformate (4.7 g, 1.0 eq) followed by N-methylmorpholine (2.5 g, 1.1 eq). The resulting solution was allowed to warm to room temperature and stirred overnight. The solvent was evaporated under vacuum and the residue dissolved in ethyl acetate (70 ml);

this solution was washed with water (3 x 50 ml), hydrochloric acid (2M, 2 x 50 ml), saturated aqueous sodium bicarbonate solution (2 x 30 ml) and brine (1 x 20 ml), then dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave the crude product as a pale yellow oil, which was chromatographed on silica gel, eluting with mixtures of hexane and ethyl acetate (from 1-10% of ethyl acetate), to yield the pure title compound as an oil (6.8 g, 81%), $[\alpha]_D$ - 20° (c = 0.1, MeOH). Found: C,43.58; H,3.50; N,3.86. $C_{13}H_{12}Cl_3NO_4$ requires C,44.28; H,3.43; N,3.97%.

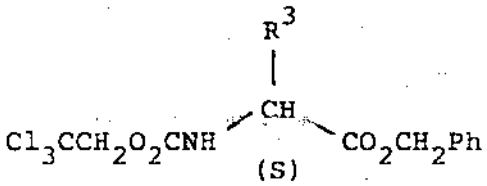
PREPARATION 58

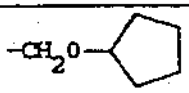
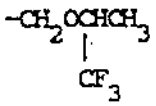
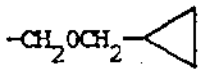
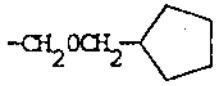
N-(2,2,2-Trichloroethoxycarbonyl)-O-(2-butynyl)-(S)-serine benzyl ester

Boron trifluoride etherate (1 drop) was added to a solution of 2-butyn-1-ol (0.206 g, 2eq) and (S)-N-(2,2,2-trichloroethoxy-carbonyl)-aziridine-2-carboxylic acid benzyl ester (0.52 g, 1.0 eq) in dry dichloromethane (3 ml) and the reaction stirred for 1 hour at room temperature. The solvent was evaporated under vacuum, the residue dissolved in ethyl acetate (20 ml) and the solution washed with water (2 x 10 ml), hydrochloric acid (2M, 2 x 10 ml), saturated aqueous sodium bicarbonate solution (1 x 10 ml) and brine (1 x 10 ml), then dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave an oil which was chromatographed over silica gel, eluting with mixtures of hexane and ethyl acetate (from 1 to 4% of ethyl acetate) to yield the title compound as an oil (48 g, 77%), $[\alpha]_D$ -10° (c = 0.1, MeOH). Rf 0.7 (SS 2). Found: C,48.01; H,4.15; N,3.30. $C_{17}H_{13}Cl_3NO_5$ requires C,48.30; H,4.29; N,3.31%.

PREPARATIONS 59-65

The following compounds were prepared according to the method described above:



Prep. No.	R^3	Rf	Analysis % (Theoretical in brackets) C	H	N
59	$-CH_2O(CH_2)_3CH_3$	0.81 (SS 2)	47.64 (47.85	4.94 5.19	3.02 3.28)
60		0.40 (SS 1)	48.56 (49.28	5.06 5.05	3.10 3.19)
61	$-CH_2OCH(CH_3)_2$	0.44 (SS 1)	46.38 (46.56	4.84 4.88	3.36 3.39)
62		0.40 (SS 1)	41.58 (41.18	3.83 3.67	3.06 3.00)
63	$-CH_2OCH_2CF_3$	0.35 (SS 1)	40.44 (39.80	3.51 3.34	3.06 3.10)
64		0.42 (SS 1)	48.20 (48.07	5.23 4.75	3.32 3.29)
65		0.47 (SS 6)	43.05 (43.04	5.49 5.68	3.60 3.59)

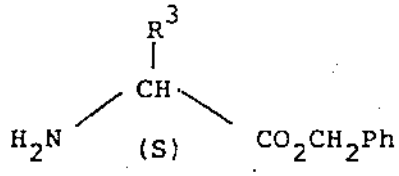
PREPARATION 66 (DEPROTECTION METHOD E)

O-(2-Butynyl)-(S)-serine benzyl ester

Zinc dust (500 mg) was added in one portion to a solution of N-(2,2,2-trichloroethoxycarbonyl)-O-(2-butynyl)-(S)-serine benzyl ester (0.44 g, 1.0 eq) in acetic acid (25 ml) and the mixture stirred at room temperature for 1.5 hours. The zinc was removed by filtration and washed with acetic acid, then the filtrate evaporated under vacuum and the residue azeotroped with toluene. The residue was dissolved in ethyl acetate (20 ml) and the solution washed with saturated aqueous sodium bicarbonate solution (10 ml); the resultant precipitate of sodium acetate was removed by filtration and the filtrate washed again with saturated aqueous sodium bicarbonate solution. The organic phase was extracted with hydrochloric acid (2M, 2 x 100 ml), then the combined extracts overlaid with ethyl acetate and neutralised with solid sodium bicarbonate. The organic layer was separated and the aqueous phase reextracted with ethyl acetate, then the combined organic phases dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate provided the title compound as a yellow oil (200 mg, 78%), Rf 0.71 (SS 19).

PREPARATIONS 67-73

The following compounds were prepared by treatment with zinc in acetic acid according to the method described above:



Preparation No.	R^3	Rf
67	$-CH_2O(CH_2)_3CH_3$	0.62 (SS 19)
68	$-CH_2O$	0.18 (SS 20)
69	$-CH_2OCH(CH_3)_2$	0.18 (SS 20)
70	$-CH_2OCHCH_3$ CF_3	0.17/0.20 (SS 20)
71	$-CH_2OCH_2CF_3$	0.18 (SS 20)
72	$-CH_2OCH_2-$	0.18 (SS 20)
73	$-CH_2OCH_2$	0.31 (SS 22)

PREPARATION 74

4-Methoxymethyl-(S)-phenylalanine t-butyl ester

To a vigorously stirred solution of sodium hydroxide (11.5 g, 0.29 mol) in water (23 ml) were added, sequentially, a solution of (4-methoxymethyl)benzyl bromide (3.1 g, 14.4 mmol) in dichloromethane (30 ml), N-diphenylmethylene glycine t-butyl ester (4.26 g, 14.4 mmol) and N-benzylcinchonidinium chloride (1.21 g, 2.9 mmol). After 2.5 hours the reaction mixture was diluted with dichloromethane (100 ml), then the organic phase separated, washed to neutrality with water, dried ($MgSO_4$) and evaporated under vacuum to provide an oil (7.2 g). Chromatography on silica gel (600 g) using a 4:1 mixture of hexane and ether as eluent afforded a white solid (473 g, 76%) which, on crystallisation from hexane, yielded racemic material (1.71 g), m.p. 81-82°C. Further chromatography of the crystallisation mother liquor on silica gel using the same eluent gave the required (S)-enantiomer as a clear oil (2.44 g, 39%), Rf 0.30 (SS 13), $[\alpha]_D^{25}$ -145° (c = 1.08, CH_2Cl_2). Found: C,77.93; H,7.21; N,3.23. $C_{28}H_{31}NO_3$ requires C,78.29; H,7.27; N,3.26%.

A solution of this product (2.3 g, 5.56 mmol) in ether (50 ml) was vigorously stirred with a mixture of 0.5M hydrochloric acid (12.2 ml) and water (40 ml). After 9 hours the aqueous phase was removed and the ether phase treated two further times in the same way. The combined aqueous phases were basified with 1M aqueous sodium hydroxide solution and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give an oil (960 mg) which was chromatographed on silica gel, using ethyl acetate as eluent, to afford the title compound

as a clear oil (860 mg, 59%), Rf 0.35 (SS 8), $[\alpha]_D^{25}$ + 9.7° (c = 1.65, CH_2Cl_2). Found: C,67.73; H,8.54; N,5.10. $C_{15}H_{23}NO_3$ requires C,67.90; H,8.74; N,5.28%.

PREPARATION 75

O-n-Propyl-(S)-serine ethyl ester

a) N-(Triphenylmethyl)-O-(2-propenyl)-(S)-serine ethyl ester (Preparation 23, 1.0 g, 2.4 mmol), dissolved in ethanol (36 ml) and water (4 ml), was hydrogenated over 5% palladium on charcoal (300 mg) at 50 p.s.i. (3.45 bar) and room temperature. After three hours the mixture was filtered through a short arbacel column and the filtrate, on evaporation under vacuum, gave a clear oil (916 mg). Chromatography on silica gel, eluting with a 1:4 mixture of ethyl acetate and hexane gave N-triphenylmethyl-O-n-propyl-(S)-serine ethyl ester (697 mg, 69%). Found: C,78.13; H,8.96; N,3.31. $C_{27}H_{31}NO_3$ requires C,77.66; H,7.48; N,3.35%.

b) The above intermediate (667 mg, 1.6 mmol) was dissolved in a 1.7% solution of concentrated hydrochloric acid in acetone (30 ml); after five hours a further amount (5 ml) of the above acid solution was added to complete the reaction. After a further half hour the mixture was evaporated under vacuum and the residue dried azeotropically with dichloromethane. Trituration with diethyl ether and filtration gave the required product as a white solid (247 mg, 73%), Rf 0.19 (SS 22). Found: C,45.56; H,8.23; N,6.50. $C_8H_{18}ClNO_3$ requires C,45.39; H,8.57; N,6.62%.

PREPARATION 76

3-[2-(R,S)-Tetrahydrofuryl]-(S)-alanine (3-phenyl)propyl ester

a) 3-(2-Furyl)-(S)-alanine (prepared by the method of H. K. Chenault et al, J. Amer. Chem. Soc., 1981, 111, 6354) was reacted with di-t-butyl dicarbonate to give N-t-butoxycarbonyl-3-(2-furyl)-(S)-alanine as a colourless oil, Rf 0.6 (SS 21).

b) The previous product (3.0 g, 0.12 mol) in ethyl acetate (40 ml) was hydrogenated over platinum oxide (200 mg) at 60 p.s.i. (4.1 bar) and room temperature for 2 hours, when uptake was complete. The catalyst was removed by filtration, the filtrate evaporated under vacuum and the residue chromatographed on silica gel eluting with a mixture of dichloromethane, methanol, acetic acid and hexane (90:10:1:150) to give N-t-butoxycarbonyl-3-[(2-(R,S)-tetrahydrofuryl)]-(S)-alanine (2.04 g) as a mixture of two diastereoisomers, Rf 0.20 (SS 26).

c) Alkylation of the previous product with (3-phenyl)propyl bromide following the procedure of Preparation 1, followed by removal of the N-t-butoxycarbonyl protecting group with hydrogen chloride, gave the title compound as a colourless oil, Rf 0.30 (SS 22).

PREPARATION 77

2(S)-trans 1-(4-Ethoxy-2-butenyl)glycine methyl ester hydrochloride

a) n-Butyllithium (3.15 ml, 7.875 mmol, 2.5M in hexane) was added dropwise over 10 minutes under nitrogen to a stirred solution of 2,5-dihydro-3,6-methoxy-2(R)-(2-propyl)pyrazine (1.38 g, 7.49 mmol) in dry tetrahydrofuran, whilst keeping the

temperature below -68°C. After 15 minutes a solution of trans 1-bromo-4-ethoxy-2-butene (1.34 g, 7.49 mmole) in tetrahydrofuran (5 ml) was added over 10 minutes at -78°C. The reaction mixture was then allowed to warm to room temperature overnight, being kept initially at -78°C for at least 5 hours. The solvent was removed under vacuum and the residue partitioned between diethyl ether and water. The organic phase, on drying ($MgSO_4$) and evaporation, gave a golden oil (1.35 g, 65%) which was stirred with 0.25M hydrochloric acid (42.8 ml) for 24 hours. The mixture was evaporated under vacuum and the residue dried azeotropically with dichloromethane followed by toluene.

Di-t-butyl dicarbonate (3.13 g, 14.34 mmol) was added to an ice-cooled solution of the above mixture of esters (2.02 g) and N-methylmorpholine (1.58 ml) in dry dichloromethane (35 ml), and the resulting solution stood at room temperature for 4 days. The solvent was removed under vacuum and the residue partitioned between diethyl ether and water. The organic phase was washed sequentially with water, 1M hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and water, then dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate gave a yellow liquid (1.34 g) which was chromatographed on silica gel; elution with increasing proportions of diethyl ether in hexane gave N-t-butoxycarbonyl-2(S)-trans 1-(4-ethoxy-2-butenyl)glycine methyl ester as an oil (565 mg, 41%), Rf 0.38 (SS 2). Found: C,58.29; H,8.50; N,5.21. $C_{14}H_{25}NO_5$ requires C,58.51; H,8.77; N,4.87%. $[\alpha]_D^{25}$ + 18.6° (c = 1.07, CH_2Cl_2).

b) A stirred, ice-cold solution of the above product (492 mg, 1.7 mmol) in dry diethyl ether (15 ml) was saturated over 1.5 hours with hydrogen chloride gas. After being stirred at 0°C for a further 3 hours, the solution was evaporated under vacuum and the residue dried azeotropically with dichloromethane (x3) to give the title product as a pale yellow foam (320 mg, 84%), Rf 0.32 (SS 14). Found: C, 47.17; H,7.79; N,6.40. $C_9H_{18}ClNO_3$. 0.05 CH_2Cl_2 requires C,47.68; H,7.56; N,6.14%.

PREPARATION 78

2(S)-trans 1-(4-Methoxy-2-butenyl)glycine methyl ester hydrochloride

This was similarly prepared following the procedures described above and was obtained as a white powder Rf 0.30 (SS 22). Found: C,45.17; H,7.54; N,6.71. $C_8H_{16}NClO_3$; 0.2 H_2O requires C,45.05; H,7.75; N,6.57%.

PREPARATION 79

2(S)-(4-Methoxy-1-butyl)glycine methyl ester

This compound was obtained from the previous product (free base), according to Preparation 75a, as a yellow oil, Rf 0.15 (SS 22).

PREPARATION 80

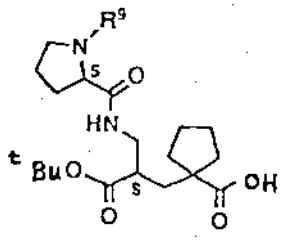
1-{3-[N-t-Butoxycarbonyl-(S)-prolylamino]-2(S)-t-butoxycarbonyl-propyl}cyclopentane carboxylic acid

N-t-Butoxycarbonyl-(S)-proline 4-nitrophenyl ester (2.89 g,

8.59 mmol) was added to a stirred suspension of 1-[3-amino-2(S)-t-butoxycarbonylpropyl]cyclopentane carboxylic acid sodium salt (EP-A-358398; 1.70 g, 5.90 mmol) in dry dichloromethane (30 ml). After 24 hours the reaction mixture was evaporated under vacuum and the residue allowed to stand for a further 24 hours before being partitioned between ethyl acetate (200 ml) and 2M hydrochloric acid (100 ml). The organic phase was separated, washed successively with 2M hydrochloric acid (2 x 50 ml), saturated aqueous sodium bicarbonate solution (4 x 50 ml), more 2M hydrochloric acid (50 ml) and saturated brine (50 ml), dried ($MgSO_4$), filtered, and the filtrate evaporated under vacuum. The resulting yellow oil (4.59 g) was purified by chromatography on silica gel (200 g), using an elution gradient of 1% acetic acid in ethyl acetate / 0 to 10% methanol, to furnish the title compound as a cream foam (1.096 g, 40%), Rf 0.53 (SS 14), $[\alpha]_D^{25}$ -161° (c = 0.1, MeOH). Found: C,61.20; H,8.81; N,5.43. $C_{24}H_{40}N_2O_7$ requires C,61.51; H,8.60; N,5.98%.

PREPARATIONS 81-82

The following compounds of formula (V) were prepared from the appropriate proline derivatives using the procedure described above for Preparation 80.



Preparation No.	R^9	Rf	Analysis % (Theoretical in brackets) C	H	N
81	$PhCH_2CO_2-$	0.25 (SS 8)	64.75 (64.52	7.60 7.62	5.53 5.57)
82	$(Cl)_3CCH_2CO_2-$	0.50 (SS 21)	48.74 (48.58	5.85 6.12	5.69 5.15)

PREPARATION 83

1-[3-Benzyloxycarbonylamino-2(S)-t-butoxycarbonylpropyl]cyclopentane carboxylic acid

To a stirred, ice-cold suspension of 1-[3-amino-2(S)-t-butoxycarbonylpropyl]cyclopentane carboxylic acid sodium salt (1.0 g, 3.4 mmol) in dry dichloromethane (15 ml) were added, sequentially, N-methylmorpholine (0.4 ml, 4.0 mmol) and N-benzyloxycarbonyloxysuccinimide (930 mg, 3.75 mmol). After 1 hour the ice bath was removed and stirring was continued for 24 hours. The reaction mixture was evaporated under vacuum, then the residue partitioned between ethyl acetate and water. The organic phase was separated, washed with 1M hydrochloric acid and water, dried ($MgSO_4$) and filtered. Evaporation under vacuum of the filtrate provided an oil (1.4 g) which was purified by chromatography on silica gel, using a 7:3 mixture of ether and hexane as eluent, to give the title compound as a gum (900 mg), Rf 0.50 (SS 2).

Biological activity

The following Table illustrates the dual in vitro enzyme inhibitory activities for a range of the compounds of the invention.

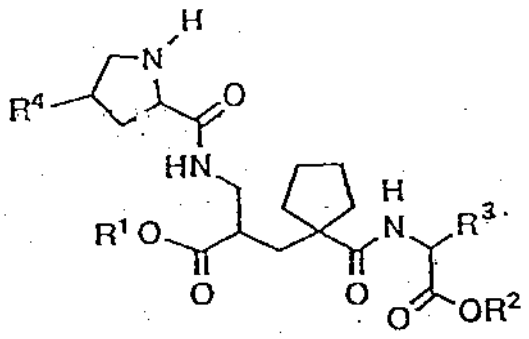
EXAMPLE NUMBER	IC_{50} (M)	
	ANGIOTENSIN CONVERTING ENZYME (ACE)	NEUTRAL METALLOENDOPEPTIDASE (E.C. 3.4.24.11)
86	1.3×10^{-8}	3.0×10^{-8}
87	1.4×10^{-8}	2.0×10^{-8}
92	2.6×10^{-8}	2.0×10^{-8}
128	1.6×10^{-8}	4.1×10^{-8}
130	4.0×10^{-9}	1.8×10^{-8}
131	3.7×10^{-8}	4.8×10^{-8}
133	3.2×10^{-8}	4.0×10^{-8}
134	1.6×10^{-8}	3.4×10^{-8}
136	1.5×10^{-8}	1.5×10^{-8}
137	1.4×10^{-8}	3.6×10^{-8}
138	2.4×10^{-9}	3.2×10^{-8}
144	6.6×10^{-8}	3.3×10^{-8}
145	1.1×10^{-8}	4.1×10^{-8}

Safety profile

The prodrugs of the invention have been tested orally in rat at doses up to 10 mg/Kg and the diacids of the invention have been tested intravenously in rat at doses up to 10 mg/Kg. No signs of adverse acute toxicity were observed.

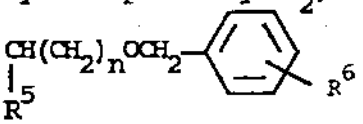
CLAIMS

1. A compound of formula:



(I)

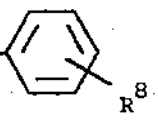
wherein R^1 and R^2 are each independently H or a biolabile ester-forming group, and either or both of OR^1 and OR^2 may optionally be replaced by NH_2;

R^3 is (a) 

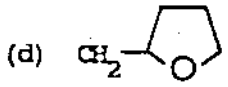
wherein R^5 is H or methyl, R^6 is H or halo, and n is 0 or 1;

(b) CH_2OR^7

wherein R^7 is C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, (C_1-C_4 alkoxy)C_1-C_6 alkyl, (C_1-C_4 alkoxy)C_3-C_6 alkenyl, (halo)C_3-C_6 alkenyl, (C_3-C_7 cycloalkyl)C_1-C_6 alkyl or (CF_3)C_1-C_6 alkyl;

(c) 

wherein R^8 is CH_2OH, CH_2OCH_3, $OCH(R^5)CH_2OH$ or $OCH_2CH_2OCH_3$ and R^5 is as previously defined;

(d)  or

(e) (C_1-C_4 alkoxy)C_3-C_6 alkenyl or (C_1-C_4 alkoxy)C_2-C_6 alkyl;

and R^4 is H or hydroxy;

and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 wherein R^1 and R^2 are each independently selected from H, C_1-C_5 alkyl, C_5-C_7 cycloalkyl, (cyclohexyl)C_1-C_3 alkyl, (phenyl)C_1-C_3 alkyl, 1-(C_2-C_5 alkanoyloxy)C_1-C_4 alkyl, 1-(C_5-C_6 cycloalkylacetoxy)C_1-C_4 alkyl, 1-(C_5-C_7 cycloalkylcarboxy)C_1-C_4 alkyl, 1-(2-indanylcarboxy)C_1-C_4 alkyl, 1-(benzoyloxy)C_1-C_4 alkyl, 3-phthalidyl, 1-(C_1-C_4 alkoxy-carbonyloxy)C_1-C_4 alkyl, [4-(5-[C_1-C_4 alkyl]-1,3-dioxolen-2-onyl)]methyl, acetonyl, indanyl and pyridyl.

3. A compound as claimed in claim 2 wherein R^1 and R^2 are each independently selected from H, methyl, ethyl, (3-cyclohexyl)-propyl, (3-phenyl)propyl, pivaloyloxymethyl, 1-(cyclohexyl-acetoxy)ethyl, 1-(cyclohexylcarboxy)ethyl, 1-(2-indanylcarboxy)-ethyl, 1-(benzoyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl or [4-(5-methyl-1,3-dioxolen-2-onyl)]methyl.

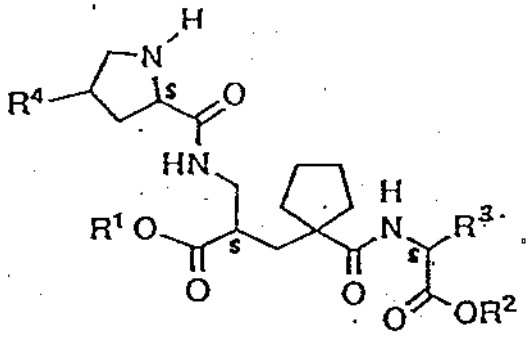
4. A compound as claimed in claim 3 wherein R^3 is benzyloxy-methyl, 1-(2-butenyl)oxymethyl, 1-(4-methoxy-2-butenyl)oxymethyl or 2-chloro-2-propenyloxymethyl, and R^4 is H.

5. A compound as claimed in claim 4 wherein R^1 is H, and R^2 is methyl, (3-phenyl)propyl or (3-cyclohexyl)propyl.

6. A compound as claimed in claim 4 wherein R^1 is pivaloyloxymethyl, 1-(cyclohexylacetoxy)ethyl, 1-(cyclohexylcarboxy)ethyl, 1-(2-indanylcarboxy)ethyl, 1-(benzoyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl or [4-(5-methyl-1,3-dioxolen-2-onyl)]methyl, and R^2 is ethyl.

7. A compound as claimed in claim 1 wherein both R^1 and R^2 are H.

8. A compound as claimed in claims 1 to 7 wherein the preferred stereoisomer is of formula:

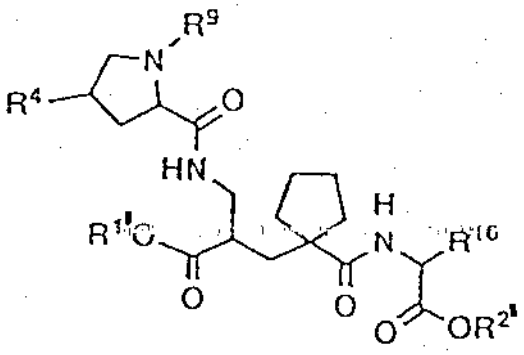


9. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

10. A compound of formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either, for use in medicine.

11. The use of a compound of formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either, for the manufacture of a medicament for the treatment of hypertension, heart failure or renal insufficiency.

12. A compound of formula:



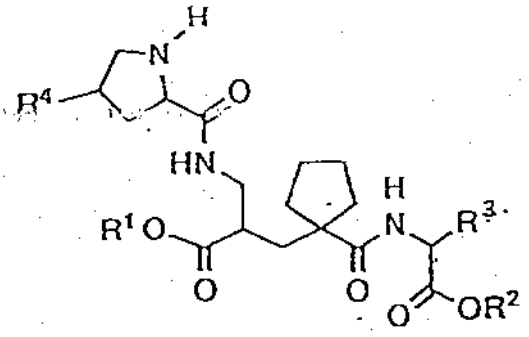
(IV)

wherein $R^{1'}$ and $R^{2'}$ are as defined in claim 1 for R^1 and R^2 respectively but are not H, and $OR^{1'}$ and $OR^{2'}$ are as defined in claim 1 for OR^1 and OR^2, R^4 is as defined in claim 1, R^9 is a conventional amino acid N-protecting group and R^{10} is as defined in claim 1 for R^3 with any reactive groups therein optionally protected.

13. A compound as claimed in claim 12 wherein $R^{1'}$ and $R^{2'}$ are each independently selected from t-butyl and benzyl.

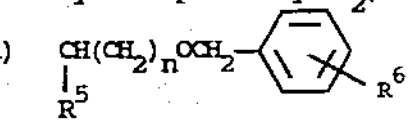
14. A method for the prophylactic or curative treatment of hypertension, heart failure or renal insufficiency in a human being, which comprises administering to said human being an effective amount of a compound of formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either.

15. A process for the preparation of a compound of formula:



(I)

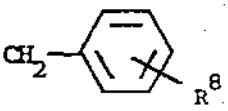
wherein R^1 and R^2 are each independently H or a biolabile ester-forming group, and either or both of OR^1 and OR^2 may optionally be replaced by NH_2;

R^3 is (a) 

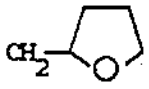
wherein R^5 is H or methyl, R^6 is H or halo, and n is 0 or 1;

(b) CH_2OR^7

wherein R^7 is C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, (C_1-C_4 alkoxy)C_1-C_6 alkyl, (C_1-C_4 alkoxy)C_3-C_6 alkenyl, (halo)C_3-C_6 alkenyl, (C_3-C_7 cycloalkyl)C_1-C_6 alkyl or (CF_3)C_1-C_6 alkyl;

(c) 

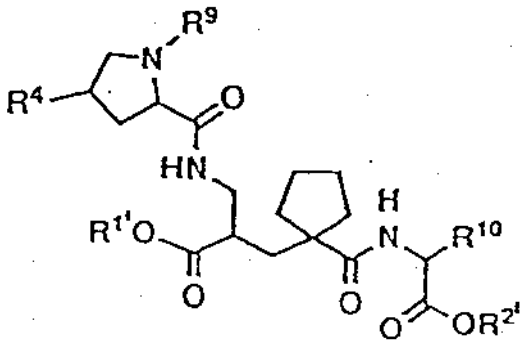
wherein R^8 is CH_2OH, CH_2OCH_3, $OCH(R^5)CH_2OH$ or $OCH_2CH_2OCH_3$ and R^5 is as previously defined;

(d)  or

(e) (C_1-C_4 alkoxy)C_3-C_6 alkenyl or (C_1-C_4 alkoxy)C_2-C_6 alkyl;

and R^4 is H or hydroxy;

or a pharmaceutically acceptable salt thereof, which comprises removing R^9, any protecting group present in R^{10}, and optionally either one or both of any biolabile ester-forming groups $R^{1'}$ and $R^{2'}$ which may be present, from a compound of formula:



(IV)

wherein R^4 is as previously defined, R^9 is a conventional amino acid N-protecting group, R^{10} is as defined for R^3 with any reactive groups therein optionally protected, and $R^{1'}$ and $R^{2'}$ are as defined for R^1 and R^2 but are not H, and $OR^{1'}$ and $OR^{2'}$ are as defined for OR^1 and OR^2, and optionally isolating as, or forming, a pharmaceutically acceptable salt of the product.

16. A process as claimed in claim 15 wherein R^1 and R^2 are each independently selected from H, C_1-C_5 alkyl, C_5-C_7 cycloalkyl,

(cyclohexyl)C_1-C_3 alkyl, (phenyl)C_1-C_3 alkyl, 1-(C_2-C_5 alkanoyloxy)C_1-C_4 alkyl, 1-(C_5-C_6 cycloalkylacetoxy)C_1-C_4 alkyl, 1-(C_5-C_7 cycloalkylcarboxy)C_1-C_4 alkyl, 1-(2-indanylcarboxy)C_1-C_4 alkyl, 1-(benzoyloxy)C_1-C_4 alkyl, 3-phthalidyl, 1-(C_1-C_4 alkoxycarbonyloxy)C_1-C_4 alkyl, [4-(5-[C_1-C_4 alkyl]-1,3-dioxolen-2-onyl)]methyl, acetonyl, indanyl and pyridyl.

17. A process as claimed in claim 16 wherein R^1 and R^2 are each independently selected from H, methyl, ethyl, (3-cyclohexyl)-propyl, (3-phenyl)propyl, pivaloyloxymethyl, 1-(cyclohexylacetoxy)ethyl, 1-(cyclohexylcarboxy)ethyl, 1-(2-indanylcarboxy)-ethyl, 1-(benzoyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl or [4-(5-methyl-1,3-dioxolen-2-onyl)]methyl.

18. A process as claimed in claim 17 wherein R^1 is H, and R^2 is methyl, (3-phenyl)propyl or (3-cyclohexyl)propyl.

19. A process as claimed in claim 17 wherein R^1 is pivaloyloxymethyl, 1-(cyclohexylacetoxy)ethyl, 1-(cyclohexylcarboxy)ethyl, 1-(2-indanylcarboxy)ethyl, 1-(benzoyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl or [4-(5-methyl-1,3-dioxolen-2-onyl)]-methyl, and R^2 is ethyl.

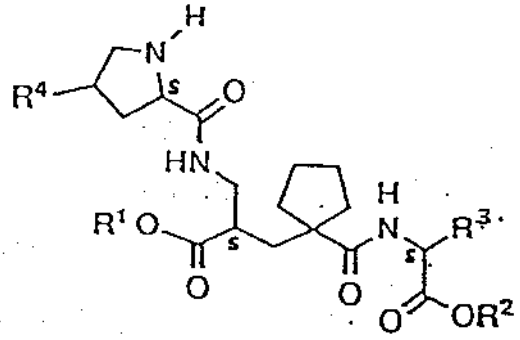
20. A process as claimed in any one of claims 15 to 19 wherein R^9 is t-butoxycarbonyl, benzyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl and is removed by acidolysis, hydrogenolysis and treatment with zinc in glacial acetic acid respectively.

21. A process for the preparation of a compound of formula (I) wherein both R^1 and R^2 are H and R^3 and R^4 are as defined in claim 15, or a pharmaceutically acceptable salt thereof, which comprises subjecting a compound of formula (I) wherein R^1 is H, R^2 is a biolabile ester-forming group and R^3 and R^4 are as defined in

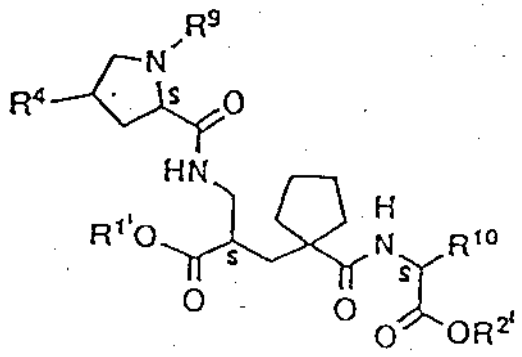
claim 15 to base hydrolysis and optionally isolating as, or forming, a pharmaceutically acceptable salt of the product.

22. A process as claimed in any one of claims 15 to 21 wherein R^3 is benzyloxymethyl, 1-(2-butenyl)oxymethyl, 1-(4-methoxy-2-butenyl)oxymethyl or 2-chloro-2-propenyloxymethyl, and R^4 is H.

23. A process as claimed in any one of claims 15 to 22 wherein the preferred stereoisomer of the product is of formula:



and that of the precursor intermediate is of formula:



INTERNATIONAL SEARCH REPORT

International Applicat. . No PCT/EP 92/00321

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 207/16 A 61 K 31/40 C 07 D 405/12
C 07 D 401/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 207/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0358398 (PFIZER) 14 March 1990, see claim 1 (cited in the application) ---	1-23
A	Journal of Medicinal Chemistry, vol. 15, no. 8, 1972, M.C. KHOSLA et al.: "Synthesis of some analogs of angiotensin II as specific antagonists of the parent hormone", pages 792-795, see entire publication ---	1-23
A	Journal of Medicinal Chemistry, vol. 13, no. 2. March 1970, N.C. CHATURVEDI et al.: "Analogs of angiotensin II. I. Solid phase synthesis", pages 177-181, see entire publication ---	1-23
A	EP,A,0274234 (PFIZER) 13 July 1988, see entire document -----	1-23

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26-03-1992	27 APR 1992
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme N. KUIPER

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 14 is directed to a method of treatment of (diagnostic method practised on) the human/ animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200321

SA 56109

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 17/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0358398	14-03-90	AU-B- 604195	06-12-90
		AU-A- 4105289	08-03-90
		JP-A- 2124862	14-05-90
EP-A- 0274234	13-07-88	AU-B- 595082	22-03-90
		AU-A- 8240787	07-07-88
		DE-A- 3772950	17-10-91
		JP-A- 63165353	08-07-88
		SU-A- 1612996	07-12-90
		US-A- 5030654	09-07-91

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 257/06, 257/04, 285/08
C07D 277/46, 405/12, 417/12
C07D 277/56, A61K 31/41

A1

(11) International Publication Number: WO 93/09101

(43) International Publication Date: 13 May 1993 (13.05.93)

(21) International Application Number: PCT/JP92/01406

(22) International Filing Date: 30 October 1992 (30.10.92)

(30) Priority data:
9123353.6 4 November 1991 (04.11.91) GB

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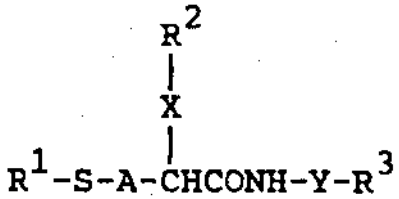

[I]

(57) Abstract

This invention relates to new mercapto-amide derivatives having an inhibitory activity against the neutral endopeptidase and represented by general formula (I), wherein R^1 is hydrogen or a mercapto-protective group, R^2 is lower alkyl or aryl which may be substituted with lower alkylenedioxy, R^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which may be substituted with substituent(s) selected from the group consisting of acyl and acyl(lower)alkyl, A is lower alkylene, X is lower alkylene or S, and Y is a single bond or lower alkylene, provided that when R^3 is tetrazolyl or thiazolyl, then Y is lower alkylene, and pharmaceutically acceptable salts thereof, to processes for the preparation thereof and to a pharmaceutical composition comprising the same.

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DESCRIPTION

MERCAPTO-AMIDE DERIVATIVES AS INHIBITORS OF THE NEUTRAL ENDOPEPTIDASE.

TECHNICAL FIELD

This invention relates to new mercapto-amide derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some mercapto-amide derivatives have been known as inhibitor enkephalinase which is an enkephalin-degrading enzyme, for example, in EP Patent Application Publication Nos. 0 110 484, 0 115 997, 0 159 254, 0 280 627 and 0 419 327.

DISCLOSURE OF INVENTION

This invention relates to new mercapto-amide derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to new mercapto-amide derivatives and pharmaceutically acceptable salts thereof which possess an inhibitory activity against the neutral endopeptidase (hereinafter NEP), e.g. neutral endopeptidase EC 3. 4. 24. 11, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the treatment and/or prevention of various cardiovascular disorders such as hypertension, heart failure, angina pectoris or the like, renal insufficiency, cyclic edema, hyperaldosteronism, hypercalciuria and the like in human beings or animals. Additionally, the object compound is expected to be useful as therapeutical and/or preventive agents for glaucoma, asthma, inflammation, pain, epilepsy, dementia, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome); the

modulation of gastric acid secretion and the treatment of hyperreninaemia.

One object of this invention is to provide new and useful mercapto-amide derivatives which possess an inhibitory activity against NEP.

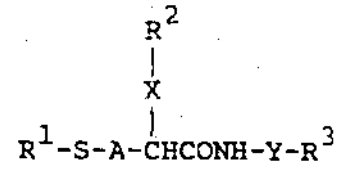
Another object of this invention is to provide processes for the preparation of said mercapto-amide derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said mercapto-amide derivatives and pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention of aforesaid diseases in human beings or animals, using said mercapto-amide derivatives and pharmaceutically acceptable salts thereof.

It is well known that NEP is involved in the breakdown of several peptide hormones, including atrial natriuretic peptides (hereinafter, ANP) which has potent vasodilatory, diuretic and natriuritic activities, and enkephalin which is a endogenous morphine-like peptide. Thus, NEP inhibitors can potentiate the biological effects of ANP and enkephalin. Therefore, the compounds inhibiting NEP are useful for the treatment and/or prevention of various cardiovascular disorders such as hypertension, heart failure, angina pectoris or the like, renal insufficiency, cyclic edema, hyperaldosteronism, hypercalciuria, and the other diseases mentioned above.

The object mercapto-amide derivatives of this invention are new and can be represented by the following general formula [I] :

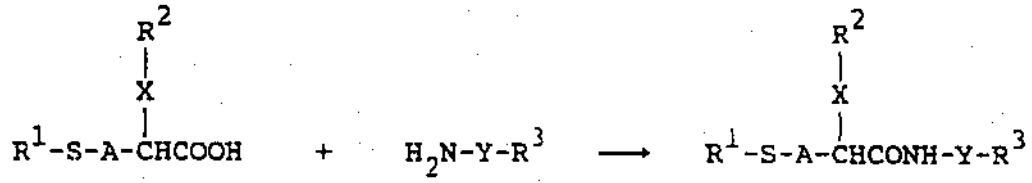


[I]

wherein R^1 is hydrogen or a mercapto-protective group,
R^2 is lower alkyl or aryl which may be substituted with lower alkylenedioxy,
R^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which may be substituted with substituent(s) selected from the group consisting of acyl and acyl(lower)alkyl,
A is lower alkylene,
X is lower alkylene or S, and
Y is a single bond or lower alkylene,
provided that when R^3 is tetrazolyl or thiazolyl, then Y is lower alkylene,
and pharmaceutically acceptable salts thereof.

The object compound [I] or its salt can be prepared by the following processes.

Process 1

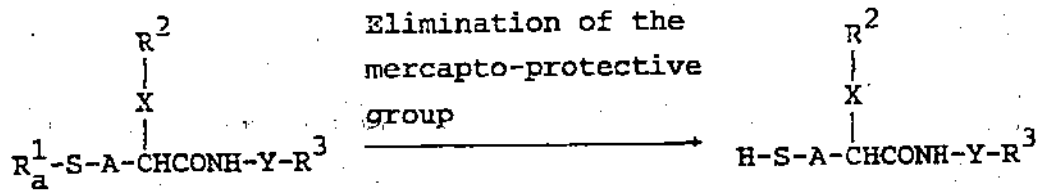


[II] or its reactive derivative at the carboxy group or a salt thereof

[III] or its salt

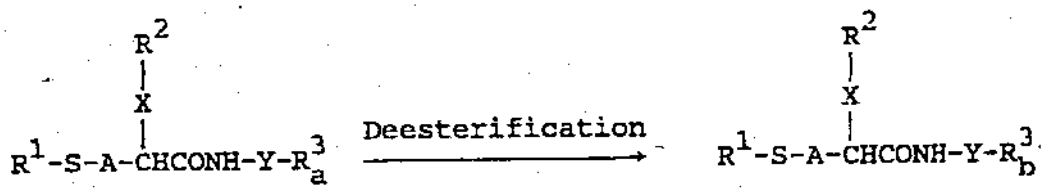
[I] or its salt

Process 2



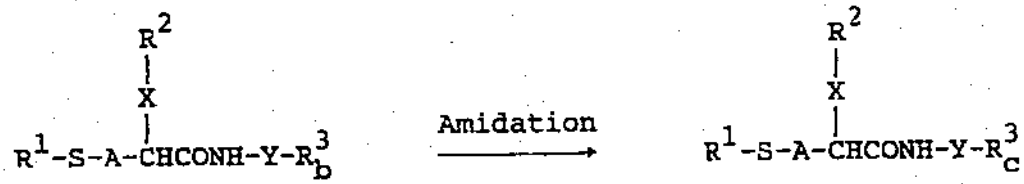
[Ia] or its salt → [Ib] or its salt

Process 3



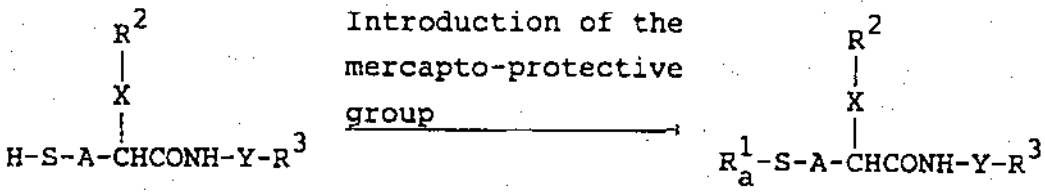
[Ic] or its salt → [Id] or its salt

Process 4



[Id] or its reactive derivative at the carboxy group or a salt thereof → [Ie] or its salt

Process 5



[Ib]
or its salt

[Ia]
or its salt

wherein R^1_a is a mercapto-protective group,
R^3_a is tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of esterified carboxy and esterified carboxy(lower)alkyl,
R^3_b is tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of carboxy and carboxy(lower)alkyl,
R^3_c is tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of N-containing heterocycliccarbonyl, N-containing heterocycliccarbonyl(lower)-alkyl, a group of the formula : $-CO-Z-OR^4$, wherein Z is amino acid(s) residue, and R^4 is hydrogen or a carboxy protective group, lower alkyl substituted with a group of the formula : $-CO-Z-OR^4$, wherein Z and R^4 are each as defined above, carbamoyl and carbamoyl(lower)alkyl, carbamoyl of which may be substituted with substituent(s) selected from the group consisting of lower alkyl, cyclo(lower)alkyl, aryl,

ar(lower)alkyl, lower alkoxy(lower)alkyl and a heterocyclic group, and

R^1, R^2, R^3, A, X and Y are each as defined above.

In the above and subsequent descriptions of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The lower moiety in the term "cyclo(lower)alkyl" is intended to mean a group having 3 to 6 carbon atoms.

Suitable lower alkyl moiety in the terms "acyl(lower)alkyl" "esterified carboxy(lower)alkyl", "carboxy(lower)alkyl", "carbamoyl(lower)alkyl", "ar(lower)alkyl", "lower alkoxy(lower)alkyl" and "N-containing heterocycliccarbonyl(lower)alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which preferable one is methyl, ethyl or isopropyl.

Suitable "cyclo(lower)alkyl" may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Suitable "aryl" may be phenyl, naphthyl, phenyl substituted with lower alkyl [e.g. tolyl, mesityl, cumenyl, xylyl, diethylphenyl, diisopropylphenyl, di-tert-butylphenyl, etc.] and the like, in which preferable one is phenyl or tolyl.

Suitable "ar(lower)alkyl" may be benzyl, phenethyl, diphenylmethyl, triphenylmethyl, naphthylmethyl, and the like, in which preferable one is benzyl.

Suitable lower alkoxy moiety in the term "lower alkoxy(lower)alkyl" may be methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy and the like,

in which preferable one is methoxy.

Suitable "lower alkylene" may be a straight or branched one such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene, ethylethylene, or the like, in which preferable one is methylene.

Suitable "lower alkylenedioxy" may be a straight or branched one such as methylenedioxy, ethylenedioxy, trimethylenedioxy, dimethylmethylenedioxy, propylenedioxy, or the like, in which preferable one is methylenedioxy.

Suitable "mercapto-protective group" may be lower alkyl [e.g. tert-butyl, etc.], lower alkoxy(lower)alkyl [e.g. methoxymethyl, isobutoxymethyl, etc.], substituted or unsubstituted ar(lower)alkyl [e.g. benzyl, methoxybenzyl, nitrobenzyl, diphenylmethyl, bis(methoxyphenyl)methyl, triphenylmethyl, etc.], substituted or unsubstituted aryl [e.g. phenyl, dinitrophenyl, etc.], acyl such as lower alkanoyl [e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.], lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.], aroyl [e.g. benzoyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g. benzyloxycarbonyl, methoxybenzyloxycarbonyl, etc.], a group of the formula: $-S-A-\underset{\underset{X-R^2}{|}}{CH}CONH-Y-R^3$, wherein R^2, R^3, A, X and Y are each as defined above, and the like, in which preferable one is lower alkanoyl or aroyl and the most preferable one is acetyl or benzoyl.

Suitable "acyl" and acyl moiety in the term "acyl(lower)alkyl" may include carboxy; esterified carboxy; a group of the formula : $-CO-Z-OR^4$, wherein Z and R^4 are each as defined above; carbamoyl optionally

substituted with substituent(s) selected from the group consisting of lower alkyl, cyclo(lower)alkyl, aryl, ar(lower)alkyl, lower alkoxy(lower)alkyl and a heterocyclic group ; lower alkanoyl; aroyl; a heterocycliccarbonyl; lower alkylsulfonyl; and the like, in which preferable one is carboxy, esterified carboxy, a group of the formula : $-CO-Z-OR^4$, wherein Z and R^4 are each as defined above or carbamoyl optionally substituted with substituent(s) selected from the group consisting of lower alkyl, ar(lower)alkyl and lower alkoxy(lower)alkyl .

The esterified carboxy may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.] and the like, in which preferable one is lower alkoxycarbonyl or ar(lower)alkoxycarbonyl.

The lower alkanoyl may be formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like.

The aroyl may be benzoyl, naphthoyl, benzoyl substituted with lower alkyl [e.g. toluoyl, xyloyl, etc.] and the like.

Suitable "heterocyclic group" and heterocyclic moiety in the term "heterocycliccarbonyl" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

The preferred examples of thus defined "heterocyclic

group" may be unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

saturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) for example, oxazolyl, isoxazolyl, oxadiazolyl, etc.;

saturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzofuranyl, etc.; or the like.

Suitable "amino acid(s) residue" means a bivalent residue derived from amino acid(s), and such amino acid may be neutral amino acid such as glycine, D- or L-alanine, β-alanine, D- or L-valine, D- or L-leucine, D- or L-isoleucine, D- or L-serine, D- or L-threonine, D- or L-cysteine, D- or L-methionine, D- or L-phenylalanine, D- or L-tryptophan, D- or L-tyrosine, D- or L-proline, D- or L-4-hydroxyproline, D- or L-pyroglutamic acid, acidic amino acid such as D- or L-glutamic acid, D- or L-aspartic acid, D- or L-β-aspartic acid, D- or L-glutamine, D- or L-asparagine, and basic amino acid such as D- or L-lysine, D- or L-arginine, D- or L-histidine, D- or L-ornithine, and combination of two of such amino acid, in which preferable one is phenylalanine.

Suitable "carboxy protective group" may include a conventional protective group, which is used in the field of amino acid and peptide chemistry, that may be lower alkyl as mentioned above, aryl (e.g. phenyl, tolyl, naphthyl, etc.), ar(lower)alkyl (e.g. benzyl, phenethyl, etc.), and the like, in which preferable one is tert-butyl.

Suitable "N-containing heterocycliccarbonyl" and N-containing heterocyclic moiety in the term "N-containing heterocycliccarbonyl(lower)alkyl" may be pyrrolidinylcarbonyl, imidazolidinylcarbonyl, piperidinocarbonyl, piperazinylcarbonyl, N-methylpiperazinylcarbonyl or the like.

Preferable compound [I] is one which has hydrogen or

lower alkanoyl for R^1; phenyl optionally substituted with methylenedioxy for R^2; tetrazolyl substituted with carboxy(lower)alkyl or esterified carboxy(lower)alkyl, thiazolyl substituted with carboxy, esterified carboxy, carboxy(lower)alkyl or esterified carboxy(lower)alkyl, or thiadiazolyl substituted with carboxy or esterified carboxy for R^3; methylene for A; methylene for X and a single bond for Y; or hydrogen, lower alkanoyl or aroyl for R^1; phenyl for R^2; tetrazolyl substituted with carbamoyl(lower)alkyl or lower alkylcarbamoyl(lower)alkyl for R^3; methylene for A; methylene for X and a single bond for Y.

More preferable compound [I] is one which has hydrogen for R^1, phenyl for R^2, carboxymethyltetrazolyl, carboxymethylthiazolyl, carboxythiazolyl or carboxythiadiazolyl for R^3, methylene for A, methylene for X and a single bond for Y; or acetyl for R^1, phenyl for R^2, methylcarbamoylmethyltetrazolyl or dimethylcarbamoylmethyltetrazolyl for R^3, methylene for A, methylene for X and a single bond for Y.

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base addition salt [e.g. trimethylamine salt, triethylamine salt, etc.] or the like.

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The compound [I] or its salt can be prepared by reacting a compound [II] or its reactive derivative at the carboxy group or a salt thereof with a compound [III] or

its salt.

Suitable salts of the compound [II] and its reactive derivative at the carboxy group can be referred to the same salt as exemplified for the compound [I].

Suitable salt of the compound [III] may be an acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfoante, etc.] or the like.

Suitable reactive derivative at the carboxy group of the compound [II] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid; etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester,

piperidyl ester, 8-quinolyl thioester, etc.], or an ester with an N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound [II] to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [II] is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; diphenylphosphinic chloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-

chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 2

The compound [Ib] or its salt can be prepared by subjecting a compound [Ia] or its salt to elimination reaction of the mercapto-protective group.

Suitable salts of the compounds [Ia] and [Ib] may be the same as those exemplified for the compound [I].

The reaction is carried out in accordance with a conventional method such as hydrolysis or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate, thereof, ammonia, cysteamine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like. Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.].

The reaction is usually carried out in a solvent such

as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

In this reaction, in case that the compound [Ia] having tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of esterified carboxy and esterified carboxy(lower)alkyl for R^3 is used as a starting compound, the compound [Ib] having tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of carboxy and carboxy(lower)alkyl for R^3 may be obtained according to reaction conditions. This case is also included within the scope of the present reaction.

Process 3

The compound [Id] or its salt can be prepared by subjecting a compound [Ic] or its salt to deesterification reaction.

Suitable salts of the compounds [Ic] and [Id] may be the same as those exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and the reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 2.

In this reaction, in case that the compound [Ic] having acyl for R^1 is used as a starting compound, the compound [Id] having hydrogen for R^1 may be obtained according to reaction conditions. This case is also included within the scope of the present reaction.

Process 4

The compound [Ie] or its salt can be prepared by reacting a compound [Id] or its reactive derivative at the carboxy group or a salt thereof with an amine.

Suitable salts of the compounds [Ie] and [Id] and its reactive derivative at the carboxy group may be the same as those exemplified for the compound [I].

Suitable "amine" may be ammonia, lower alkylamine, cyclo(lower)alkylamine, arylamine, ar(lower)alkylamine, lower alkoxy(lower)alkylamine, amine substituted with a heterocyclic group, an amino acid, an amino acid ester, N-containing heterocyclic compound and the like.

The lower alkylamine may be mono or di(lower)alkylamine such as methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, pentylamine, hexylamine, dimethylamine, diethylamine, dipropylamine, dibutylamine, di-isopropylamine, dipentylamine, dihexylamine or the like, in which preferable one is methylamine or dimethylamine.

The arylamine may be aniline, naphthylamine and the like. The cyclo(lower)alkylamine may be cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclohexylamine and the like, in which preferable one is cyclopropylamine.

The amino acid may be glycine, alanine, β-alanine, phenylalanine, isoleucine, tyrosine and the like, in which preferable one is phenylalanine.

The amino acid ester may be lower alkyl ester of above-mentioned amino acid and the like, in which preferable one is phenylalanine tert-butyl ester.

The ar(lower)alkylamine may be benzylamine, phenylethylamine, phenylpropylamine and the like, in which preferable one is benzylamine.

The lower alkoxy(lower)alkylamine may be methoxymethylamine, methoxyethylamine, ethoxymethylamine, ethoxyethylamine and the like, in which preferable one is

methoxyethylamine.

The amine substituted with a heterocyclic group may be one substituted with a heterocyclic group as afore-mentioned such as aminothiazole, aminothiadiazole, aminotriazole, aminotetrazole or the like.

The N-containing heterocyclic compound may be saturated 5 or 6-membered N-, or N- and S-, or N- and O-containing heterocyclic compound such as pyrrolidine, imidazolidine, piperidine, piperazine, N-(lower)alkylpiperazine [e.g. N-methylpiperazine, N-ethylpiperazine, etc.], morpholine, thiomorpholine or the like.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and the reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

In this reaction, in case that the compound [Id] having acyl for R^1 is used as a starting compound, the compound [Ie] having hydrogen for R^1 may be obtained according to reaction conditions. This case is also included within the scope of the present reaction.

Process 5

The compound [Ia] or its salt can be prepared by subjecting a compound [Ib] or its salt to introduction reaction of the mercapto-protective group.

Suitable salts of the compounds [Ia] and [Ib] may be the same as those exemplified for the compound [I].

Suitable introducing agent of the mercapto-protective group used in this reaction may be alkylating agent, which is capable of introducing the alkyl group as afore-mentioned such as isobutylene, lower alkoxy(lower)alkyl halide [e.g. methoxymethyl chloride, isobutoxymethyl chloride, etc.], substituted or

unsubstituted ar(lower)alkyl halide [e.g. benzyl chloride, methoxybenzyl chloride, nitrobenzyl chloride, etc.] or the like, acylating agent, which is capable of introducing the acyl group as afore-mentioned, such as carboxylic acid, carbonic acid, sulfonic acid, carbamic acid and their reactive derivative, for example, an acid halide, an acid anhydride, an activated amide, an activated ester, isocyanate, and the like. Preferable example of such reactive derivative may include acid chloride, acid bromide, a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, alkyl carbonate (e.g. methyl carbonate, ethyl carbonate, propyl carbonate, etc.), aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, trifluoroacetic acid, etc.), aromatic carboxylic acid (e.g. benzoic acid, etc.), a symmetrical acid anhydride, an activated acid amide with a heterocyclic compound containing imino function such as imidazole, 4-substituted imidazole, dimethylpyrazole, triazole and tetrazole, an activated ester (e.g. p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyridyl ester, piperidinyl ester, 8-quinolyl thioester, or an ester with a N-hydroxy compound such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxybenzotriazole, 1-hydroxy-6-chlorobenzotriazole, etc.), isocyanate, and the like.

This reaction is preferably conducted in the presence of an organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal hydrogen carbonate (e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, 4-N,N-dimethylaminopyridine, etc.), quinoline, and the like.

In case that the acylating agent is used in a free form or its salt in this reaction, the reaction is preferably conducted in the presence of a conventional condensing agent such as a carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.], a ketenimine compound (e.g. N,N'-carbonylbis(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, etc.); an olefinic or acetylenic ether compound (e.g. ethoxyacetylene, β-cyclovinylethyl ether), a sulfonic acid ester of N-hydroxybenzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, etc.] or the like.

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as dioxane, chloroform, dichlormethane,

tetrahydrofuran, pyridine, benzene, N,N-dimethylformamide, etc., and further in case that the base or the introducing agent of the mercapto-protective group is in liquid, it can be used as a solvent.

The reaction temperature is not critical and the reaction can be carried out under cooling to heating.

In this reaction, in case that the compound [Ib] having tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of carboxy and carboxy(lower)alkyl for R^3 is used as a starting compound, the compound [Ia] having tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of esterified carboxy and esterified carboxy(lower)alkyl for R^3 may be obtained according to reaction conditions. This case is also included within the scope of the present reaction.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

The object compound [I] and pharmaceutically acceptable salts thereof which possess an inhibitory activity against NEP, and are useful for the treatment and/or prevention of various cardiovascular disorders such as hypertension, heart failure, angina pectoris or the like, renal insufficiency, cyclic edema, hyperaldosteronism, hypercalciuria and the like in human beings or animals. Additionally, the object compound [I] is expected to be useful as therapeutical and/or

preventive agents for glaucoma, asthma, inflammation, pain, epilepsy, dementia, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome); the modulation of gastric acid secretion and the treatment of hyperreninaemia.

In order to illustrate the usefulness of the object compound [I], the pharmacological data of the compound [I] are shown in the following.

Test :

Neutral endopeptidase (NEP) inhibitory activity

Method :

Purified NEP was used, which was prepared from male Sprague-Dawley rat kidney by the method of J.L. Sonnenberg et al. described in Peptide, Vol. 9, page 173-180 (1988). NEP inhibitory activity was determined as follows.

The incubation mixture (total volume of 262 µl) contained 0.1M Tris buffer (pH 7.4), 0.1 mg/ml α-hANP (α-human ANP), test compound (dissolved in 2 µl N,N-dimethylformamide) and NEP (45-50 U/ml). The reaction mixture was incubated for 15 min. at 37°C and was terminated with the addition of 50 µl 10% acetic acid. Fifty microliters of the reaction mixture was injected into a HPLC and measured the hydrolysis of α-hANP by the reverse phase HPLC using C_{18} column (YMC, ODS-A 200S). A 15 min. linear gradient elution from 0.05% trifluoroacetic acid : 60% CH_3CN (70:30) to 0.05% trifluoroacetic acid : 60% CH_3CN (54:46) was used. NEP inhibitory activity was defined as the inhibition of hydrolysis of α-hANP.

Results :

Test Compound (Example No.)	IC_{50} (M)
3	4.6×10^{-8}
4-2)	6.8×10^{-8}
4-3)	2.2×10^{-8}
7	2.7×10^{-8}
8-1)	2.2×10^{-8}
8-4)	2.0×10^{-8}
8-5)	4.9×10^{-8}
8-6)	2.3×10^{-8}
21	2.8×10^{-8}
22	3.0×10^{-8}

For therapeutic purpose, the compound [I] of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid, semi-solid or liquid excipient suitable for oral, parenteral or external (topical) administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be include in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg,

100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

A mixture of 1H-5-aminotetrazole (7.24 g), tert-butyl 3-bromopropionate (15.07 g) and powdered potassium carbonate (11.76 g) in acetone (100 ml) was stirred for 8.5 hours under refluxing, and filtered. After evaporation of the solvent, the residue was purified by silica gel column chromatography using a mixture of chloroform and methanol (50:1 to 20:1) as an eluent to afford tert-butyl 2-(5-amino-2H-tetrazol-2-yl)propionate (1.56 g).

IR (Film) : 3340, 3240, 1725 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35 (9H, s), 2.86 (2H, t, J=6.3Hz), 4.56 (2H, t, J=6.3Hz), 5.99 (2H, br s)

MASS (m/z) : 214

Preparation 2

The following compound was obtained according to a similar manner to that of Preparation 1.

Ethyl 2-(5-amino-2H-tetrazol-2-yl)propionate

mp : 72-74°C

IR (Nujol) : 3400, 3320, 1740 cm^{-1}

NMR (DMSO-d_6, δ) : 1.17 (3H, t, J=7.1Hz), 1.72 (3H, d, J=7.2Hz), 4.15 (2H, q, J=7.1Hz), 5.68 (1H, q, J=7.2Hz), 6.12 (2H, br s)

MASS (m/z) : 185

Preparation 3

To a mixture of thiophenol (11.02 g) and sodium hydroxide (4.00 g) in ethanol (60 ml) was added dropwise a solution of tert-butyl 2-bromopropionate (20.91 g) in ethanol (21 ml) at 0°C for 10 minutes. The reaction mixture was stirred overnight at ambient temperature and evaporated in vacuo. The residue was partitioned between water and diethyl ether. The organic layer was washed successively with saturated sodium bicarbonate solution, water and brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and n-hexane (1:100 to 1:20) as an eluent to afford tert-butyl 2-phenylthiopropionate (23.00 g).

IR (Film) : 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35 (9H, s), 1.44 (3H, d, J=7.1Hz), 3.73 (1H, q, J=7.1Hz), 7.2-7.6 (5H, m)

MASS (m/z) : 238

Preparation 4

To a solution of tert-butyl 2-phenylthiopropionate (7.15 g) in diethyl ether (100 ml) was added dropwise a solution of m-chloroperbenzoic acid (80%, 6.47 g) in diethyl ether (30 ml) at 0°C for 20 minutes. The reaction mixture was stirred at 0°C for 10 minutes, evaporated in vacuo and diluted with dichloromethane. The solution was washed successively with sodium thiosulfonate solution, saturated sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and n-hexane (1:9) as an eluent to afford tert-butyl 2-phenylsulfinylpropionate (8.13 g).

IR (Film) : 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 and 1.47 (all 3H, each d,

J=7.1Hz), 1.37 and 1.41 (all 9H, each s), 3.42 and 3.71 (all 1H, each q, J=7.1Hz), 7.45-7.7 (5H, m)

MASS (m/z) : 254

Preparation 5

A mixture of tert-butyl 2-phenylsulfinylpropionate (4.34 g), acetic anhydride (2.42 ml) and methanesulfonic acid (0.12 ml) in dibromomethane (107 ml) was stirred for 6 hours under reflux and evaporated in vacuo. The residue was partitioned with water and diethyl ester. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. To the residue was added thioacetic acid (2.43 ml). The reaction mixture was stirred for 2 hours at 60°C and evaporated in vacuo twice with toluene for removal of excess thioacetic acid. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and n-hexane (1:20) as an eluent to afford tert-butyl 3-acetylthio-2-phenylthiopropionate (2.72 g).

IR (Film) : 1720, 1685 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (9H, s), 2.32 (3H, s), 3.14 (1H, dd, J=9.9Hz, 13.6Hz), 3.35 (1H, dd, J=5.5Hz, 13.6Hz), 3.68 (1H, dd, J=5.5Hz, 9.9Hz), 7.25-7.6 (5H, m)

MASS (m/z) : 312, 256, 238, 236

Preparation 6

To a solution of tert-butyl 3-acetylthio-2-phenylthiopropionate (2.19 g) in dichloromethane (22 ml) was added trifluoroacetic acid (5.4 ml) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and at ambient temperature for 2 hours and evaporated in vacuo. The residue was purified by silica gel column chromatography using a mixture of methanol and chloroform

(1:50) as an eluent to afford 3-acetylthio-2-phenylthiopropionic acid (1.13 g).

IR (Film) : 2630, 1700 cm^{-1}

NMR ($CDCl_3$, δ) : 2.35 (3H, s), 3.14 (1H, dd, J=9.8Hz, 13.7Hz), 3.37 (1H, dd, J=5.7Hz, 13.7Hz), 3.76 (1H, dd, J=5.7Hz, 9.8Hz), 7.25-7.6 (5H, m), 9.90 (1H, br s)

MASS (m/z) : 256, 238, 180

Example 1

To a suspension of methyl 5-amino-2H-tetrazol-2-ylacetate (0.94 g) and pyridine (0.58 ml) in dichloromethane (17 ml) was added dropwise a solution of 2-acetylthiomethyl-3-phenylpropionyl chloride (1.69 g) in dichloromethane (2.8 ml) under ice-water cooling. The reaction mixture was stirred at 3.5 to 4.0°C for 1.5 hours and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 5% hydrochloric acid, and the organic layer was washed successively with water, aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel using a mixture of chloroform and methanol (100:1) as an eluent to give an oily product of methyl 5-(2-acetylthiomethyl-3-phenylpropionamido)-2H-tetrazol-2-ylacetate (1.98 g).

IR ($CHCl_3$) : 3420, 3240, 1750, 1720, 1680, 1530 cm^{-1}

NMR ($CDCl_3$, δ) : 2.30 (3H, s), 2.8-3.2 (5H, m), 3.81 (3H, s), 5.40 (2H, s), 7.1-7.3 (5H, m), 9.66 (1H, br s)

MASS (m/z) : 377, 334, 302, 288

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

1) Methyl 5-(2-acetylthiomethyl-3-phenylpropionamido)-1H-tetrazol-1-ylacetate
mp : 100-101°C
IR (Nujol) : 3180, 1750, 1710, 1690 cm^{-1}
NMR ($CDCl_3$, δ) : 2.28 (3H, s), 2.9-3.4 (5H, m), 3.80 (3H, s), 5.24 (2H, s), 7.1-7.3 (5H, m), 11.0 (1H, br s),
MASS (m/z) : 377, 335, 302, 288

2) Ethyl 2-(2-acetylthiomethyl-3-phenylpropionamido)-thiazol-4-ylacetate
IR (Film) : 3250, 1720, 1680, 1650 cm^{-1}
NMR ($CDCl_3$, δ) : 1.24 (3H, t, J=7.1Hz), 2.30 (3H, s), 2.7-3.2 (5H, m), 4.15 (2H, quartet, J=7.1Hz), 6.79 (1H, s), 7.0-7.3 (5H, m), 9.4 (1H, br s)
MASS (m/z) : 406, 363, 330, 317

3) Methyl 2-(2-acetylthiomethyl-3-phenylpropionamido)-thiazol-4-ylcarboxylate
mp : 140-141°C
IR (Nujol) : 3260, 3220, 1715, 1680, 1540 cm^{-1}
NMR ($CDCl_3$, δ) : 2.28 (3H, s), 2.8-3.3 (5H, m), 3.88 (3H, s), 7.0-7.3 (5H, m), 7.86 (1H, s), 10.23 (1H, br s)
MASS (m/z) : 378, 335, 289

4) Methyl 5-[2-acetylthiomethyl-3-(3,4-methylenedioxyphenyl)propionamido]-2H-tetrazol-2-ylacetate
NMR ($CDCl_3$, δ) : 2.30 (3H, s), 2.7-3.2 (5H, m), 3.81 (3H, s), 5.41 (2H, s), 5.88 (2H, s), 6.65 (2H, s), 6.71 (1H, s), 9.74 (1H, br s)

Example 3

To a solution of methyl 5-(2-acetylthiomethyl-3-

phenylpropionamido)-2H-tetrazol-2-ylacetate (1.01 g) in methanol (6.4 ml) was added 1N aqueous sodium hydroxide solution (6.42 ml) and the resulting solution was stirred for 30 minutes under ice-cooling. The reaction mixture was neutralized with 1N hydrochloric acid (6.4 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of toluene, ethyl acetate, and acetic acid (20:2:1) and recrystallized from diisopropyl alcohol to give crystals of 5-(2-mercaptomethyl-3-phenylpropionamido)-2H-tetrazol-2-ylacetic acid (0.63 g).

mp : 173-175°C (dec.)

IR (Nujol) : 3200, 1760, 1690, 1680, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.35 (1H, t, J=8.1Hz), 2.5-3.1 (5H, m), 5.57 (2H, s), 7.1-7.4 (5H, m), 11.22 (1H, s)

MASS (m/z) : 321, 288, 274

Example 4

The following compounds were obtained according to a similar manner to that of Example 3.

1) 5-(2-Mercaptomethyl-3-phenylpropionamido)-1H-tetrazol-1-ylacetic acid

IR ($CHCl_3$) : 3220, 1725, 1570 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35 (1H, t, J=8.1Hz), 2.4-3.0 (5H, m), 5.37 (2H, s), 6.8-7.3 (5H, m), 9.22 (1H, br s), 10.69 (1H, br s)

2) 2-(2-Mercaptomethyl-3-phenylpropionamido)thiazol-4-ylacetic acid

mp : 149-150°C (dec.)

IR (Nujol) : 3180, 2560, 1685, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (1H, t, J=8.1Hz), 2.5-3.1 (5H, m), 3.58 (2H, s), 6.93 (1H, s), 7.1-7.4 (5H, m), 12.27 (2H, br s)
MASS (m/z) : 336, 303, 289

3) 2-(2-Mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid
mp : 202-204°C
IR (Nujol) : 3170, 3140, 1680, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 2.40 (1H, t, J=8.1Hz), 2.6-3.1 (5H, m), 7.1-7.3 (5H, m), 7.96 (1H, s), 12.56 (1H, s), 12.84 (1H, br s)
MASS (m/z) : 322, 289, 275

4) 5-[2-Acetylthiomethyl-3-(3,4-methylenedioxyphenyl)-propionamido]-2H-tetrazol-2-ylacetic acid
mp : 159-161°C
IR (Nujol) : 3220, 1760, 1700, 1570, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 2.33 (1H, t, J=8.1Hz), 2.5-3.1 (5H, m), 5.60 (2H, s), 5.96 (2H, s), 6.66 (1H, dd, J=7.9Hz, 1.5Hz), 6.80 (1H, d, J=7.9Hz), 6.82 (1H, d, J=1.5Hz), 11.21 (1H, s)
MASS (m/z) : 365, 321, 290

Example 5

To a solution of ethyl 5-amino-1,2,4-thiadiazol-3-ylcarboxylate (0.50 g) in a mixture of pyridine (0.49 ml) and dichloromethane (5.0 ml) was added dropwise a solution of 2-acetylthiomethyl-3-phenylpropionyl chloride (0.77 g) in dichloromethane (7.7 ml) at 0°C for 5 minutes. The reaction mixture was stirred at the same temperature for 1 hour, diluted with ethyl acetate and washed successively with 5% aqueous hydrochloric acid, water, saturated sodium bicarbonate solution and brine. The extract was dried over anhydrous magnesium sulfate and evaporated in vacuo.

The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and n-hexane (1:3) as an eluent to afford a colorless oil of ethyl 5-(2-acetylthiomethyl-3-phenylpropionamido)-1,2,4-thiadiazol-3-ylcarboxylate (0.77 g).

IR (Film) : 3200, 1720, 1680, 1530 cm^{-1}

NMR ($CDCl_3$, δ) : 1.44 (3H, t, J=7.1Hz), 2.28 (3H, s), 2.9-3.4 (5H, m), 4.46 (2H, q, J=7.1Hz), 7.0-7.2 (5H, m), 10.95 (1H, br s)

MASS (m/z) : 393, 363, 317, 304

Example 6

The following compounds were obtained according to a similar manner to that of Example 5.

1) Ethyl 5-[2-acetylthiomethyl-3-(3,4-methylenedioxyphenyl)propionamido]-1,2,4-thiadiazol-3-ylcarboxylate

IR (Film) : 3500 (br), 3200 (br), 1700 (br)

NMR ($CDCl_3$, δ) : 1.45 (3H, t, J=7.1Hz), 2.29 (3H, s), 2.8-3.3 (5H, m), 4.48 (2H, q, J=7.1Hz), 5.88 (2H, s), 6.53 (1H, dd, J=1.5Hz, 8.0Hz), 6.55-6.65 (2H, m), 10.94 (1H, br s)

MASS (m/z) : 437 (M^+)

2) Benzyl 5-(2-acetylthiomethyl-3-phenylpropionamido)-2H-tetrazol-2-ylacetate

IR (Film) : 3225, 1750-1660 (br), 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.7-2.85 (1H, m), 2.9-3.1 (4H, m), 5.19 (2H, s), 5.84 (2H, s), 7.15-7.35 (5H, m), 7.39 (5H, br s), 11.28 (1H, br s)

MASS (m/z) : 453, 411

Example 7

To a solution of ethyl 5-(2-acetylthiomethyl-3-

phenylpropionamido)-1,2,4-thiadiazol-3-ylcarboxylate (0.67 g) in methanol (6.8 ml) was added 1N aqueous sodium hydroxide solution (6.8 ml) at 0°C at nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 1 hour and evaporated. The residue was partitioned with water and diethyl ether. The aqueous layer was neutralized with 1N aqueous hydrochloric acid (6.8 ml) to afford white precipitate. The precipitate was recrystallized from 33% aqueous ethanol to afford a white crystal of 5-(2-mercaptomethyl-3-phenylpropionamido)-1,2,4-thiadiazol-3-ylcarboxylic acid (0.28 g).

mp : 188-189°C (dec.)

IR (Nujol) : 3150, 2800-2400, 1710, 1680, 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 2.45-2.6 (1H, m), 2.65-2.85 (2H, m), 2.9-3.05 (2H, m), 3.1-3.3 (1H, m), 7.05-7.35 (5H, m), 13.38 (1H, br s), 13.67 (1H, br s)

MASS (m/z) : 323, 277

Example 8

The following compounds were obtained according to a similar manner to that of Example 7.

1) 5-[2-Mercaptomethyl-3-(3,4-methylenedioxyphenyl)-propionamido]-1,2,4-thiadiazol-3-ylcarboxylic acid

mp : 180-182°C (dec.)

IR (Nujol) : 3150, 2800-2400, 1715, 1680, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 2.45-2.6 (1H, m), 2.65-2.9 (4H, m), 3.0-3.15 (1H, m), 5.96 (2H, s), 6.61 (1H, dd, J=1.5Hz, 8.0Hz), 6.7-6.85 (2H, m), 13.37 (1H, br s), 13.68 (1H, br s)

MASS (m/z) : 323

2) 5-[(S)-2-Mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetic acid

mp : 172-174°C

IR (Nujol) : 3230, 2710, 2600, 2520, 1740, 1690, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (1H, t, J=8.1Hz), 2.4-3.2 (5H, m), 5.60 (1H, s), 7.1-7.4 (5H, m), 11.23 (1H, s), 13.5 (1H, br s)

3) 5-[(R)-2-Mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetic acid

IR (Nujol) : 3200, 1730, 1680, 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (1H, t, J=8.1Hz), 2.5-3.1 (5H, m), 5.60 (2H, s), 7.1-7.4 (5H, m), 11.22 (1H, s), 13.7 (1H, br)

MASS (m/z) : 321, 288, 274

4) 2-{5-[(S)-Mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl}propionic acid

IR (Film) : 3400, 3000-2700, 1710, 1690, 1570, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 1.78 (3H, d, J=7.3Hz), 2.35 (1H, br t), 2.55-3.05 (5H, m), 5.78 (1H, q, J=7.3Hz), 7.1-7.35 (5H, m), 11.22 (1H, br s)

MASS (m/z) : 335

5) 5-(2-Mercaptomethyl-4-methylpentanoylamino)-2H-tetrazol-2-ylacetic acid

mp : 155-157°C

IR (Nujol) : 3265, 3225, 2715, 2600, 2530, 1735, 1685, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, d, J=6.1Hz), 0.91 (3H, d, J=6.1Hz), 1.2-1.4 (1H, m), 1.4-1.7 (2H, m), 2.28 (1H, br t), 2.6-2.9 (3H, m), 5.61 (2H, s), 11.24 (1H, br s), 13.70 (1H, br s)

6) 5-[(S)-2-Mercaptomethyl-3-(2-methylphenyl)-propionamido]-2H-tetrazol-2-ylacetic acid

mp : 180-182°C
IR (Nujol) : 3220, 1730, 1680, 1575, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 2.31 (3H, s), 2.39 (1H, t, J=8.0Hz), 2.5-3.1 (5H, m), 5.59 (2H, s), 7.0-7.2 (4H, m), 11.17 (1H, s), 13.7 (1H, br s)
MASS (m/z) : 335, 302, 288
$[\alpha]_D^{25.6}$: 87.8° (C=0.5, MeOH)

Example 9

1) To a solution of (S)-2-acetylthiomethyl-3-phenylpropionic acid (1 g) in dry dichloromethane (10 ml) was added thionyl chloride (0.92 ml) and N,N-dimethylformamide (1 drop). The reaction mixture was stirred for 2 hours at ambient temperature and evaporated to give (S)-2-acetylthiomethyl-3-phenylpropionyl chloride (1.10 g).

2) To a solution of tert-butyl 5-amino-2H-tetrazol-2-ylacetate (1.13 g) and pyridine (0.55 ml) in dry dichloromethane (15 ml) was added dropwise (S)-2-acetylthiomethyl-3-phenylpropionyl chloride (1.46 g) in dry dichloromethane (5 ml) at 5°C. The reaction mixture was stirred for 30 minutes at 5°C and for 1 hour at ambient temperature. Evaporation of the solvent in vacuo gave a residue, to which was added ethyl acetate. The solution was washed successively with 1N aqueous hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography using a mixture of methanol and chloroform (1:100) as an eluent to afford tert-butyl 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate (1.75 g).

IR (Film) : 3225-3275 (br), 1750 (br), 1685 (br), 1530-1560 cm^{-1}
NMR ($CDCl_3$, δ) : 1.50 (9H, s), 2.33 (3H, s), 2.92-3.20 (5H, m), 5.27 (2H, s), 7.14-7.26 (5H,

m), 8.81 (1H, br s)
MASS (m/z) : 419

Example 10

The following compounds were obtained according to a similar manner to that of Example 9.

1) Benzyl 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate
mp : 96-100°C
IR (Nujol) : 3270, 1745, 1688, 1545, 1415, 1343 cm^{-1}
NMR ($CDCl_3$, δ) : 2.32 (3H, s), 2.92-3.20 (5H, m), 5.23 (2H, s), 5.41 (2H, s), 7.15-7.26 (5H, m), 7.33-7.37 (5H, m), 8.78 (1H, br s)
MASS (m/z) : 453
$[\alpha]_D^{16.4}$: -25.3° (C=0.49, CH_3OH)

2) 5-[(S)-2-Acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate
IR (Nujol) : 3220, 1750, 1690, 1540 cm^{-1}
NMR ($CDCl_3$, δ) : 2.35 (3H, s), 2.8-3.4 (5H, m), 3.81 (3H, s), 5.38 (2H, s), 7.1-7.4 (5H, m), 8.51 (1H, br s)
MASS (m/z) : 377

3) Methyl 5-[(R)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate
IR ($CHCl_3$) : 3230, 1760, 1695, 1550 cm^{-1}
NMR ($CDCl_3$, δ) : 2.31 (3H, s), 2.9-3.3 (5H, m), 3.8 (3H, s), 5.39 (2H, s), 7.1-7.3 (5H, m), 9.31 (1H, br s)
MASS (m/z) : 378, 288

4) tert-Butyl 3-{5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl}propionate

mp : 83-86°C
IR (Nujol) : 3220, 1710, 1690, 1565, 1535 cm^{-1}
NMR ($CDCl_3$, δ) : 1.44 (9H, s), 2.30 (3H, s), 3.02 (2H, t, J=7.2Hz), 2.85-3.2 (5H, m), 4.82 (2H, t, J=7.2Hz), 7.1-7.25 (5H, m), 9.39 (1H, br s)
MASS (m/z) : 434

5) tert-Butyl 5-(3-acetylthio-2-phenylthiopropionamido)-2H-tetrazol-2-ylacetate
mp : 130-133°C
IR (Nujol) : 3280, 3240, 3090, 1745, 1690, 1680, 1565, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 1.48 (9H, s), 2.33 (3H, s), 3.35 (1H, dd, J=8.8Hz, 13.8Hz), 3.45 (1H, dd, J=5.8Hz, 13.8Hz), 3.9-4.1 (1H, m), 5.28 (2H, s), 7.25-7.35 (3H, m), 7.45-7.55 (2H, m), 9.59 (1H, br s)
MASS (m/z) : 438

6) Ethyl 2-{5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl}propionate
mp : 109-113°C
IR (Nujol) : 3220, 3050, 1740, 1715, 1685, 1560, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7.1Hz), 2.01 (3H, d, J=7.4Hz), 2.30 (3H, br s), 2.85-3.2 (5H, m), 4.23 (2H, q, J=7.1Hz), 5.57 (1H, q, J=7.4Hz), 7.05-7.25 (5H, m), 9.67 (1H, br s)
MASS (m/z) : 405

7) Methyl 5-(2-acetylthiomethyl-4-methylpentanoylamino)-2H-tetrazol-2-ylacetate
IR (Film) : 3230, 1750, 1685, 1535 cm^{-1}
NMR ($CDCl_3$, δ) : 0.94 (6H, d, J=6.1Hz), 1.4-1.55 (1H, m), 1.6-1.9 (2H, m), 2.30 (3H, s), 2.8-3.0

(1H, m), 3.08 (1H, dd, J=8.4Hz, 13.5Hz), 3.20 (1H, dd, J=5.6Hz, 13.5Hz), 3.82 (3H, s), 5.44 (2H, s), 10.36 (1H, br s)
MASS (m/z) : 328, 300

8) Methyl 5-[(S)-2-acetylthiomethyl-3-(2-methylphenyl)-propionamido]-2H-tetrazol-2-ylacetate
IR (Nujol) : 3230, 1750, 1680, 1540 cm^{-1}
NMR ($CDCl_3$, δ) : 2.32 (6H, s), 2.8-3.4 (5H, m), 3.81 (3H, s), 5.38 (2H, s), 7.0-7.2 (4H, m), 8.93 (1H, br s)
MASS (m/z) : 392, 391, 316, 302

Example 11

To a solution of tert-butyl 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate (1.74 g) in dichloromethane (18 ml) was added trifluoroacetic acid (3.2 ml) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and at ambient temperature overnight. Removal of the solvent in vacuo gave a residue which was purified by silica gel column chromatography using a mixture of methanol and chloroform (1:50) as an eluent and then triturated with diethyl ether to afford 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetic acid (0.45 g).

mp : 126-130°C
IR (Nujol) : 3225, 1760, 1685-1695, 1565, 1540 cm^{-1}
NMR ($CDCl_3$, δ) : 2.30 (3H, s), 2.76-2.89 (1H, m), 2.95-3.03 (4H, m), 5.60 (2H, s), 7.20-7.33 (5H, m)
MASS (m/z) : 363
$[\alpha]_D^{16.7}$: -25.5° (C=0.51, CH_3OH)

Example 12

The following compounds were obtained according to a

similar manner to that of Example 11.

1) N-{5-[(S)-2-Acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetyl}phenylalanine
mp : 122-126°C (dec.)
IR (Nujol) : 3290, 3220, 2800-2500, 1675, 1560 cm^{-1}
NMR (DMSO-d_6, δ) : 2.29 (3H, s), 2.7-3.2 (8H, m), 4.3-4.45 (1H, m), 5.33 (1H, d, J=17Hz), 5.41 (1H, d, J=17Hz), 7.1-7.3 (10H, m), 8.62 (1H, d, J=7.9Hz), 11.24 (1H, br s)
MASS (m/z) : 434
$[\alpha]_D^{28}$: 14.26° (C=1.15, CH_3OH)

2) 3-{5-[(S)-2-Acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl}propionic acid
IR (Film) : 3400, 1685, 1570 cm^{-1}
NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.7-2.85 (1H, m), 2.9-3.1 (6H, m), 4.76 (2H, t, J=6.5Hz), 7.15-7.35 (5H, m), 11.19 (1H, br s)
MASS (m/z) : 377

3) 5-(3-Acetylthio-2-phenylthiopropionamido)-2H-tetrazol-2-ylacetic acid
IR (KBr) : 3000-2700, 1684, 1585 cm^{-1}
NMR (DMSO-d_6, δ) : 2.34 (3H, s), 3.13 (1H, dd, J=10.5Hz, 13.4Hz), 3.31 (1H, dd, J=4.9Hz, 13.4Hz), 4.05-4.2 (1H, m), 5.31 (2H, s), 7.3-7.5 (5H, m), 11.55 (1H, br s)
MASS (m/z) : 306

Example 13

To a suspension of benzyl 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate (0.5 g) in methanol (2.5 ml) was added dropwise 25% aqueous methylamine (0.68 g) at ambient temperature under nitrogen

atmosphere. The mixture was stirred for 20 minutes and then poured into water (30 ml). The formed precipitate was collected by filtration and purified by column chromatography on silica gel (10 g) using a mixture of chloroform and methanol (20:1) as an eluent. The fractions containing the desired product were collected and concentrated under reduced pressure and the residue was suspended in diethyl ether, and collected by filtration to give 5-[(S)-2-mercaptomethyl-3-phenyl-propionamido]-2H-tetrazol-2-yl-N-methylacetamide (0.12 g).

mp : 195-197°C

IR (Nujol) : 3360, 3220, 1680, 1580, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (1H, t, J=8.3Hz), 2.64-2.98 (8H, m), 5.33 (2H, s), 7.18-7.32 (5H, m), 8.36 (1H, m), 11.2 (1H, s)

MASS (m/z) : 304, 301, 287

$[\alpha]_D^{22.4}$: 69.6° (C=0.49, CH_3OH)

Example 14

To a suspension of benzyl 5-[(S)-2-acetylthio-methyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate (2.27 g) in methanol (9.9 ml) was added 28% aqueous ammonia solution under nitrogen atmosphere. The mixture was stirred for 20 minutes at ambient temperature and then poured into water (50 ml) containing potassium bisulfate (8.17 g). The formed precipitate was collected by filtration, washed with water, and dried under reduced pressure to give 5-[(S)-2-mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetamide (1.60 g).

mp : 174-176°C

IR (Nujol) : 3390, 3260, 3220, 1675, 1608, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (1H, t, J=8.0Hz), 2.5-3.1 (5H, m), 5.32 (2H, s), 7.1-7.4 (5H, m), 7.52 (1H, br s), 7.85 (1H, br s), 11.20 (1H, br s)

MASS (m/z) : 320, 287, 273

$[\alpha]_D^{22.5}$: 73.2 (C=0.50, CH_3OH)

Example 15

To a suspension of benzyl 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetate (1.93 g) in ethanol (7 ml) was added dropwise 28% aqueous ammonia solution (2.87 ml) under a nitrogen atmosphere. The resulting mixture was stirred for 20 minutes at ambient temperature, poured into 5% aqueous sodium bisulfate solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and methanol (10:1) as an eluent to afford 5-[(S)-2-mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetamide (1.04 g).

mp : 172-174°C

IR (Nujol) : 3370, 3250, 3200, 1670, 1605, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (1H, t, J=8.1Hz), 2.5-3.1 (5H, m), 5.33 (2H, s), 7.1-7.4 (5H, m), 7.85 (1H, br s), 8.31 (1H, br s), 11.21 (1H, s)

MASS (m/z) : 320

Example 16

The following compounds were obtained according to a similar manner to that of Example 15.

1) 5-[(S)-2-Mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl-N,N-dimethylacetamide

IR (Nujol) : 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.65 (1H, t, J=8.5Hz), 2.5-2.8 (1H, m), 2.8-3.1 (4H, m), 3.00 (3H, t), 3.10 (3H, s), 5.47 (2H, s), 7.0-7.4 (5H, m), 9.34 (1H, br s)

MASS (m/z) : 348, 301

2) 5-[(S)-2-Mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl-N-(2-methoxyethyl)acetamide
mp : 150-152°C
IR (Nujol) : 3300, 3200, 1675, 1575, 1545 cm^{-1}
NMR (DMSO-d_6, δ) : 2.34 (1H, t, J=7.9Hz), 2.5-3.2 (5H, m), 3.2-3.5 (7H, m), 5.36 (2H, s), 7.1-7.4 (5H, m), 8.56 (1H, br t, J=5Hz), 11.21 (1H, br s)
MASS (m/z) : 378

3) 5-[(S)-2-Mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl-N-benzylacetamide
mp : 129-132°C
IR (Nujol) : 3270, 1675, 1660, 1540 cm^{-1}
NMR ($CDCl_3$, δ) : 1.53 (1H, t, J=8.5Hz), 2.4-2.7 (3H, m), 2.7-3.1 (4H, m), 4.42 (1H, d, J=5.6Hz), 5.41 (2H, s), 7.0-7.4 (10H, m), 9.67 (1H, br s)
MASS (m/z) : 410, 363

Example 17

To a suspension of 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetic acid (0.45 g), methylamine hydrochloride (0.084 g), and 1-hydroxybenzotriazole (0.17 g) in dichloromethane (4.5 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (0.21 g) under ice-water cooling. The mixture was stirred overnight at ambient temperature and then evaporated in vacuo. The residue was diluted with chloroform, washed successively with 5% hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was evaporated in vacuo to give crude powder (0.41 g), which was recrystallized from a mixture of ethanol and diethyl ether to give 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl-N-methylacetamide (0.18 g).

mp : 168-170°C
IR (Nujol) : 3340, 3180, 1670, 1565, 1535 cm^{-1}
NMR ($CDCl_3$, δ) : 2.34 (3H, s), 2.83 (3H, d, J=4.8Hz), 2.9-3.3 (5H, m), 5.30 (2H, s), 6.27 (1H, br), 7.1-7.3 (5H, m), 8.76 (1H, br s)
MASS (m/z) : 376, 287

Example 18

The following compounds were obtained according to a similar manner to that of Example 17.

1) 5-[(S)-2-Acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl-N,N-dimethylacetamide
mp : 145-149°C (dec.)
IR (Nujol) : 3220, 1680, 1655, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 2.31 (3H, s), 2.99 (3H, s), 3.09 (3H, s), 2.83-3.2 (5H, m), 5.46 (2H, s), 7.1-7.3 (5H, m), 9.32 (1H, br s)
MASS (m/z) : 391
$[\alpha]_D^{23}$: -33.30° (C=1.06, $CHCl_3$)

2) 5-[(S)-2-Acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl-N-(2-methoxyethyl)acetamide
mp : 103-105°C
IR (Nujol) : 3290, 3190, 1700, 1670, 1570, 1540 cm^{-1}
NMR ($CDCl_3$, δ) : 2.32 (3H, s), 2.9-3.3 (5H, m), 3.31 (3H, s), 3.4-3.5 (4H, m), 5.32 (2H, s), 6.73 (1H, br s), 7.1-7.4 (5H, m), 9.20 (1H, br s)
MASS (m/z) : 420, 331

3) N-{5-[(S)-2-Acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetyl}phenylalanine tert-butyl ester
IR (Film) : 3320, 1730, 1680, 1535 cm^{-1}
NMR ($CDCl_3$, δ) : 1.39 (9H, s), 2.31 (3H, s), 2.9-3.25 (7H, m), 4.65-4.8 (1H, m), 5.32 (2H,

s), 6.82 (1H, d, J=7.5Hz), 7.05-7.3 (10H, m), 9.19 (1H, br s)

MASS (m/z) : 567

$[\alpha]_D^{23}$: 11.91° (C=0.99, $CHCl_3$)

Example 19

To a suspension of 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetic acid (545 mg), benzylamine (177 mg), and 1-hydroxybenzotriazole (203 mg) in dichloromethane (10 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (316 mg) under ice-cooling. The resulting mixture was stirred for 2 hours at the same temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and 5% hydrochloric acid. The organic layer was washed successively with saturated aqueous sodium bisulfate solution and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of chloroform and methanol (15:1) as an eluent to afford 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl-N-benzylacetamide (502 mg).

mp : 162-163°C

IR (Nujol) : 3280, 1685, 1645, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.7-3.2 (5H, m), 4.34 (2H, d, J=5.8Hz), 5.44 (2H, s), 7.1-7.4 (10H, m), 8.96 (1H, t, J=5.8Hz), 11.25 (1H, s)

MASS (m/z) : 452

$[\alpha]_D^{22}$: -19.8° (C=0.5, DMF)

Example 20

A suspension of 5-[(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetic acid (3.63 g) in 9.4% aqueous ammonia (20 ml) was stirred for 20 minutes at ambient temperature under nitrogen atmosphere to give

clear solution. The solution was poured into water (88.5 ml) containing potassium bisulfate (17.7 g) and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was suspended in ethyl acetate and filtered to give 5-[(S)-2-mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetic acid (2.66 g).

mp : 172-174°C

IR (Nujol) : 3230, 2710, 2600, 2520, 1740, 1690, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (1H, t, J=8.1Hz), 2.4-3.2 (5H, m), 5.60 (1H, s), 7.1-7.4 (5H, m), 11.23 (1H, s), 13.5 (1H, br s)

$[\alpha]_D^{26}$: 69.2° (C=0.5, CH_3OH)

Example 21

To a suspension of 3-[5-(S)-2-acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl}propionic acid (0.57 g) in water (1 ml) was added 28% aqueous ammonia solution (1 ml) at ambient temperature under a nitrogen atmosphere. The reaction mixture was stirred for 10 minutes at ambient temperature, acidified with 10% aqueous potassium bisulfate (30 ml) and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography using a mixture of chloroform and methanol (30:1) to afford 3-{5-[(S)-2-mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-yl]propionic acid (0.32 g).

IR (Film) : 3400, 3000-2500, 1700, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (1H, t, J=8.1Hz), 2.55-3.1 (7H, m), 4.76 (2H, t, J=6.5Hz), 7.1-7.35 (5H, m), 11.15 (1H, br s)

MASS (m/z) : 335

Example 22

The following compound was obtained according to a similar manner to that of Example 21.

5-(3-Mercapto-2-phenylthiopropionamido)-2H-tetrazol-2-ylacetic acid

mp : 196-199°C (dec.)

IR (Nujol) : 3175, 2560, 1760, 1685, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.65-3.0 (2H, m), 3.95-4.25 (1H, m), 5.63 (2H, s), 7.25-7.4 (6H, m), 11.61 (1H, br s), 13.75 (1H, br s)

MASS (m/z) : 306

Example 23

To a suspension of 5-[(S)-2-mercaptomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetamide (0.83 g) and pyridine (0.32 ml) in dichloromethane (15 ml) was added dropwise benzoyl chloride (0.22 ml) under a nitrogen atmosphere at 0-5°C. The resulting mixture was stirred at 0-5°C for an hour, evaporated, and partitioned between ethyl acetate and water. The organic layer was washed successively with 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of chloroform and methanol (10:1) as an eluent. The fractions containing the object compound were collected, concentrated in vacuo, and recrystallized from ethanol to afford 5-[(S)-2-benzoylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetamide (0.84 g).

mp : 180-182°C

IR (Nujol) : 3410, 3260, 1675, 1650, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.7-3.4 (5H, m), 5.32 (2H, s), 7.1-7.4 (5H, m), 7.4-8.0 (7H, m), 11.27 (1H, s)

MASS (m/z) : 424

$[\alpha]_D^{28.0}$: -66.0° (C=0.5, DMF)

Example 24

The following compound was obtained according to a similar manner to that of Example 23.

5-[(S)-2-Acetylthiomethyl-3-phenylpropionamido]-2H-tetrazol-2-ylacetamide

mp : 166-167°C

IR (Nujol) : 3375, 3270, 3210, 1675, 1610, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.6-3.1 (5H, m), 5.33 (2H, s), 7.1-7.4 (5H, m), 7.52 (1H, br s), 7.84 (1H, br s)

MASS (m/z) : 363

Example 25

To a solution of 5-aminomethyl-1H-tetrazole hydrochloride (1.36 g) in dry pyridine (15 ml) was added dropwise a solution of 2-acetylthiomethyl-3-phenylpropionyl chloride (2.57 g) in dry dichloromethane (5 ml) at 0°C for 5 minutes. The reaction mixture was stirred for 4.5 hours at ambient temperature, poured into cold 10% aqueous hydrochloric acid, and extracted with ethyl acetate to give insoluble products. This was triturated with ethanol to give 5-[(2-acetylthiomethyl-3-phenylpropionylaminomethyl]-1H-tetrazole (0.53 g).

mp : 175-176°C (dec.)

IR (Nujol) : 3275, 1690, 1650, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.27 (3H, s), 2.6-3.0 (5H, m), 4.49 (2H, d, J=5.7Hz), 7.05-7.3 (5H, m), 8.74 (1H, br t)

MASS (m/z) : 319

Example 26

To a suspension of 5-[(2-acetylthiomethyl-3-

phenylpropionyl)aminomethyl]-1H-tetrazole (0.18 g) in methanol (3.6 ml) was added cysteamine (0.05 g) at 0°C. The reaction mixture was stirred for 6 hours, stand overnight at ambient temperature, and evaporated in vacuo. The residue was acidified with 10% aqueous hydrochloric acid and the insoluble product was triturated with water to give 5-[(2-mercaptomethyl-3-phenylpropionyl)amino-methyl]-1H-tetrazole (0.07 g).

mp : 157-160°C (dec.)

IR (Nujol) : 3280, 2800-2500, 1690, 1655, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 2.15-2.35 (1H, m), 2.4-3.0 (5H, m), 4.52 (2H, d, J=5.7Hz), 5.95 (2H, s), 6.57 (1H, d, J=9.5Hz), 6.65-6.8 (2H, m), 8.69 (1H, br t)

MASS (m/z) : 321

Example 27

A solution of 5-[(S)-2-mercaptomethyl-3-phenyl-propionamido]-2H-tetrazol-2-ylacetic acid (0.82 g) in dimethyl sulfoxide (45 ml) was stirred overnight at 70°C, cooled to ambient temperature, and thereto was added 1N aqueous sodium hydroxide (6.1 ml). The resulting mixture was washed with ethyl acetate, and the aqueous layer was acidified by 1N hydrochloric acid, extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was triturated with chloroform to afford bis[(S)-(2-carboxymethyl-2H-tetrazol-5-ylcarbamoyl)-3-phenylpropyl] disulfide (0.74 g).

mp : 146°C

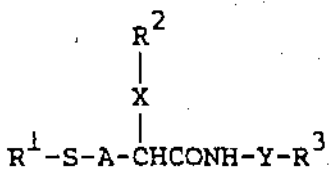
IR (Nujol) : 1750, 1695, 1580, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.5-3.1 (10H, m), 5.57 (4H, s), 7.0-7.4 (10H, m), 11.30 (2H, s)

FAB-MASS (m/z) : 641

CLAIMS

1. A compound of the formula :



[I]

wherein R^1 is hydrogen or a mercapto-protective group,
R^2 is lower alkyl or aryl which may be substituted with lower alkylenedioxy,
R^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which may be substituted with substituent(s) selected from the group consisting of acyl and acyl(lower)alkyl,
A is lower alkylene,
X is lower alkylene or S, and
Y is a single bond or lower alkylene,
provided that when R^3 is tetrazolyl or thiazolyl, then Y is lower alkylene,
and pharmaceutically acceptable salts thereof.

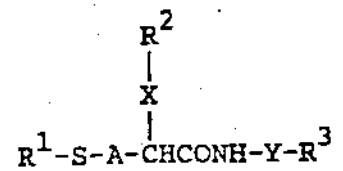
2. A compound according to claim 1,
wherein R^2 is aryl which may be substituted with lower alkylenedioxy,
R^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of acyl and acyl(lower)alkyl,
X is lower alkylene, and

Y is a single bond.

3. A compound according to claim 2, wherein R^1 is hydrogen or lower alkanoyl, R^2 is phenyl optionally substituted with methylenedioxy, R^3 is tetrazolyl substituted with carboxy(lower)alkyl, esterified carboxy(lower)alkyl, carbamoyl(lower)alkyl or lower alkylcarbamoyl(lower)alkyl, thiazolyl substituted with carboxy, esterified carboxy, carboxy(lower)alkyl or esterified carboxy(lower)alkyl, or thiadiazolyl substituted with carboxy or esterified carboxy, A is methylene, and X is methylene.

4. A compound according to claim 3, wherein R^1 is hydrogen or acetyl, R^2 is phenyl, and R^3 is tetrazolyl substituted with carboxymethyl, methylcarbamoylmethyl or dimethylcarbamoylmethyl; carboxymethylthiazolyl; carboxythiazolyl; or carboxythiadiazolyl.

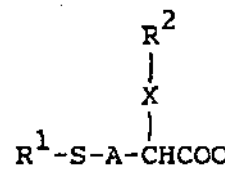
5. A process for preparing a compound of the formula :



[I]

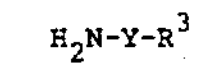
wherein R^1 is hydrogen or a mercapto-protective group,
R^2 is lower alkyl or aryl which may be substituted with lower alkylenedioxy,
R^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which may be substituted with substituent(s) selected from the group consisting of acyl and acyl(lower)alkyl,
A is lower alkylene,
X is lower alkylene or S, and
Y is a single bond or lower alkylene,
provided that when R^3 is tetrazolyl or thiazolyl, then Y is lower alkylene,
or salts thereof, which comprises

a) reacting a compound of the formula :



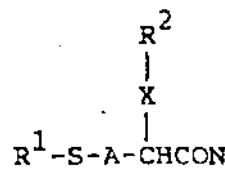
[II]

or its reactive derivative at the carboxy group or a salt thereof with a compound of the formula :



[III]

or its salt to provide a compound of the formula :

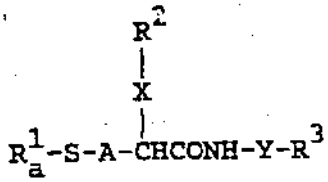


[I]

or its salt, in the above formulas,

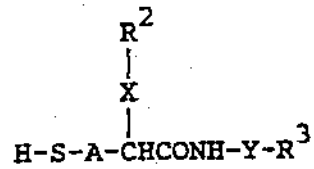
R^1, R^2, R^3, A, X and Y are each as defined above, or

b) subjecting a compound of the formula :



[Ia]

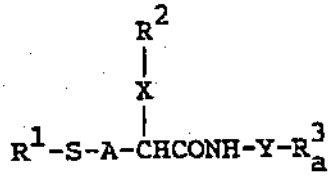
or its salt to elimination reaction of the mercapto-protective group to provide a compound of the formula :



[Ib]

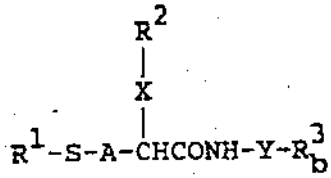
or its salt, in the above formulas,
R^1_a is a mercapto-protective group, and
R^2, R^3, A, X and Y are each as defined above, or

c) subjecting a compound of the formula :



[Ic]

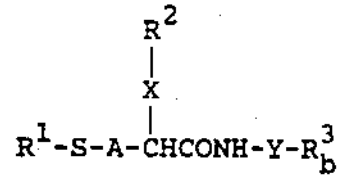
or its salt to deesterification reaction to provide a compound of the formula :



[Id]

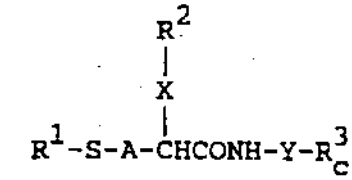
or its salt, in the above formulas,
R_a^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of esterified carboxy and esterified carboxy(lower)alkyl,
R_b^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of carboxy and carboxy(lower)alkyl, and
R^1, R^2, A, X and Y are each as defined above, or

d) reacting a compound of the formula :



[Id]

or its reactive derivative at the carboxy group or a salt thereof with an amine to provide a compound of the formula :



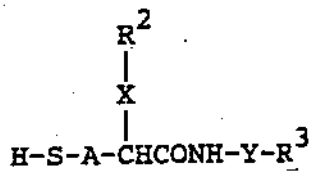
[Ie]

or its salt, in the above formulas,
R_c^3 is tetrazolyl, thiazolyl or thiadiazolyl, each of which is substituted with substituent(s) selected from the group consisting of N-containing heterocycliccarbonyl, N-containing heterocycliccarbonyl(lower)alkyl, a group of the formula : $-CO-Z-OR^4$, wherein Z is amino acid(s) residue, and R^4 is hydrogen or a

carboxy protective group, lower alkyl substituted with a group of the formula : $-CO-Z-OR^4$, wherein Z and R^4 are each as defined above, carbamoyl and carbamoyl(lower)-alkyl, carbamoyl of which may be substituted with substituent(s) selected from the group consisting of lower alkyl, cyclo(lower)alkyl, aryl, ar(lower)alkyl, lower alkoxy(lower)alkyl and a heterocyclic group, and

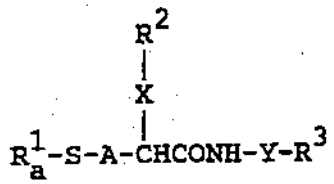
R^1, R^2, R^3_b, A, X and Y are each as defined above, or

e) subjecting a compound of the formula :



[Ib]

or its salt to introduction reaction of the mercapto-protective group to provide a compound of the formula :



[Ia]

or its salt, in the above formulas, R^1_a, R^2, R^3, A, X and Y are each as defined above.

6. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A compound of claim 1 for use as a medicament.

8. A method of the therapeutic treatment and/or prevention of various cardiovascular disorders, renal insufficiency, cyclic edema, hyperaldosterronism or hypercalciuria which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

9. Use of a compound of claim 1 for the manufacture of a medicament for therapeutic treatment and/or prevention of various cardiovascular disorders, renal insufficiency, cyclic edema, hyperaldosteronism or hypercalciuria in human beings or animals.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 92/01406

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D257/06; C07D257/04; C07D285/08; C07D277/46
C07D405/12; C07D417/12; C07D277/56; A61K31/41

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 232 820 (BOEHRINGER) 19 August 1987 *Complete specification*	1-9
A	EP,A,0 115 997 (ROUSSEL-UCLAF) 15 August 1984 cited in the application *Page 11-15: examples 33,34,47* *Complete specification* *Page14-15: examples 33,34,47*	1-9

* Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 JANUARY 1993	18. 02. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LUYTEN H.W.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 92/01406

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark:Although claims 8 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. JP 9201406
SA 66407

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0232820	19-08-87	DE-A- 3604050	13-08-87
		DE-A- 3775785	20-02-92
		JP-A- 62215560	22-09-87
		US-A- 4906666	06-03-90
		US-A- 5025028	18-06-91
EP-A-0115997	15-08-84	FR-A- 2540495	10-08-84
		AU-B- 568628	07-01-88
		AU-A- 2420184	16-08-84
		CA-A- 1244029	01-11-88
		JP-A- 59148759	25-08-84
		US-A- 5098934	24-03-92

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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A61K 31/215

A1

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(71) Applicant *(for all designated States except US)*: SCHERING-PLOUGH S.P.A. [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MONOPOLI, Angela [IT/IT]; ONGINI, Ennio [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, SD, SU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: USE OF NEUTRAL ENDOPEPTIDASE INHIBITORS IN THE TREATMENT OF LEFT VENTRICULAR HYPERTROPHY

(57) Abstract

Treatment and prevention of left ventricular hypertrophy with neutral endopeptidases such as N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine and N-[2-mercaptomethyl-3-(2-methylphenyl)-propioyl]-methionine are disclosed.

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USE OF NEUTRAL ENDOPEPTIDASE INHIBITORS IN THE TREATMENT OF LEFT VENTRICULAR HYPERTROPHY

The present invention relates to the treatment and prevention of left ventricular hypertrophy (LVH) by administration of a neutral endopeptidase (NEP) inhibitor.

LVH, characterized by an increase in cardiac mass and growth of abnormal fibrous tissue which compromise cardiac function, is a condition which often occurs in conjunction with high blood pressure associated with essential hypertension. LVH is a primary risk factor associated with heart failure and therefore increases the risk of cardiovascular morbidity and mortality.

Usually, LVH is detected after high blood pressure is diagnosed, although recent reports indicate that LVH may be present before high blood pressure develops, or may be aggravated by a second condition such as atherosclerosis or diabetes mellitus. LVH is diagnosed by several methods, including electrocardiography, wherein enhanced voltage is detected, by chest X-rays, or preferably by echocardiography, which detects increased myocardial wall thickness and mass. The existing therapy for LVH associated with essential hypertension consists of control of arterial blood pressure, for example by administering one or more of a variety of drugs: diuretics such as diazoxide or hydrochlorthiazide; hypotensives such as methyldopa or hydralazine; beta-adrenergic blockers such as propranolol or labetalol; calcium antagonists such as diltiazem or nifedepine; or angiotensin converting enzyme (ACE) inhibitors such as captopril, spirapril or cilazapril. ACE inhibitors and calcium antagonists are known to reduce the mass of the hypertrophied left ventricle, however, many other drugs

routinely prescribed to treat essential hypertension, e.g. diuretics and hydralazine, either have no effect on LVH or take a long time to treat it.

NEP (EC 3.4.24.11; enkephalinase; atriopeptidase) is a zinc-containing metalloprotease which cleaves a variety of peptide substrates on the amino terminal side of aromatic amino acids. See Biochem. J., 241 (1987) p. 237-247. Substrates for this enzyme include, but are not limited to, ANP, brain natriuretic peptide, met and leu enkephalin, bradykinin, neurokinin A, and substance P. It has been previously demonstrated that inhibitors of NEP potentiate the hypotensive, diuretic, natriuretic and plasma ANP responses to pharmacological injection of ANP in experimental animals. The potentiation of ANP and the consequent use of NEP inhibitors in general to treat volume-dependent hypertension but not angiotensin II-induced hypertension was disclosed in U.S. patent 4,749,688.

We have surprisingly found that NEP inhibitors, in particular N-[2-acetylthiomethyl-3-(2-methylphenyl)-propionyl]-methionine ethyl ester and N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine, reduce LVH without having an effect on high blood pressure resulting from essential hypertension. Therefore, NEP inhibitors can be used to treat LVH when essential hypertension is not present or is not severe enough to require drug therapy. NEP inhibitors can be used in conjunction with antihypertensive drugs which do not themselves treat LVH, or NEP inhibitors can be used in combination with drugs which do treat LVH in order to provide an enhanced effect.

Another aspect of the invention relates to pharmaceutical compositions comprising a combination of an NEP inhibitor and an antihypertensive agent effective to treat or prevent LVH in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

The NEP inhibitors suitable for use in this invention include carboxyalkyl dipeptides disclosed in U.S. patent 4,610,816, herein incorporated by reference, having the formula

$R_1{}^aCH(COR_2)$-NH-$CHR_3{}^a$-$CONH(CH_2)_p{}^a$-$C(R_4{}^aR_5{}^a)$-$COR_6{}^a$

wherein preferred compounds are N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine and N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-β-alanine;

mercaptoacyl amino acids disclosed in U.S. patent 4,801,609, herein incorporated by reference, having the formulae

$$Q^bS\text{-}CH_2\text{-}CH(\text{-}(CH_2)_n{}^b\text{-}R^{1b})\text{-}C(O)\text{-}NH\text{-}CH(R^{2b})\text{-}C(O)\text{-}R^{3b} \quad \text{Ib}$$

$$Q^bS\text{-}CH_2\text{-}CH(\text{-}(CH_2)_n{}^b\text{-}R^{1ab})\text{-}C(O)\text{-}NH\text{-}CH(R^{2ab})\text{-}C(O)\text{-}R^{3b} \quad \text{IIb}$$

$$Q^bS\text{-}CH_2\text{-}CH(\text{-}(CH_2)_n{}^b\text{-}R^{1ab})\text{-}C(O)\text{-}NH\text{-}CH(R^{2b})\text{-}C(O)\text{-}R^{3ab} \quad \text{IIIb}$$

mercaptoacyl amino acids disclosed in U.S. patent 4,929,641, herein incorporated by reference, having the formula

$$Q^cS\text{-}CH_2\text{-}CH(\text{-}(CH_2)_n{}^c\text{-}R^{1c})\text{-}C(O)\text{-}NH\text{-}CH(R^{2c})\text{-}C(O)\text{-}R^{3c}$$

wherein preferred compounds are N-[2-acetylthiomethyl-3-(2-methylphenyl)propionyl]-methionine ethyl ester and N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine;

mercaptoacyl amino acids disclosed in PCT/US90/01787, herein incorporated by reference, having the formula

$$Q^dS\text{-}CH_2\text{-}CH(\text{-}(CH_2)_n{}^d\text{-}R^{1d})\text{-}C(O)\text{-}NH\text{-}CH(R^{2d})\text{-}CH(R^{4d})\text{-}(CH_2)_t{}^d\text{-}(CHR^{9d})_p{}^d\text{-}C(O)\text{-}R^{3d}$$

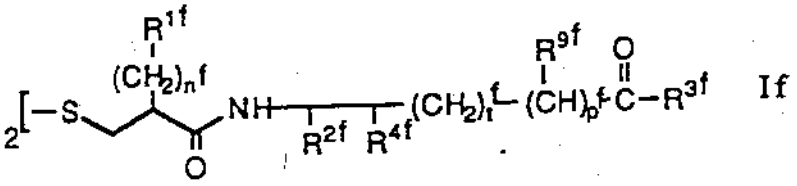
wherein preferred compounds are N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine and N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-β-alanine;

carboxyalkyl dipeptides disclosed in U.S. Serial No. 07/421,041 and corresponding PCT/US90/05640, incorporated herein by reference, having the formula

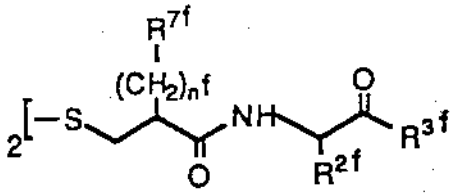
$$R^{1e}O\text{-}C(O)\text{-}CH(R^{2e})\text{-}NH\text{-}C(R^{3e}R^{4e})\text{-}C(O)\text{-}NH\text{-}(CHR^{5e})_m{}^e\text{-}(CH_2)_n{}^e\text{-}CH(R^{6e})\text{-}C(O)\text{-}R^{7e}$$

wherein preferred compounds are N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine and N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine;

disulfide derivatives of mercaptoacyl amino acids disclosed in U.S. Serial No. 07/525,370, incorporated herein by reference, having the formulae



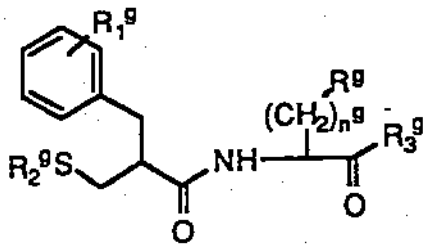
If



IIf

wherein preferred compounds are 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine and 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine;

mercaptoacyl amino acids disclosed in PCT publication WO90/02117, herein incorporated by reference, having the formula



wherein a preferred compound is N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine;

mercaptoacyl amino acids disclosed in U.S. patent 4,879,309, incorporated herein by reference, having the formula

$R_1{}^hS\text{-}CH_2\text{-}CH(\text{-}(CH_2)_n{}^h\text{-}R_2{}^h)\text{-}C(O)\text{-}NR_4{}^h\text{-}A^h\text{-}C(O)\text{-}R_3{}^h$

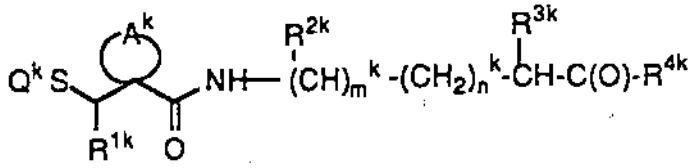
wherein preferred compounds are N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid and N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;

carboxyalkylcarbonyl amino acids disclosed in U.S. Serial No. 07/439,765 and corresponding PCT/US90/06655, herein incorporated by reference, having the formula

$R^{1i}O\text{-}C(O)\text{-}CH(R^{2i})\text{-}CH_2\text{-}C(R^{3i}R^{4i})\text{-}C(O)\text{-}NH\text{-}(CHR^{5i})_m{}^i\text{-}(CH_2)_n{}^i\text{-}CH(R^{6i})\text{-}C(O)\text{-}R^{7i}$

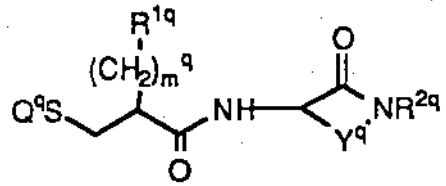
wherein a preferred compound is N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine;

mercaptocycloalkyl amino acids disclosed in U.S. Serial No. 07/455,204 and corresponding PCT/US90/07353, incorporated herein by reference, having the formula



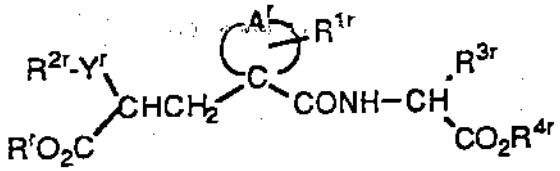
wherein a preferred compound is N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester;

mercaptoacyl aminolactams disclosed in U.S. Serial No. 07/491,148 and corresponding PCT/US91/01420, incorporated herein by reference, having the formula

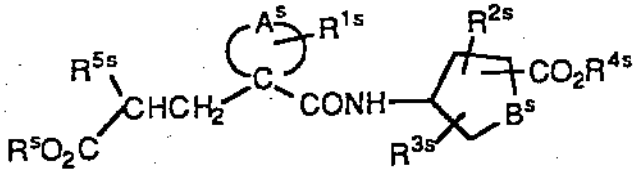


wherein a preferred compound is 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino-ε–caprolactam;

glutaryl amino acids disclosed in U.S. 4,975,444, herein incorporated by reference, having the formula



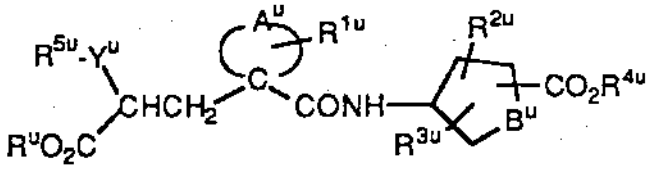
glutaryl amino acids disclosed in European Patent Application 274,234, having the formula



wherein A^s completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;
B^s is $(CH_2)_{m^s}$ wherein m^s is an integer of from 1 to 3;
each of R^s and R^{4s} is independently H, alkyl, benzyl or an alternative biolabile ester-forming group;
R^{1s} is H or alkyl;
R^{2s} and R^{3s} are each independently H, OH, alkyl or alkoxy;
and R^{5s} is alkyl, alkenyl, alkynyl, arylalkynyl, cycloalkyl, cycloalkenyl, alkoxy, $-NR^{6s}R^{7s}$, $-NR^{8s}COR^{9s}$, $-NR^{8s}SO_2R^{9s}$ or a saturated heterocyclic group;
or alkyl substituted by one or more substituents chosen from halo, hydroxy, alkoxy, hydroxyalkoxy, alkoxyalkoxy, cycloalkyl, cycloalkenyl, aryl, aryloxy, arlyoxyalkoxy, heterocyclyloxy, $-NR^{6s}R^{7s}$, $-NR^{8s}COR^{9s}$, $-NR^{8s}SO_2R^{9s}$, $-CONR^{6s}R^{7s}$, -SH, $-S(O)_p{}^sR^{10s}$, $-COR^{11s}$ or $-CO_2R^{12s}$;
wherein R^{6s} and R^{7s} are each independently H, alkyl, cycloalkyl (optionally substituted by hydroxy or alkoxy), aryl, arylalkyl, alkoxyalkyl or heterocyclyl; or the two groups R^{6s} and R^{7s} are taken together with

the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-alkyl-piperazinyl group;
R^{8s} is H or alkyl;
R^{9s} is alkyl, CF_3, aryl, aryl, alkyl, arylalkoxy, heterocyclyl, alkoxy or $-NR^{6s}R^{7s}$ wherein R^{6s} and R^{7s} are as previously defined;
R^{10s} is alkyl, aryl, heterocyclyl, or $-NR^{6s}R^{7s}$ wherein R^{6s} and R^{7s} are as previously defined;
R^{11s} is alkyl, cycloalkyl, aryl or heterocyclyl;
R^{12s} is H or alkyl;
and p^s is 0,1 or 2;
and pharmaceutically acceptable salts thereof and bioprecursors therefor; and

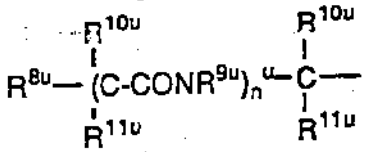
glutaryl amino acids disclosed in European Patent Application 343,911, having the formula



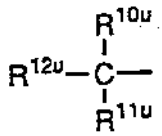
wherein A^u completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;
B^u is $(CH_2)_{m^u}$ wherein m^s is an integer of from 1 to 3;
each of R^u and R^{4u} is independently H, alkyl, benzyl or an alternative biolabile ester-forming group;
R^{1u} is H or alkyl;
R^{2u} and R^{3u} are each independently H, OH, alkyl or alkoxy, or R^{2u} and R^{3u} are linked together and are $(CH_2)_{r^u}$ wherein r^u is an integer from 1 to 4;
Y^u is an optional alkylene group of from 1 to 6 carbon atoms which may be straight or branched-chain;

and R^{5u} is $R^{6u}CONR^{9u}$-, $R^{6u}SO_2NR^{9u}$-, $R^{6u}CO_2$-, $R^{6u}CO$-, $R^{6u}SO_q{}^u$-, $R^{7u}NR^{9u}SO_2$-, or $R^{7u}OCO$-;

wherein R^{6u} is a group of the formula



R^{7u} is a group of the formula



and R^{9u} is H, alkyl, aryl, cycloalkyl, heterocyclyl, arylalkyl, or hererocyclylalkyl;

wherein R^{8u} is $R^{9u}CONR^{9u}$-, $R^{9u}SO_2NR^{9u}$-, $R^{13u}R^{14u}N$-$(CH_2)_p{}^u$-, or $R^{9u}O$-, wherein each R^{9u} is as previously defined;

R^{10u} and R^{11u} are each independently H or alkyl; or R^{10u} is H and R^{11u} is alkyl which is substituted by OH, SH, SCH_3, NH_2, arylalkyl-OCONH-, NH_2CO-, CO_2H, guanidino, aryl or heterocyclyl; or the two groups R^{10u} and R^{11u} are joined together to form, with the carbon atom to which they are attached, a 5 or 6 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be substituted by alkyl or fused to a further 5 or 6 membered saturated or unsaturated carbocyclic ring;

or R^{10u} is H, n^u is 0 and R^{8u} and R^{11u} are linked to form a 2-(N-COR^{9u}-4-aminopyrrolidinyl) group;

R^{12u} is $R^{13u}R^{14u}NCO$-, $R^{9u}OCH_2$- or heterocyclyl, wherein R^{9u} is as previously defined;

R^{13u} and R^{14u} are each independently H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl; or the two groups R^{13u} and R^{14u} are taken together to form, with the nitrogen to which they are attached, a pyrrolidinyl, piperidino, morpholino, piperazinyl, N-alkylpiperazinyl, pyrrolyl, imidazolyl, pyrazolyl or triazolyl group;

n^u is 0 or 1;

p^u is 0 or an integer of from 1 to 6;

and q^u is 0, 1 or 2;
and pharmaceutically acceptable salts thereof and bioprecursors therefor.

The above descriptions of NEP inhibitors suitable for use in the present invention were taken from the noted patents or applications. Reference should be made to such patents and applications for their full disclosures of such classes and specific compounds within those classes, and as to any typographical errors or the like which may have occurred in transcription. Also, in describing such suitable NEP inhibitors, the superscript letters a-i, k, q-s and u were included to distinguish among the various classes of compounds and the variable substituent groups thereof.

Other suitable NEP inhibitors include SQ 28603 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine), disclosed in South African Patent Application 84/0670; UK 69578 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid) and its active enantiomer(s); thiorphan and its enantiomers; retro-thiorphan; phosphoramidon; and SQ 29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]-heptanoic acid). Also suitable for use are any pro-drug forms of the above-listed NEP inhibitors, e.g., compounds in which one or more carboxylic acid groups are esterified.

Of the above NEP inhibitors, most preferred are N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, especially the S,S isomer thereof, and N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine.

When NEP inhibitors are administered in combination with other antihypertensive agents, preferred antihypertensives are ACE inhibitors and calcium antagonists. Preferred ACE inhibitors are spirapril, enalapril, ramipril, perindopril, indolapril, lysinopril, quinapril, pentopril, cilazapril, captopril, zofenopril, pivalopril and fosinopril. Preferred calcium antagonists are diltiazem, nifedipine, verapamil, nicardipine and nimodipine..

The effectiveness of NEP inhibitors in treating LVH in an animal model can be demonstrated according to the following procedures for measuring the change in heart weight and the degree of fibrosis:

Animals and treatment regimen:

Adult (16-week-old) male spontaneously hypertensive rats (SHRs) supplied by Charles River (Calco, Italy) are used. They are housed in individual cages for one week before starting the experiment, with free access to food and water. The animals are selected for stable baseline arterial pressure and assigned randomly to four groups of 12 each (first experiment). The NEP inhibitor is administered for 4 weeks at 3,10, 30, or 100 mg/kg orally twice daily (at 9:00 a.m. and 4:00 p.m.), with carboxymethylcellulose (CMC 0.5%) used as vehicle and as a control.

A second experiment involves administering an NEP inhibitor at 100 mg/kg or the vehicle as a control to two groups of SHRs twice a day for 4 weeks . Water intake, urine volume and sodium excretion are monitored by placing the rats in metabolic cages over a 16-hour period from the last daily administration of the drug to the first dosage of the following day.

In each experiment, additional animals were treated with spirapril at 1 mg/kg as a positive control.

Blood pressure and heart rate measurement:

Systolic blood pressure (SBP) and heart rate are measured in conscious animals by the tail-cuff method using a pulse detector (IITC Instruments, Woodland Hills, CA, USA) connected to a computer (Basis Trade, Verona, Italy). Animals are maintained at a temperature of 26 ± 1°C during blood pressure recording sessions and before starting the experiment, the animals undergo a week of training to stay in restraining holders. Recordings are taken once before treatment and at weekly intervals within 3 hours after the morning dose. Heart rate (HR) is determined from blood pressure tracings.

Measurement of Ventricular Hypertrophy:

At the end of the experimental period, SHRs of the first set of experiments are sacrificed by cervical dislocation, the hearts are rapidly excised, fixed in formalin 4% and the weights of the right ventricle and left ventricle inclusive of the septum are recorded.

In the second set of experiments, SHRs are anesthetized with fentanyl citrate (50µg/kg) and droperidol (250 µg/kg; Leptofen, Farmitalia Carlo Erba, Milan, Italy) and the hearts fixed by perfusion as follows. The abdominal aorta below the renal arteries is cannulated with a catheter (PE 200) filled with phosphate buffer (0.2 M, pH 7.4) and heparin (100 IU/ml), the catheter is connected to a perfusion apparatus, and perfusion is adjusted to diastolic arterial pressure measured in vivo. The heart is then arrested in diastole by an intravenous injection of 1 ml of KCl (1 meq/ml) through the jugular vein, the thorax is opened and the vena cava is cut to allow drainage of blood and perfusate. The coronary vasculature is then perfused with a glutaraldehyde-formaldehyde mixture diluted 1:1 with phosphate buffer. The heart is excised, the inner longitudinal diameter measured, and the right and left ventricle inclusive of the septum dissected from the atria and their weights recorded separately.

The left ventricle is transversely cut into 10-12 rings perpendicular to the longitudinal axis of the heart. The thickness of the left ventricular free wall and septum and the transverse luminal diameter of the ventricular chamber are measured in the intermediate slice with a stereomicroscope at a calibrated magnification of 16X, having an ocular micrometer accurate to 0.01 mm. Five to ten equally spaced measurements of the free wall and four to six of the septum are collected and their values averaged. The minimal and maximal transverse chamber diameters are measured and their geometric mean computed. The longitudinal and transverse diameters are used to compute chamber volume. The apical slice of each left ventricle is used for dry weight determinations.

Light microscopic morphometry of the left ventricle - amount of replacement fibrosis:

The four middle slices of the free wall of each ventricle are radially cut to obtain 28-30 tissue blocks extending from the endocardium to the epicardium. The specimens were postfixed in OsO_4 (1%) dehydrated in acetone and infiltrated and embedded in a fixative agent, e.g. an epoxy resin such as Araldite (Ciba Geigy). From each block, 1µm thick sections were obtained and stained with methylene blue and safranin for the morphometric evaluation of foci of replacement fibrosis. Ten consecutive fields from each endocardium, midmyocardium and epicardium in each animal are examined at a calibrated magnification of 250X with a reticle containing 42 sampling points. This reticle defines an uncompressed tissue area of 144,000 μm^2, which is used to determine the number of lesions represented by foci of fibrosis per unit area of myocardium. The number of points overlying these foci is also counted to compute the volume fraction of fibrosis in the myocardium and the average cross sectional area of the foci profiles.

Results of tests run according to the above procedures using N-[2(S)-acetylthiomethyl-3-(2-methylphenyl)propionyl]-(S)-methionine ethyl ester (Compound A) at 3 and 30 mg/kg, N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine (Compound B) at 10 and 100 mg/kg and spirapril (SPIR) (1mg/kg) are as follows (Data are expressed as means ± standard error, and analysis of variance and appropriate comparisons for each parameter were used as statistical tests. Differences were considered significant at $p< 0.05$).

Baseline blood pressure ranged from 189±4 to 197±2 mmHg. 4 weeks of treatment with either Compound A or Compound B did not significantly affect arterial pressure, even at the highest dose level tested: 189±4 mmHg before, 195±4 mmHg after 4 weeks of a 30 mg/kg dose of Compound A; 196±4 mmHg before, 190±6 mmHg after 4 weeks of a 100 mg/kg dose of Compound B. The SPIR group showed a significant reduction in systolic pressure during the treatment period:

197±2 mmHg before, 181±3 mmHg after 4 weeks of a 1 mg/kg dose of SPIR ($p< 0.05$). In all groups tested, heart rates were not significantly different from those observed in the vehicle controls.

Both Compound A and Compound B significantly reduced left ventricular weight at the highest dose level compared to the vehicle control: compared to a control weight of 1036.7± 11.2 mg, the 30 mg/kg dose level of Compound A reduced the left ventricular weight to 969.8±11.9 mg ($p< 0.01$), while the 100 mg/kg dose level of Compound B reduced the left ventricular weight to 983.5±11.3 mg ($p< 0.05$). SPIR at 1 mg/kg reduced the left ventricular weight to 948.5±11.5 ($p< 0.01$). The body weight gain was similar in all groups, indicating that the treatments did not affect SHR growth.

The extent of structural damage in the left ventricle, evaluated by morphometric analysis as the amount of fibrotic tissue, was significantly reduced by treatment with Compound B: the volume fraction of replacement connective tissue was decreased by 42% in the rats treated with Compound B compared with the vehicle control ($p< 0.01$).

A variety of pharmaceutical dosage forms are suitable for NEP administration, preferably for oral or parenteral administration, although mechanical delivery systems such as transdermal dosage forms are also contemplated.

The typical daily dosage of the NEP inhibitor for treatment or prevention of LVH is about 0.3 mg/kg to about 100 mg/kg of mammalian weight per day administered in single or divided doses. The exact dose of any NEP inhibitor to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Generally, in treating humans suffering from LVH or in preventing LVH, the NEP inhibitors of this invention can be administered in dosage ranges of about 10 to about 1000 mg NEP inhibitor per dose given 1 to 4 times a day.

Typical oral formulations for drugs used in this invention include tablets, capsules, syrups, elixirs and suspensions. Typical

injectable formulations for drugs used in this invention include solutions and suspensions.

Where NEP inhibitors are administered in combination with other antihypertensive agents, including ACE inhibitors, calcium antagonists, diuretics and beta-adrenergic blockers, the combinations can be administered from a single pharmaceutical composition which combines the actives in a pharmaceutically acceptable carrier, or the drugs may be administered separately. That is, a patient can undergo parallel courses of treatment with the two different actives; simultaneous administration of dosage forms is not required. Since the methods of this invention relating to the combinations comprise administering two different drugs, any suitable combination of dosage forms can be used, e.g. oral NEP inhibitor / oral antihypertensive agent or injectable NEP inhibitor / oral antihypertensive agent.

Since the present invention relates to methods of treating or preventing LVH with a combination of active ingredients, i.e. an NEP inhibitor and an antihypertensive agent, wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit which combines two separate units, an NEP pharmaceutical composition and an antihypertensive composition (particularly an ACE inhibitor or a calcium antagonist composition), in one package is contemplated. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

CLAIMS

1. A method of treating left ventricular hypertrophy comprising administering an effective amount of a neutral endopeptidase inhibitor to a mammal in need of such treatment.

2. A method of claim 1 wherein the neutral endopeptidase inhibitor is selected from the group consisting of:

N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine;

N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-β-alanine;

N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester;

N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine;

N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine;

N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-β-alanine;

N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentyl-carbonyl]-(S)-isoserine;

N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine;

1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine;

1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine;

N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methyl-mercapto)methionine;

N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;

N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;

N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine;

N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester;

3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino-ε-caprolactam;

SQ 28603; UK 69578; thiorphan; retro-thiorphan; phosphoramidon; and SQ 29072; or a pharmaceutically acceptable ester thereof.

3. A method of claim 1 wherein the neutral endopeptidase inhibitor is N-[2-acetylthiomethyl-3-(2-methylphenyl)-propionyl]-methionine ethyl ester or N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine.

4. A method of preventing left ventricular hypertrophy comprising administering an effective amount of a neutral endopeptidase inhibitor to said mammal in need of such treatment.

5. A method of claim 4 wherein the neutral endopeptidase inhibitor is selected from the group consisting of

N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine;

N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-β-alanine;

N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester;

N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine;

N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine;

N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-β-alanine;

N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentyl-carbonyl]-(S)-isoserine;

N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine;

1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine;

1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine;

N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methyl-mercapto)methionine;

N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;

N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;

N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine;

N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester;

3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino-ε-caprolactam;

SQ 28603; UK 69578; thiorphan; retro-thiorphan; phosphoramidon; and SQ 29072; or a pharmaceutically acceptable ester thereof.

6. A method of claim 4 wherein the neutral endopeptidase inhibitor is N-[2-acetylthiomethyl-3-(2-methylphenyl)-propionyl]-methionine ethyl ester or N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine.

7. A method of treating or preventing left ventricular hypertrophy comprising administering to a mammal in need of such treatment an effective amount of a combination of an neutral endopeptidase inhibitor and an antihypertensive agent.

8. A method of claim 7 wherein the antihypertensive agent is an angiotensin converting enzyme inhibitor or a calcium channel blocker.

9. A method of claim 8 wherein the neutral endopeptidase inhibitor is selected from the group consisting of

N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine;

N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-β-alanine;
N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester;
N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine;
N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine;
N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-β-alanine;
N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentyl-carbonyl]-(S)-isoserine;
N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine;
1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine;
1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine;
N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methyl-mercapto)methionine;
N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;
N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;
N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine;
N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester;
3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino-ε-caprolactam;
SQ 28603; UK 69578; thiorphan; retro-thiorphan; phosphoramidon; and SQ 29072; or a pharmaceutically acceptable ester thereof.

10. A pharmaceutical composition comprising a combination of an antihypertensive agent and a neutral endopeptidase inhibitor in an amount effective to treat or prevent left ventricular hypertrophy in a pharmaceutically acceptable carrier.

11. A composition of claim 10 wherein the antihypertensive agent is an angiotensin converting enzyme inhibitor or a calcium antagonist and the neutral endopeptidase inhibitor is selected from the group consisting of

N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-β-alanine;

N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-β-alanine;

N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester;

N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine;

N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine;

N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-β-alanine;

N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentyl-carbonyl]-(S)-isoserine;

N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine;

1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine;

1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine;

N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methyl-mercapto)methionine;

N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;

N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid;

N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine;

N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester;

3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino-ε-caprolactam;

SQ 28603; UK 69578; thiorphan; retro-thiorphan; phosphoramidon; and SQ 29072; or a pharmaceutically acceptable ester thereof.

12. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat left ventricular hypertrophy in a mammal which comprises in one container a pharmaceutical composition comprising an antihypertensive agent and in a second container a pharmaceutical composition comprising a neutral endopeptidase inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/02338

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/00 A 61 K 31/195 A 61 K 31/335
A 61 K 31/215

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
O	J. Hypertension (Proceedings of the 5th European Meeting on Hypertension, June 1991), vol. 9, suppl. 6, 31 December 1991, A. MONOPOLI et al.: "Chronic inhibition of neutral endopeptidase reduces left ventricular hypertrophy without changing blood pressure in spontaneously hypertensive rats", pages S246-S247, see page S247, left-hand column	1-12
Y	Am. Rev. Resp. Dis., vol. 143, (4 part 2), 1991, T. KRAUSZ et al.: "Inhibition of neutral endopeptidase 24.11 attenuates pulmonary vascular remodeling and right ventricular hypertrophy in the rat", page A184, see right-hand column, abstract 2	1-9
X	WO,A,9113870 (SCHERING) 19 September 1991, see page 1, lines 1-8; pages 22,23	10-12
Y		1-9

-/-

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09-04-1992	29. 04. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Maria Peis Maria Peis

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	WO,A,9109840 (SCHERING) 11 July 1991, see page 1, lines 1-8; page 27, lines 3-10; claim 10	10-12
Y		1-9
Y	J. Thorac. Cardiovasc. Surg., vol. 84, no. 4, 1982, D.F. LARSON et al.: "Concurrent left and right ventricular hypertrophy in dog models of right ventricular overload", pages 543-547, see page 543, right-hand column, lines 20-12; page 546, right-hand column, lines 21-26	1-9

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9102338 SA 54472

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 23/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 9113870	19-09-91	US-A-	5075302	24-12-91
		AU-A-	7456691	10-10-91
WO-A- 9109840	11-07-91	AU-A-	7168091	24-07-91

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世界知的所有権機関
国 際 事 務 局

特許協力条約に基づいて公開された国際出願

(51) 国際特許分類5
C07C 259/06, C07D 259/08, 207/16, 209/20, 213/75, C07K 5/06, A61K 31/195, 31/215, 31/40, 31/405, 31/44, 37/64

A1

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(43) 国際公開日 1994年7月21日(21.07.94)

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(22) 国際出願日 1993年1月14日(14. 01. 93)

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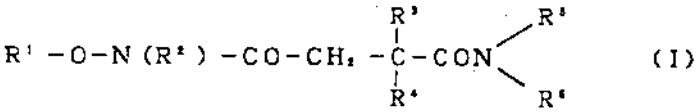
(81) 指定国
AT(欧州特許), BE(欧州特許), CA, CH(欧州特許), DE(欧州特許), DK(欧州特許), ES(欧州特許), FR(欧州特許), GB(欧州特許), GR(欧州特許), HU, IE(欧州特許), IT(欧州特許), JP, KR, LU(欧州特許), MC(欧州特許), NL(欧州特許), PT(欧州特許), SE(欧州特許), US.

添付公開書類 国際調査報告書

(54) Title : PROPIONAMIDE DERIVATIVE AND MEDICINAL USE THEREOF

(54) 発明の名称 プロピオン酸アミド誘導体およびその医薬用途



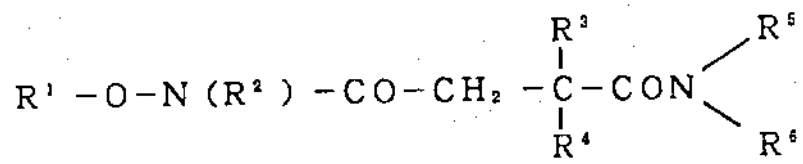
(I)

(57) Abstract

A propionamide derivative represented by general formula (I) and a salt thereof, wherein R^1 and R^2 represent each hydrogen, etc.; R^3 and R^4 are combined together to represent optionally substituted C_2-C_7 alkylene, etc.; R^5 represents hydrogen, etc.; and R^6 represents -X-CO-O-R^7, etc. These compounds inhibit a neutral endopeptidase activity, have an improved oral absorbability, and can potentiate the biological effects of an atrial natriuretic peptide which is a potent natriuretic, diuretic and hypotensive hormone. Therefore, they are useful for treating various diseases of the circulatory organs, including hypertension, cardiac insufficiency, angina pectoris, renal insufficiency, premenstrual syndrome, cyclic edema, Ménière disease, aldosteronism (primary and secondary), pulmonary edema, hypereninemia, ascites and hypercalciuria, and for treating glaucoma. They are useful also for treating gastrointestinal diseases, particularly diarrhea and irritable colon syndrome, and pains.

(57) 要約

一般式



(I)

(式中、R^1，R^2 は水素などを、R^3，R^4 は一緒になって置換基を有していてもよい炭素数2～7個のアルキレンなどを、R^5 は水素などを、R^6 は－X－CO－O－R^7 などを示す。)

により表されるプロピオン酸アミド誘導体およびその塩。

本発明の新規なプロピオン酸アミド誘導体およびその塩は、中性エンドペプチダーゼ活性阻害作用を有し、経口吸収も改善されたものであり、強力なナトリウム排泄性、利尿性、血圧降下性のホルモンである心房性ナトリウム利尿ペプチドの生物学的効果を強化することができ、したがって、本化合物は、高血圧、心不全、狭心症、腎不全、月経前症候群、周期性浮腫、メニエール病、高アルドステロン症（一次および二次）、肺水腫、高レニン血症、腹水症および高カルシウム尿症を含む多くの循環器系疾患の治療または緑内障の治療に有用である。

また、本発明の化合物は胃腸障害（特に下痢および過敏性大腸症候群）の治療、疼痛の治療においても有用である。

情報としての用途のみ

PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AM アルメニア
AT オーストリア
AU オーストラリア
BB バルバドス
BE ベルギー
BF ブルキナ・ファソ
BG ブルガリア
BJ ベナン
BR ブラジル
BY ベラルーシ
CA カナダ
CF 中央アフリカ共和国
CG コンゴー
CH スイス
CI コート・ジボアール
CM カメルーン
CN 中国
CS チェコスロヴァキア
CZ チェッコ共和国
DE ドイツ
DK デンマーク
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GB イギリス
GE グルジア
GN ギニア
GR ギリシャ
HU ハンガリー
IE アイルランド
IT イタリー
JP 日本
KE ケニア
KG キルギスタン
KP 朝鮮民主主義人民共和国
KR 大韓民国
KZ カザフスタン
LI リヒテンシュタイン
LK スリランカ
LT リトアニア
LU ルクセンブルグ
LV ラトヴィア
MC モナコ
MD モルドバ
MG マダガスカル
ML マリ
MN モンゴル
MR モーリタニア
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SN セネガル
TD チャード
TG トーゴ
TJ タジキスタン
TT トリニダード・トバゴ
UA ウクライナ
US 米国
UZ ウズベキスタン共和国
VN ヴィエトナム

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV 824503415 US	May 11, 2006
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M.

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE

Sir:

Responsive to the outstanding action dated January 12, 2006, in the above-identified application, having a period for response set to expire May 12, 2006, due to the attached petition for a one-month extension of time, Applicants respectfully request the following amendment be entered and the claims considered in light thereof.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

This listing of the claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (previously presented) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl -4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier.

2. (canceled)

3. (previously presented) The pharmaceutical composition of Claim 1, wherein *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. (previously presented) A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl -4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and in a second container a pharmaceutical composition comprising valsartan.

5. (withdrawn) A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester or its active metabolite or (2R,4S)-5-Biphenyl -4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. (canceled)

7. (withdrawn) The method of Claim 5, wherein *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof.

8-11 (cancel).

REMARKS

Reconsideration of the above-identified application as amended is requested. Claims 8-11 have been canceled without prejudice or disclaimer to presenting these claims in one or more continuing or divisional applications. Claims 5 and 7 have been withdrawn as being directed to a non-elected invention. Claims 1, 3 and 4 remain in this application.

Rejection of claims 8-11 under 35 U.S.C. §103(a)

Claims 8-11 have been rejected under 35 U.S.C. §103(a) over Ksander (U.S. Patent No. 5,217,996). Without commenting as to the propriety of the rejection, Applicants have deleted claims 8-11 solely to expedite prosecution. Accordingly, this rejection has been rendered moot and should be withdrawn.

Rejection of claims 1, 3 and 4 under 35 U.S.C. §103(a)

Claims 1, 3 and 4 have been rejected under 35 U.S.C. §103(a) over Ksander U.S. Patent No. 5,217,996 ('996 patent) and Buhlmayer et al. U.S. Patent No. 5,399,578 ('578 patent). The Examiner states that to employ combinations of specific NEP inhibitor and valsartan would have been obvious because all the components are well known individually for treating hypertension and that one of ordinary skill in the art would have been motivated to combine specific NEP inhibitor and valsartan in a single composition in order to achieve an expected benefit of antihypertensive effect of the combination. Specifically, the Examiner alleges that the motivation for combining the components flows from their individually known common utility. In view of the evidence and argumentation submitted herein, Applicants respectfully traverse this rejection.

Attached hereto is the Declaration of Gary Ksander, co-inventor of the present invention and sole inventor of the Ksander patent. Applicants respectfully submit that the Ksander Declaration rebuts the alleged *prima facie* case of obviousness as set forth above. The Ksander Declaration provides evidence that the '996 patent in combination with the '578 would not motivate one of ordinary skill in the art to combine the *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl -4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof with valsartan to make the combination of the claimed invention. Dr. Ksander is one of ordinary skill in the art and is the sole inventor of the '996 patent. Dr. Ksander makes it clear that having knowledge of both the '996 patent and the '578 patent would not motivate one of ordinary skill to make the combination of the claimed invention.

Neither the '996 patent nor the '578 make any mention of combining their respective compounds with any other compounds. Further, there is no motivation to combine based on the teachings of these references according to the Ksander Declaration. Without the requisite

motivation to combine, a claimed invention cannot properly be considered obvious. Accordingly, the rejection has been traversed and should be withdrawn.

Without admitting that the claimed invention is obvious, but in addressing the Examiner's allegation of *prima facie* obviousness, Applicants are attaching the Declaration of Dr. Randy Webb. As clearly shown, the Webb Declaration provides sufficient evidence to show that the combination of the claimed invention has a synergistic, unexpected and surprising effect on the treatment of hypertension when compared to monotherapy. It is well established under the law, that a showing of unexpected or surprising properties of a claimed invention is sufficient evidence to overcome a *prima facie* obviousness rejection. The Webb Declaration sets forth evidence that the combination of the present invention unexpectedly and surprisingly lowers blood pressure more than would be expected from monotherapy of the specific NEP inhibitor and valsartan alone.

Although the combination of the present invention was not synergistic when administered to the spontaneously hypertensive rat (SHR) animal model of hypertension, the Webb Declaration provides a sufficient explanation of why this is the case. Further, and most importantly, even in light of the SHR model results, the Webb Declaration attests that the overall results of the effects of the combination of the invention on blood pressure lowering is still synergistic, unexpected and surprising.

Applicants submit that the showing of unexpected results in the Webb Declaration is sufficient to rebut the obviousness rejection entered in the office action. In *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995), the Court stated that, "...when an applicant demonstrates substantially improved results, as Soni did here, and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." Applicants demonstrated such substantially improved results in the Webb Declaration. Moreover, Applicants state in the specification at page 7, line 17 that, "It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone ... ." Admittedly, this statement was based on insight at the time of the filing of the application. Nevertheless, Applicants conceived of improved results at the time of filing and since there is no evidence to the contrary, the claims of the present application are not obvious under *Soni*.

As further evidence that the combination of the claimed invention is not obvious, the Webb Declaration provides evidence that the combination of the present invention has other therapeutic benefits not found in valsartan or *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester (AHU377) monotherapy. Hypertensive patients have underlying markers indicative of their disease state. For example, endothelial dysfunction, cardiac fibrosis and collagen deposition leading to cardiac vascular remodeling is indicative of a hypertensive disease state. The Webb Declaration provides evidence that the combination of the present invention provides an overall improvement of

endothelial function, cardiac fibrosis and cardiac vascular remodeling and fibrosis of intramyocardial coronary arteries in stroke prone spontaneously hypertensive rats (SHRsp) as compared to monotherapy with valsartan or AHU377. This is a further unexpected benefit of the combination of the claimed invention.

In light of the above, Applicants respectfully submit that the clear evidence of unexpected and surprising findings with the combination of the present invention as compared to monotherapy and the additional unexpected therapeutic benefits of the claimed invention, rebuts and therefore overcomes any *prima facie* case of obviousness set forth by the Examiner.

In view of the foregoing, Applicant submits that all rejections have been traversed and should be withdrawn and that the Application is now in condition for allowance and respectfully requests early notice to that effect.

Respectfully submitted,

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Date: May 11, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander et al.

Art Unit: 1617
Examiner: Kim, Jennifer M.

APPLICATION NO: 10/341,868

FILED: January 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Gary Ksander, being duly warned, hereby declare as follows:

1. I am a citizen of the United States of America, residing at 37 The Flume, Amherst, NH 03031

2. I am a named inventor of the invention presently claimed in the application identified in the caption above (which is referred to in this document as "the Application").

3. I received a Ph.D. in Organic Chemistry from the University of California at Santa Cruz in 1978. I have carried out research in the area of Cardiovascular and Metabolic Diseases for 21 years, and I have published eighteen articles on my research in this area. Presently, I am at Novartis Inc., and conduct research in Cambridge Mass. My background is presented in more detail in my *Curriculum Vitae*, which is attached to this Declaration as EXHIBIT 1.

4 I have read and understand the January 12, 2006 Office Action issued in the Application and the Ksander (U.S. Patent No. 5,217,996) and Buhlmayer et al. (U.S. Patent No. 5,399,578) references cited in. I am aware that the claims 1, 3 and 4 of the present Application have been rejected as obvious over U.S. Patent No. 5,217,996 and U.S. Patent No. 5,399,578 in said office action.

5. I am the sole inventor in US Patent No. 5,217,996 identified above. The '578 patent issued to Ciba-Geigy Corp. (predecessor to Novartis Corporation) in 1995. The '578 covers valsartan which is an important product for Novartis. I worked at Ciba-Geigy before and at the time of issuance of the '578 patent and still work at Novartis now. I have been affiliated with the cardiovascular and metabolic therapeutic area with Novartis for the past 21 years and was therefore aware of the work being done on valsartan and the corresponding patenting thereof. I became aware of the '578 patent at or immediately after the time of its issuance and I familiar with the subject matter thereof.

6. Even though I was aware of the '996 patent and the '578 as early as 1995, it did not occur to me to combine (i) *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester or (ii) (2R,4S)-5-Biphenyl -4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid with valsartan for the treatment of hypertension until several years thereafter.

7. It was not until several years after my awareness of these two patents, while collaborating with my co-inventor Randy Webb, did I conceive of the combination of the claimed invention for the treatment of hypertension.

8. Our conception of the combination invention was based on information and factors other than those disclosed in the two references cited against the present application. Therefore, I was not motivated to arrive at the claimed invention based on knowledge of the '996 patent and '578 patent.

9. Based on the above, and on my expertise and experience, it is my opinion that the two references would not motivate one of ordinary skill in the art to make the present invention and that therefore the present invention is not obvious over these two references.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 9, 2006

Gary Ksander

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EDUCATION

1978-1981	Postdoctoral Research, ETH, Zurich, Switzerland working for Prof. A. Eschenmosher.
1974-1978	PhD. in Organic Chemistry, University of California at Santa Cruz. Research Advisor: Prof. J. McMurry
1974	MS. in Organic Chemistry, San Jose State University
1972	BS. Chemistry, San Jose State University

WORK EXPERIENCE

1981- 1982	Medicinal Research Chemist, Ciba Geigy Corporation
1982- 1986	Senior Research Scientist, Ciba Geigy Corporation
1987	Senior Staff Scientist, Ciba Geigy Corporation
1988	Assistant Director, Ciba Geigy Corporation
1993-1997	Distinguished Research Scientist, Ciba Geigy Corporation
1997-2002	Distinguished Fellow, Novartis Pharmaceutical Corporation
2003-present	Head Cardiovascular Chemistry
Project Leader:	
	ACE/Thromboxane Inhibitors
	Neutral Endopeptidase Inhibitors
	Endothelin Converting Enzyme Inhibitors
	Endothelin Antagonists
	Microsomal Triglyceride Transfer Protein Inhibitors
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CASE 4-32219A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Ksander et al.

APPLICATION NO: 10/341,868

FILED: January 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M.

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Randy Lee Webb, being duly warned, hereby declare as follows:

1. I am a citizen of the United States of America, residing at 17 Honeymoon Lane, Flemington, New Jersey 08822.

2. I am a named inventor of the invention presently claimed in U.S. application Serial No. 10/341,868 identified in the caption above (which is referred to in this document as "the Application").

3. I received a Ph.D. in Pharmacology from the University of Iowa in 1984. I have carried out research in the area of hypertension and cardiovascular disease for 30 years, including 21 years at Ciba/Novartis and I have published 64 papers and 3 book chapters on my research in this area. Presently, I am at Novartis Inc., where I am head of Hypertension Research and conduct research in the identification of novel therapeutic targets for hypertension and the development of new antihypertensive drugs. My background is presented in more detail in my *Curriculum Vitae*, which is attached to this Declaration as EXHIBIT 1.

4 I have read and understand the January 12, 2006 Office Action issued in the Application and the Ksander (U.S. Patent No. 5,217,996) and Buhlmayer et al. (U.S. Patent No. 5,399,578) references cited therein

5. The experiments summarized in the paragraphs below were carried out by me or under my direction and supervision, or by collaborators with my full participation and understanding. The experimental results, as explained below, provide evidence that the pharmaceutical combination of 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-3-methylbutanoic acid ethyl ester (AHU377) and valsartan as claimed in the Application (the combination of the present invention), has (i) synergy in lowering mean arterial pressure in animal models of hypertension as compared to monotherapy with either active agent alone and that this synergy is an unexpected and surprising blood pressure lowering effect which would not be expected by one of ordinary skill in the art and (2) has added therapeutic benefits in the treatment of hypertension compared to valsartan monotherapy and AHU377 monotherapy.

6. As described in greater detail below, the experiments show that : (1) administration of a combination of valsartan at 30 mg/kg/day and AHU377 at 30 mg/kg/day to Dahl salt sensitive rats provides a synergistic, unexpected and surprising antihypertensive effect and the combination of valsartan at 100 mg/kg/day and AHU377 at 30 mg/kg/day also elicited a synergistic, unexpected and surprising antihypertensive effect, even though in Dahl salt sensitive rats valsartan alone has no discernable effect and AHU377 only has an effect at a 100 mg/kg/day dose; (2) administration of a combination of the claimed invention to stroke prone male spontaneously hypertensive rats (SHRsp) had a synergistic, unexpected and surprising antihypertensive effect, even though the combination of valsartan and AHU377 did not significantly reduce blood pressure in SHR; and (3) the combination of the claimed invention has the added therapeutic benefits in the treatment of hypertension of improved cardiac fibrosis and vascular remodeling and fibrosis of mesenteric and intramyocardial coronary arteries thereby reducing hypertension by decreasing media/lumen ratio of intramyocardial coronary arteries as compared to valsartan monotherapy and AHU377 monotherapy. In summary, the experiments show that the combination of valsartan and AHU377 has a synergistic, unexpected and surprising antihypertensive effect and has added therapeutic benefits in the treatment of hypertension.

7. The experiments on the SHR and Dahl salt-sensitive animal models of hypertension were performed to assess and compare the efficacy on hypertension of the combination of the Application with valsartan and AHU377 administered as monotherapy. In the experiments

performed on the SHRsp rats, the objective was to assess the efficacy on hypertension, oxidative stress, endothelial function and vascular remodeling of the combination of the claimed invention with a combined angiotensin converting enzyme inhibitor and neutral endopeptidase inhibitor (ACE/NEP inhibitor), valsartan monotherapy, AHU377 monotherapy and hydralazine monotherapy.

8. The experiments on the SHR model of hypertension were carried out as follows: Procedure: All SHR were implanted with radiotransmitters between the ages of 15 to 16 weeks old according to the procedures described previously in Webb and Yao, Novartis Study Report, PKF-99-00909. Rats were allowed a minimum of 7-10 days to recover from surgery prior to the start of experimentation. SHR were allocated to four treatment groups depending upon baseline blood pressure measurements and with the goal of having similar group mean blood pressure values at the start of the study. Baseline blood pressure represents the overall average blood pressure recorded over 3 consecutive days. Blood pressure was collected for 10 seconds every 10 minutes throughout the day and thus, 144 pressure measurements were recorded every 24 hours. All treatments commenced in SHR between 17-18 weeks of age. Drugs were administered by oral gavage, once daily to conscious SHR in four separate groups as follows:

Drug Treatment

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Group 1	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle
Group 2	Vehicle	Vehicle	Val 3	Val 10	Val 30	Val 100
Group 3	NEPI 30	NEPI 30	NEPI 30 Val 3	NEPI 30 Val 10	NEPI 30 Val 30	NEPI 30 Val 100
Group 4	NEPI 30	NEPI 100	NEPI 100 Val 3	NEPI 100 Val 10	NEPI 100 Val 30	NEPI 100 Val 100

Treatments: Vehicle, 3% cornstarch; NEPI, AHU377 ; Val, valsartan. Valsartan was administered in ascending dosages of 3, 10, 30 and 100 mg/kg/day on a background of either vehicle, AHU377 at 30 mg/kg/day or AHU377 at 100 mg/kg/day. Each dose of valsartan was given for a period of one week.

Starting at week 3, valsartan was given at 3, 10, 30 and 100 mg/kg/day in one week intervals, either alone or adjunctively with NVP-AHU377-AB. Results in the SHR were analyzed by a mixed effects model (MEM) using the average weekly blood pressure and secondly, the average weekly slope of the blood pressure effect (Brown and Prescott, 1999). This analysis is similar to an analysis of variance but generally considered to be more efficient and sensitive since missing data due to an animal death does not have to be excluded. The daily observations of blood pressure (24 hr averages) and heart rate are repeated throughout the study protocol. All values were considered significant when $P < 0.05$.

9. The experiments on the Dahl salt sensitive rats were carried out as follows:

Procedure: Radiotransmitters were implanted into Dahl salt-sensitive rats at 7 weeks of age. All animals were placed on a high salt diet (8%) between 7 and 8 weeks of age (approximately 12 days prior to the start of the study) and maintained on this regimen for the duration of the study. Drug treatment was initiated at 9 weeks of age and was continued for 3 weeks. Drugs were administered once daily by oral gavage. The effects of valsartan alone and in combination with AHU377 were assessed using a 3 X 3 factorial design as follows:

Protocol design for the 3 X 3 factorial study in Dahl salt-sensitive Rats

Vehicle n = 8	Val 30 n = 8	Val 100 n = 8
NEPI 30 n = 8	Val 30 + NEPI 30 n = 8	Val 100 + NEPI 30 n = 8
NEPI 100 n = 7	Val 30 + NEPI 100 n = 8	Val 100 + NEPI 100 n = 8

NEPI 30 and 100 represent AHU377 administered by oral gavage at a dose of 30 and 100 mg/kg/day, respectively. Val 30 and 100 depict valsartan given at a dose of 30 and 100 mg/kg/day, respectively. Vehicle was 3% cornstarch given at 2 ml/kg body weight.

10. The experiments on the SHRsp were carried out as follows:

Animal Experiments: Male SHRSP were obtained from a colony originally acquired from the National Institutes of Health (NIH), and maintained locally. Rats were housed at 22°C and 60% humidity under a 12-hour light/dark cycle. Starting at 10 weeks of age, SHRSP were fed powdered diet (Agribrands Purina, Drummondville, QC, Canada) containing the combined valsartan (10mg/kg/day)/AHU377 (100mg/kg/day, NEPI), CGS 30440 (10mg/kg/day, a combined ACEI/NEPI), valsartan alone (10mg/kg/day), AHU377 (100mg/kg/day), or hydralazine (25mg/kg/day). Wistar-Kyoto rats (WKY) served as normotensive controls. Systolic blood pressure (BP) was measured initially by the tail-cuff method under slight restraint and was monitored weekly for the last 5 weeks by radio-telemetry as previously described (Amiri F, et al., *Circulation.* 2004;110:2233-2240). After 10 weeks of treatment, rats were killed humanely.

Preparation and Study of Mesenteric Resistance Arteries: Third-order branch of the mesenteric vasculature was isolated and mounted on a pressurized myograph as described previously (Savoia C, et al., *J Hypertens.* 2005;23:1037-1045.). Endothelium-dependent and independent relaxations

were assessed in norepinephrine (10^{-5}mol/L) pre-contracted vessels with acetylcholine and sodium nitroprusside, respectively. Lumen and media dimensions were measured while intraluminal pressure maintained at 45mmHg upon vessel deactivation with 10mmol/L EGTA (Virdis A, et al., *Hypertension.* 2002;40:504-510). Thereafter, vessels were fixed with 4% paraformaldehyde for histology.

Measurement of NADPH Oxidase Activity: Vascular NADPH oxidase activity was measured in aortic segments and mesenteric arteries by lucigenin chemiluminescence (5μmol/L), using NADPH (100μmol/L) as substrate, as previously described ((Virdis A, et al., *Hypertension.* 2002;40:504-510)). Lucigenin signal specificity was tested by adding both diphenylene iodinium, a flavoprotein inhibitor, and tempol, a superoxide dismutase mimetic.

Histology and Immunohistochemistry: Four animals per group were perfused with 4% paraformadehyde *in vivo*. Once mesenteric arteries were removed, heart and aorta were embedded in paraffin, and serially sectioned (5μm) for histological and immunohistochemical studies. As previously described (Pu Q, et al., *Am J Hypertens.* 2001;14:1067-1072.), severity of vascular and cardiac fibrosis was evaluated with Sirius red staining and analyzed by image analysis system (Northern Eclipse 5.0, EMPIX Imaging Inc., Mississauga, ON, Canada), by an investigator unaware of the experimental group examined. Collagen density was defined as the ratio of the area stained to the total tissue area and expressed as percentage. Macrophage infiltration was assessed by immunostaining with a monoclonal antibody against rat monocytes/macrophages (ED-1, Serotec, Raleigh, NC) as previously described (Pu Q, et al., *J Hypertens.* 2005;23:401-409).

Preparation of Vascular Tissue for Western Blotting: Samples were extracted (Amiri F, et al., *Circulation.* 2004;110:2233-2240) and expression of nitric oxide synthase (NOS) was assessed with endothelial NOS (eNOS) antibody (BD Biosciences, San Jose, CA) as previously described (Javeshghani D, et al., *Hypertension.* 2003;42:761-767). Signals were revealed with chemiluminescence and visualized autoradiographically. Subsequently membranes were stripped (Pierce Biotechnology, Rockford, IL) and re-probed with beta-actin (Sigma Chemicals, Mississauga, ON, CAN) to verify equal loading. Optical density of bands was quantified by ImageQuant 5.0 (Molecular Dynamics, Sunnyvale, CA), and expressed as arbitrary units.

Gelatin Zymography and Reverse Zymography: Protein was extracted from frozen aorta by homogenization as previously described (Brassard P, et al., *Hypertension.* 2005; 46:598-606), while latent and activated gelatinases were detected with SDS-PAGE gelatin zymography (Galis ZS, et al., *Circ Res.* 1994;75:181-189; Brassard P, et al., *Hypertension.* 2005; 46:598-606). After gel staining, MMPs were identified based on gelatin lysis at 62kDa and 82kDa for activated MMP-2 and MMP-9, respectively. Gelatinolytic bands were quantified using ImageQuant software 5.0. Reverse zymography was performed as previously described (Brassard P, et al., *Hypertension.*

2005; 46:598-606) where stained bands represent gelatinase inhibitory activity corresponding to TIMPs.

Data Analysis: Data are presented as mean±SEM and analyzed by repeated measures ANOVA followed by Newman-Keuls *post-hoc* test. $P<0.05$ was considered significant.

11. SHR Results:

	Blood Pressure (mmHg)					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Group 1	146 ± 2	147 ± 1	148 ± 1	149 ± 1	149 ± 2	148 ± 2
Group 2	149 ± 3	150 ± 4	146 ± 3	142 ± 4	135 ± 4	120 ± 5
Group 3	148 ± 2	148 ± 2	145 ± 2	143 ± 4	137 ± 3	124 ± 2
Group 4	146 ± 5	145 ± 4	138 ± 5	136 ± 5	128 ± 4	117 ± 5

12. Dahl Salt Sensitive Results for Valsartan Monotherapy:

	Dose mg/kg/day	Final BP mmHg	Improvement over vehicle mmHg
Vehicle		193 ± 5	
Valsartan	30	191 ± 6	-2
Valsartan	100	196 ± 7	+3

13. Dahl Salt Sensitive Results for AHU377 Monotherapy:

	Dose mg/kg/day	Final BP mmHg	Improvement over vehicle mmHg
Vehicle		193 ± 5	
AHU377	30	191 ± 5	-2
AHU377	100	177 ± 5	-16

14. Dahl Salt Sensitive Results for Valsartan and AHU377 combination therapy:

	Dose mg/kg/day	Final BP mmHg	Improvement over vehicle mmHg	Expected Improvement mmHg	Improvement Factor mmHg
Vehicle		193 ± 5			
Vals:AHU377	30:30	176 ± 6	-17	-4	-13
Vals:AHU377	30:100	179 ± 6	-14	-18	+4
Vals:AHU377	100:30	174 ± 5	-19	+1	-18
Vals:AHU377	100:100	182 ± 8	-11	-13	+2

15. SHRsp Model Results for Valsartan and AHU377 monotherapy and combination therapy for Systolic Blood Pressure (SBP):

	Dose mg/kg/day	Final SBP mmHg	SBP Reduction	Expected Improvement mmHg	Improvement Factor mmHg
SHRsp		195 ± 6			
Valsartan	10	176 ± 6	-19		
AHU377	100	199 ± 6	+4		
Vals:AHU377	10:100	167 ± 5	-28	-15	-13
ACE/NEP inhibitor	10	152 ± 2	-43		

SHRsp Model Results for Valsartan and AHU377 monotherapy and combination therapy for Diastolic Blood Pressure (DBP)

	Dose mg/kg/day	Final SBP mmHg	SBP Reduction	Expected Improvement mmHg	Improvement Factor mmHg
SHRsp		142±3			
Valsartan	10	137±7	-4.6		
AHU377	100	151±8	+9.5		
Vals:AHU377	10:100	118±5	-23.8	+4.9	-28.7
ACE/NEP inhibitor	10	108±3	-34		

16. Based on the above, the combination therapy of the claimed invention was clearly shown to demonstrate synergism with respect to blood pressure lowering, for both the Dahl study at 30:30 and 100:30 (Valsartan to NVP-AHU377-AB, respectively (mg/kg/day)); and in the SHRsp study. This synergy is illustrated by the improvement factors reported in the preceding table, where the improvement factors are calculated by subtracting the expected additivity of independent events from the combination therapy. In paragraphs 14 and 15 above, synergy is shown by the negative number set forth in the "Improvement Factor" column. This number is the actual blood pressure lowering effect of the combination of the present invention beyond that which is expected from the combination based on the results of monotherapy. The demonstrated synergism was both unexpected and surprising. The only exception is the SHR study, which does not show synergy. This is explained by the fact that the SHR hypertensive animal model is one in which the BP is generally stable over extended periods of time, that is, it will rise with age but does so more gradually than many other experimentally-induced models of hypertension in the rat. Additionally, it is known that angiotensin receptor blockers (ARBs) work to lower BP in these animals due to an underlying contribution of the renin angiotensin system in these animals. Blockade of the renin angiotensin system in the SHR, especially chronically, will result in blood pressure lowering. Further, NEPi, which does not block the renin angiotensin system, are known not to be effective in the SHR animal model. Therefore, combinations of valsartan and AHU did not lower BP significantly more than valsartan alone in the SHR model.

17. This makes the Dahl and SHRsp data even more unexpected. The animals in this model rapidly become moribund due to a progressive malignant hypertension, that if left untreated would result in mortalilty in one hundred percent of the animals. Therefore, the fact that the combination had synergistic effects in these models, when not having synergistic effects in the stable SHR model, is therefore even more unexpected and surprising.

18. As shown in Figure 1, attached hereto as EXHIBIT 2, experiments performed on SHRsp shows that the combination of the present invention, the dual ACEi/NEPi compound and valsartan alone normalized maximal acetylcholine relaxation responses, whereas AHU377 and hydralazine were ineffective. This shows that of the combination of the present invention has the added therapeutic value of exerting protective effects on the endothelium and thereby reducing endothelial dysfunction. Reduction of endothelial dysfunction improves vascular function and therefore helps treat hypertension. The combination of the present invention is more beneficial with respect to endothelial dysfunction than AHU377 alone although it is similar to valsartan alone.

19. As shown in Figure 2, attached hereto as EXHIBIT 3, experiments performed on SHRsp shows that the combination of the present invention, the dual ACEi/NEPi compound and valsartan alone significantly decreased media/lumen ration and collagen deposition, whereas AHU377 and hydralazine were ineffective. This is indicative of therapeutic vascular remodeling of the endothelium by the combination of the present invention. The combination of the present invention is more beneficial with respect to vascular remodeling than AHU377 alone, although it is similar to valsartan alone.

20. As shown in Figure 3, attached hereto as EXHIBIT 4, experiments performed on SHRsp shows that the combination of the present invention, the dual ACEi/NEPi compound, valsartan alone, AHU377 alone and hydralazine all decreased vascular NADPH oxidase activity significantly in SHRsp. The increased activity of NADPH oxidase seen in the SHRsp results in increased oxidative stress (reduction in reactive oxygen species) within the vessel wall. The significant reduction in NADPH oxidase activity will minimize vessel wall damage due to oxidant stress and improve vascular function.

21. As shown in Figure 4, attached hereto as EXHIBIT 5, experiments performed on SHRsp shows that the combination of the present invention and the dual ACEi/NEPi compound improved media/lumen ratio and interstitial collagen density better than valsartan alone, whereas AHU377 and hydralazine were ineffective. These effects on small arteries may be of importance in the treatment of hypertensive patients, wherein these patients have detrimental small artery remodeling in the myocardium or in other organs which may contribute to cardiovascular events. Animals treated with the combination of the present invention show a collagen density closer to the control animal (WKY) than either monotherapy with valsartan or AHU377.

22. As shown in Figure 5, attached hereto as EXHIBIT 6, experiments performed on SHRsp shows that the combination of the present invention and the dual ACEi/NEPi compound were more effective than valsartan alone, AHU377 alone or hydralazine in decreasing vascular macrophage infiltration. Vascular macrophage infiltration is a marker of inflammation and leads to vascular damage and diminished vessel wall function such as reduced vasorelaxant capacity.

23. As shown in Figure 6, attached hereto as EXHIBIT 7,SHRsp exhibited reduced MMP-2 activity with concurrent increase in TIMP-2 activation, thus resulting in increased cardiac and vascular collagen deposition due to a reduction in collagen degradation. The combination of the present invention as well as dual ACEI/NEPI increased MMP-2 activity and decreased TIMP-2

activity, whereas valsartan or NEPI alone had no effect. Therefore, the combination of the present invention shows an added therapeutic value in the protection of the vessel wall and in the treatment of hypertension not shown by monotherapy.

24. In summary, based on my expertise and experience and on my evaluation of the results set forth above, it is my opinion that the combination of the present invention unexpectedly and surprisingly lowers blood pressure as compared to the monotherapy and shows an added therapeutic value in the treatment of hypertension as compared to monotherapy of valsartan or NVP-AHU377-AB.

25. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 11, 2006

Randy Lee Webb

Randy Lee Webb

Curriculum Vitae

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Education

Rutgers University, New Brunswick, NJ, **B.S. Biology** - 1976
Fairleigh Dickinson University, Teaneck, NJ, **M.S. Physiology** - 1979
University of Iowa, Iowa City, Iowa, **Ph.D. Pharmacology** - 1984
NIH Predoctoral Trainee - University of Iowa, 1979-1983
NRSA Postdoctoral Fellowship - Medical College of Wisconsin, 1984

Appointments and Honors

Co-chairman – ANF: Metabolism and Receptors, FASEB, Las Vegas, NV, May, 1988.

Scientific Advisory Board and session chairman - Fourth International Conference on Endothelin, London, England, April 23-26, 1995.

Research Peer Review Committee, American Heart Association, New Jersey Affiliate and Northeast Affiliate Consortium Group 3 Reviewer, 1997-2001.

Discipline Expert and member of the Novartis Scientific Council on Pharmacology (1999)

> International Council within Novartis Research consisting of 16 members with quarterly meetings (Basel), review policies within Research, establish guidelines for Research efforts across disciplines, organize workshops, prepare position papers, etc.

Member of the Novartis Global CV Council (2001-2004)

> Represent CV Research and serve on a panel with 7 International CV experts to provide feedback to Novartis on trends, controversies, opportunities for optimizing current products and to make recommendations regarding CV portfolio strategy.

Member - Novartis Metabolic/Cardiovascular Franchise Board (2002-2004)

Management team includes members from Research, Clinical Development, Marketing and Business Development and Licensing. Board members review on a monthly basis all Metab/CV programs/products within Franchise to set development and commercial strategy and to ensure alignment within the Novartis portfolio. Evaluate in-licensing opportunities and acquisitions.

Inventor – U.S. Patent 6,204,281 (2001)
Inventor – U.S. Patent 6,395,728 (2002)

Employment Experience

2003-present	Executive Director, Cardiovascular Research, Novartis Institutes for BioMedical Research
2002-2003	Executive Director, Cardiovascular Disease Pharmacology, Metabolic and Cardiovascular Diseases, Novartis Pharma.
2000-2001	Principal Fellow, Novartis Pharma.
1997-1999	Senior Fellow, Novartis Pharma.
1995-1996	Senior Research Fellow I, Ciba Pharma.
1991-1994	Staff Scientist, Ciba Geigy Pharma.
1988-1990	Senior Research Scientist, Ciba Geigy Pharma.
1984-1987	Senior Scientist, Ciba Geigy Pharma., Summit, NJ
1976-1979	Pharmacologist, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ

Team Membership

2000-2001	Research Representative – Diovan International Project Team Roles/Responsibilities – Coordinate all preclinical (External/Internal Investigators) studies, review and critique scientific aspects and align with IPT strategy for Product Lifecycle Management, oversee financial support for external collaborations, represent Research on all matters pertaining to product, attend monthly team meetings, various conferences with investigators, serve as a scientific consultant to the Diovan Brand Team and prepare/present lectures for Novartis International Scientific Symposia.
1998	Research Representative - Diovan Life Cycle Management Team Cardioprotection Task Force – member
1997	International Project Team Member, International Clinical Team Member (CGP 60536B, renin inhibitor) and Preclinical Research Coordinator
1993-1995	Valsartan (Angiotensin II Antagonist) Project Team Member
1989-1993	Project Team Member, Preclinical Research Coordinator - Benazepril/Amlodipine (LOTREL™)

Leadership Skills

2004-	Fully Integrated Program (FIP) Head for hypertension

Roles/Responsibilities – oversight of all hypertension projects, including setting project/program strategy, review of progress, resource allocation, project prioritization. Also, responsible for coordinating compound progression up to entry of compounds into Phase I.

2000 Program Team Leader – VPI program

Roles/Responsibilities – supervise multi-disciplinary team consisting of approximately 20 team members (chemistry, pharmacology, pharmacokinetics, cellular biology; MDs, PhDs, MS and BS level), identify, evaluate and recommend compounds for further development

1999- Cardioprotection/CHF/Hypertension Indication Team Leader

Roles/Responsibilities – 6 PhD Research team members, review all in-licensing opportunities related to Cardioprotection (hypertension, post-MI, CHF, ischemia/reperfusion), make recommendations to Metabolic and Cardiovascular Diseases Therapeutic Area Board, propose novel targets/mechanisms for new programs within therapeutic area

1995-1996 Chairman, International Strategic Alignment Committee (Renal Disease)

Roles/Responsibilities – 9 member task force consisting of MDs and PhDs from Clinical, DRA, Marketing, Research + 2 external consultants (nephrologists), prepared strategic proposal/documentation for initiating therapeutic programs in kidney disease and presented to Global Head of Pharmaceutical Division

1991-1995 Co-Leader - Endothelin Receptor Antagonists

1988-1991 Co-Leader - Adenosine

1986-1988 Deputy Project Leader - Adenosine

Organizational Skills

Organized and Chaired International Renal Advisory Board Meeting, December, 1995, San Diego, CA.

One-day CIBA workshop consisting of 8 International Opinion Leaders on Kidney Disease; incorporated recommendations for novel targets, research approaches, etc. into a Renal Strategic Proposal for CIBA senior management.

Organized and Chaired Novartis International Hypertension Workshop – March 20-21, 2000

Two day workshop with internal participants from various line functions and 5 International Consultants and consisted of a series of seminars and a roundtable discussion covering all aspects of Hypertension Research. A final report was prepared with specific recommendations and conclusions and was presented to management at the Annual Portfolio Review.

IND/NDA/IB Preparation

Ismelin (guanethidine) - "orphan IND" Section 6A/IND

CGS 14831 (benazeprilat, ACE inhibitor) Section 6A/IND

Lotensin HCT™ (Benazepril/Hydrochlorothiazide) NDA Submission

Lotensin™ (Benazepril) - Biology Compound Sponsor - 1989-present,

Summary Basis of Approval, 1990

LOTREL™ (Benazepril/Amlodipine) - NDA Submission (1993); Summary Basis of Approval (1994); FDA Advisory Board Meeting, invited guest, NIH Campus, June, 1994; Investigators' Brochure, June, 2003.

Diovan™(Valsartan) - Hypertension NDA Submission, December, 1995.

Diovan-HCT™ (Valsartan/Hydrochlorothiazide) - Hypertension NDA Submission, March, 1997

Diovan™ (Valsartan) – Heart Failure sNDA Submission (Preclinical report) and European Dossier for Heart Failure Submission (Preclinical Expert Report), April 2001, FDA Cardio-renal Advisory Committee Meeting, designated Novartis participant, October 11, 2001, Investigator's Brochure Edition 13, May, 2001.

Diovan™ - valsartan/simvastatin preclinical summary IND filed September, 2001.

Invited Conference Participant/Lecturer

1. Neural Control of the Circulation, FASEB Summer Conference, Saxtons River, VT, July 1982.

2. Vasopressin Conference, Aspen, Colorado, August 1984.

3. Cardiovascular Residency Program, Georgetown University Medical School, April 27-29, 1987.

4. "Identification of adenosine A_2-selective agonists: Novel antihypertensive agents?" Ciba Geigy Ltd., Basel, Switzerland, June 27, 1991.

5. "Highly selective adenosine A_2 agonists: Cardiovascular actions during acute and chronic administration." Presented at Purines '92, University of Milan, Milan, Italy, June 21-24, 1992.

6. Data Sciences, Inc., Experimental Biology Telemetry Tutorial, "Pharmacological evaluations using radiotelemetry n conscious rats", Anaheim, CA., April, 1994.

7. "Therapeutic potential of AT_1 receptor antagonists in chronic renal disease", Valsartan Diabetic Nephropathy Advisory Meeting, Short Hills, NJ, June 5, 1994.

8. "Telemetric monitoring of cardiovascular parameters in conscious rats." Tri-Branch AALAS Conference, Philadelphia, PA, June 7-8, 1994.

9. "Role of ET_B receptors in cardiovascular and renal function." Endothelin Inhibitors: Advances in Therapeutic Application and Development, IBC Conference, Philadelphia, PA., June 9-10, 1994.

10. "Long-term monitoring of cardiovascular parameters in conscious rats using radiotelemetry. International Congress of Pharmacology (IUPHAR), Telemetry Tutorial, Montreal, Canada, July 23-28, 1994.

11. Session Chairman, "Pathophysiology of Endothelin", Fourth International Conference on Endothelin, London, UK, April 23-26, 1995.

12. "Lotrel: Logical antihypertensive therapy." Lotrel Advisory Meeting, New York City, NY, May 16, 1995.

13. "Preclinical overview of benazepril/amlodipine results in experimental models of cardiovascular disease." Lotrel Investigators Meeting, San Diego, CA, July 13-16, 1995.

14. "Overview of benazepril/amlodipine results in experimental models of cardiovascular disease." Lotrel Speakers Training Meeting, Colorado Springs, CO, August 17-20, 1995.

15. "Overview of benazepril/amlodipine results in experimental models of cardiovascular disease." Lotrel Speakers Training Meeting, Phoenix, AZ, October 12-15, 1995.

16. "Inhibitors of the renin angiotensin system: Novel therapeutics for renal disease." Ciba International Advisory Meeting on Kidney Disease, San Diego, CA, November 8, 1995.

17. "Preclinical profile of the novel renin inhibitor CGP 60536B." Novartis Advisory Meeting, New York, NY, August 6-7, 1997.

18. "Chronic antihypertensive effects of combination therapy in telemetered-spontaneously hypertensive rats." American Association for Laboratory Animal Science, 49th National Meeting, Cincinnati, Ohio, October 19, 1998.

19. DIOVAN® "Preclinical research profiling in cardiovascular and renal disease" National Advisory Board Meeting, Atlanta, GA, January 22, 1999.

20. DIOVAN® "New basic science initiatives with the angiotensin II antagonist, valsartan", Heart Failure Investigators Meeting, Prague, The Czech Republic, December 2-3, 2000.

21. DIOVAN® " New Basic Science Initiatives with the Angiotensin II Antagonist, Valsartan", International Symposium "Selective Angiotensin Receptor Blockade: Treatment Strategies along the Cardiovascular Continuum", May 12-13, 2001, Paris, France (1000 participants from 45 countries).

22. DIOVAN® "Update of Preclinical Results with Diovan", ARB/RAS Vascular Advisory Meeting, New York City, December 14-16, 2001.

23. "Preclinical results with the new renin inhibitor, aliskiren", Aliskiren Advisory Board Meeting, Zurich, Switzerland, March 4, 2002.

24. Aliskiren Advisory Board Meeting, New York City, NY, September 23, 2002.

25. Aliskiren Nephrology Advisory Board Meeting and Aliskiren Global Advisory Board Meeting, Boston, MA, April 2-3, 2004. "Preclinical evidence of efficacy and safety".

26. Diovan Lifecycle Planning Meeting, New Orleans, LA, November 10, 2004. "Development Candidates for Hypertension – Preclinical Review".

27. Novartis Metabolic Syndrome Advisory Board Meeting. London, UK, February 28-March 2, 2005.

28. Panelist at The 4th Annual Waterbury Forum, "State of the Heart: The Future of Cardiac Care in Connecticut", Post University, Waterbury, CT, April 14, 2005.

29. ARB/RAS Vascular Advisory Board: International Summit, Budapest, Hungary, May 20-21, 2005. "ARB/NEPI Combination Development", "Aliskiren: Preclinical Overview and Development Plan" and "Is Aldosterone a Target for Improving Intervention?".

Society Membership

Physiological Society of Philadelphia, 1986-1993.
The American Society of Hypertension, 1988 -
The New York Academy of Sciences, 1989 -
ASPET, 1993 -
Council for High Blood Pressure Research, 1998 -

Teaching Experience

Advanced Cardiovascular Pharmacology: Drug Development, New York Medical College, Valhalla, NY
Fall Semester 1994, 1996; Therapeutic Potential of the Endothelin System
Fall Semester 2002; ACE/NEP Inhibitors

Spring Semester 2005, Class #1088; The Discovery and Development of Renin Inhibitors

Scientific Journal Referee

Journal of Pharmacology and Experimental Therapeutics
Hypertension – 1996, 1997, 1998
Cardiovascular Drug Reviews
Canadian Journal of Physiology and Pharmacology – 1996
American Journal of Physiology: Heart and Circulatory – 1997, 1998
Life Sciences - 1998

Extra-curricular Activities

Judge (Team Captain - Health and Medicine) - New Jersey Regional Science Fair (High School Competition) - March 14-15, 1997 Morris County Community College; March 12-13, 1999, Morris County Community College, NJ.

Supervisory Responsibility

Executive Director (2002-) CV Pharmacology – supervision of 5 Ph.D. and 14 BS/MS scientists; direct lab reports - 1 MS scientist.

Group Leader (1991-1994) CV Pharmacology Unit – supervision of 3 Ph.D., 1 MD and 6 BS/MS scientists.

Post-doctoral trainee, Michelle Bazil, 1990-1992.

Publications

Manuscripts

1. K.H. Berecek, K.W. Barron, **R.L. Webb** and M.J. Brody. Vasopressin central nervous system interactions in the development of DOCA hypertension. Hypertension 4(Suppl. II):II131-II137, 1982.

2. K.H. Berecek, K.W. Barron, **R.L. Webb** and M.J. Brody. Relationship between vasopressin and the anteroventral third ventricle region in deoxycorticosterone/salt hypertension. (Brattleboro Rat Model). Ann. New York Acad. Sci. 394: 392-397, 1982.

3. K.H. Berecek, K.W. barron, **R.L. Webb** and M.J. Brody. Vasopressin projections and central control of cardiovascular function. (Brattleboro Rat Model). Ann. New York Acad. Sci. 394: 729-734, 1982.

4. K.H. Berecek, **R.L. Webb** and M.J. Brody. Evidence for a central role for vasopressin in cardiovascular regulation. Am. J. Physiol. 244: H852- H859, 1983.

5. S.P. Arneric, S.A. Chow, R.K. Bhatnagar, **R.L. Webb**, L.J. Fisher and J.P. Long. Evidence that central dopamine receptors modulate sympathetic neuronal activity to the adreanl medulla to alter glucoregulatory mechanisms. Neuropharmacology 23: 137-147, 1984.

6. M.J. Brody, **R.L. Webb**, M.L. Mangiapane, J.P. Porter, A.C. Bonham and A.J. Trapani. Comparative central and peripheral antihypertensive mechanisms of urapidil and prazosin. Am. J. Med. 77(4A): 74-80, 1984.

7. J.P. Porter, A.C. Bonham, M.L. Mangiapane, **R.L. Webb** and M.J. Brody. Central and peripheral cardiovascular effects of indoramin in conscious rats. Eur. J. Pharmacol. 109: 9-17, 1985.

8. A.W. Cowley, Jr., J.F. Liard, M.M. Skelton, E.W. Quillen, Jr., J.W. Osborn, Jr. and **R.L. Webb**. Vasopressin-neural interactions in the control of cardiovascular function. In: *Vasopressin*, ed. by R.W. Schrier. Raven Press, New York, 1985, pp. 1-10.

9. R.W. Lappe, **R.L. Webb** and M.J. Brody. Selective destruction of renal afferent versus efferent nerves in rat. Am. J. Physiol. 249: R634-R637, 1985.

10. **R.L. Webb**, R. Della Puca, J. Manniello, R.D. Robson, M.B. Zimmerman and R.D. Ghai. Dopaminergic mediation of the diuretic and natriuretic effects of ANF in the rat. Life Sci. 38: 2319-2327, 1986.

11. **R.L. Webb**, G.R. Ghai, B.W. Barclay, R.D. Ghai and M.B. Zimmerman. A comparison of the vasorelaxant and hemodynamic properties of synthetic atriopeptins. In: *Biologically Active Atrial Peptides*, ASH Symposium Series, ed. by J. Laragh, Raven Press, New York, 1987, pp. 335-338.

12. **R.L. Webb**, J.W. Osborn, Jr. and A.W. Cowley, Jr. Cardiovascular actions of vasopressin: baroreflex modulation in the conscious rat. Am. J. Physiol. 251: H1244-H1251, 1986.

13. **R.L. Webb** and M.J. Brody. Functional identification of the central projections of afferent renal nerves. Clin. Exp. Hyperten. (Theory and Practice), A9 (Suppl. 1): 47-57, 1987.

14. E.F. Smith, III, J.W. Egan, F.R. Goodman, M.B. Zimmerman, **R.L. Webb** and L.G.T. Ribeiro. Effects of two non-sulfhydryl angiotensin converting enzyme inhibitors, CGS 14831 and CGS 16617, on myocardial damage and left ventricular hypertrophy following coronary artery occlusion in the rat. Pharmacology, 37: 254-263, 1988.

15. L.P. Wennogle, R.D. Ghai, C. McMartin, **R.L. Webb**, M. Erion, J. Gilligan, H.H. Oei and M.B. Zimmerman. Multiple mechanisms mediate disappearance of ANF from the vascular compartment in the rat. In: *Biological and Molecular Aspects of Atrial Factors*, ed. by P. Needleman. Alan R. Liss, Inc., New York, 1988, pp. 13-27.

16. **R.L. Webb**, G.D. Yasay, Jr., C. McMartin, R.B. McNeal, Jr. and M.B. Zimmerman. Degradation of atrial natriuretic peptide: pharmacologic effects of endoprotease 24.11 inhibition. J. Cardiovasc. Pharmacol. 14: 285-293, 1989.

17. A.J. Hutchison, **R.L. Webb**, H.H. Oei, G.R. Ghai, M.B. Zimmerman and M. Williams. CGS 21680C, an A_2-selective adenosine receptor agonist with preferential hypotensive activity. J. Pharmacol. Exp. Ther. 251: 47-55, 1989.

18. M. Williams, **R.L. Webb**, H.H. Oei, M.F. Jarvis, G.R. Ghai and A.J.Hutchison. Adenosine receptor ligands as therapeutic entities: molecular specificity in relation to functional and therapeutic activity. In: *Adenosine Receptors in the Nervous System*, ed. by J.A. Ribeiro, Taylor and Francis, 1989, Symposium Proceedings, Algarve, Portugal.

19. A.J. Hutchison, M. Williams, **R.L. Webb**, H.H. Oei and M.F. Jarvis. The design of a series of highly A_2-selective adenosine agonists. Proceedings of the Purine Nucleoside and Nucleotide Meeting, Rockville, MD. Sept. 1989.

20. A.J. Hutchison, M. Williams, R. de Jesus, R. Yokoyama, H.H. Oei, G.R. Ghai, **R.L. Webb**, H.C. Zoganas, G.A. Stone and M.F. Jarvis. 2-

(Arylalkylamino)adenosine-5'-uronamides: a new class of highly selective adenosine A_2 receptor ligands. J. Med. Chem. 33: 1919-1924, 1990.

21. **R.L. Webb**, D. Miller, V. Traina and H. Gomez. Benazepril. Cardiovasc. Drug Rev. 8(2):89-104, 1990.

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55. B. Pilz, E. Shagsaduren, M. Wellner, A. Fiebeler, R. Dechend, P. Gratzer, S. Meiners, D. L. Feldman, **R. L. Webb**, F.C. Luft, and D.N. Muller. Aliskiren, a human renin inhibitor, reverses angiotensin II-induced renal and cardiac damage in dTGR in a regression study design. Submitted to the American Society of Nephrology, May, 2004.

56. V. Mellin, P. Mulder, B. DiMeglio, J.P. Henry, A.Y. Jeng, **R.L. Webb** and C. Thuillez. Long-term aldosterone synthase inhibition improves cardiac function and myocardial structure in chronic heart failure. Circulation 110(17, Suppl.3):III-102, 2004.

57. A. Fiebeler, Juerg Nussberger, E. Shagdarsuren, R. Dechend, S. Rong, N. Al-Saadi, A. Gapelyuk, A. Schirdewan, M. Wellner, A. Jeng, **R.L. Webb**, F.C. Luft, D. Mueller. Aldosterone synthase inhibitor FAD286 ameliorates angiotensin II-induced end organ damage. Circulation 100(17, Suppl. 3):II-101, 2004.

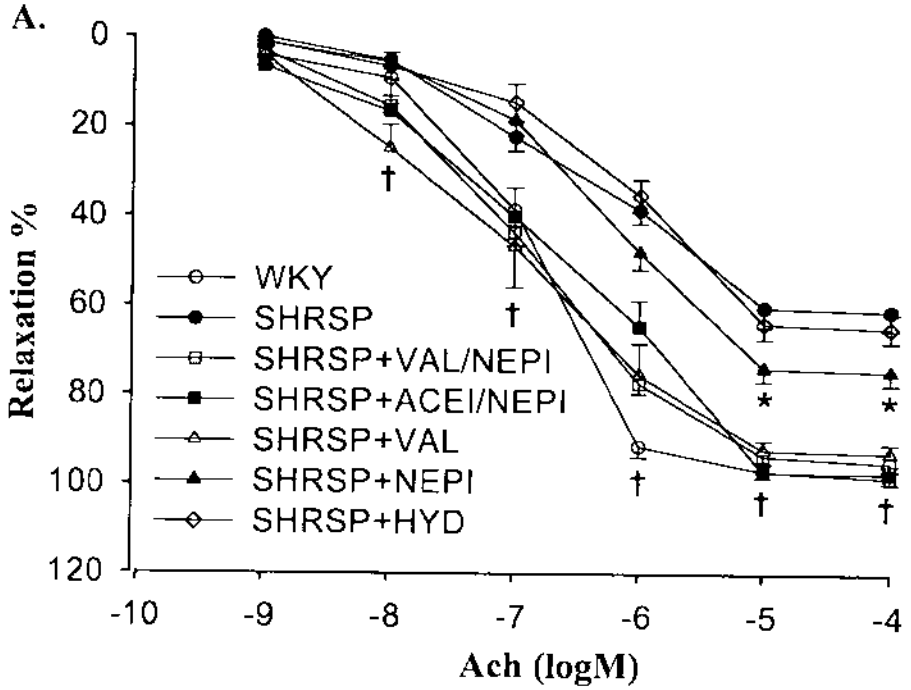
58. C. Xue, **R.L. Webb** and H.M. Siragy. Aldosterone synthase inhibitor FAD286 decreases albuminuria and renal matrix in diabetic rats. Hypertension 46(10):45, 2005.

59. D.L. Feldman, L. Jin, R. Miserendino-Moltini, H. Xuan, Y. Zhou, **R.L. Webb**. The Renin Inhibitor Aliskiren Ameliorates Hypertensive Diabetic Nephropathy in Transgenic (mRen-2)27 (Ren-2) Rats. Submitted to American Society of Nephrology, June 2005, Philadelphia, PA.

60. A. Fiebeler, E. Shagdarsuren, B. Pilz, P. Gratze, R. Dechend, D.L. Feldman, **R.L. Webb**, F.C. Luft, and D.N. Müller. Low-dose renin inhibitor and AT1-receptor blocker ameliorate angiotensin II-induced end-organ damage despite persistence of hypertension. Poster TH-PO257 to be presented at Amer. Soc. Nephrol. Meeting, November 8-13, 2005, Philadelphia, PA.

Figure 1

A.



B.

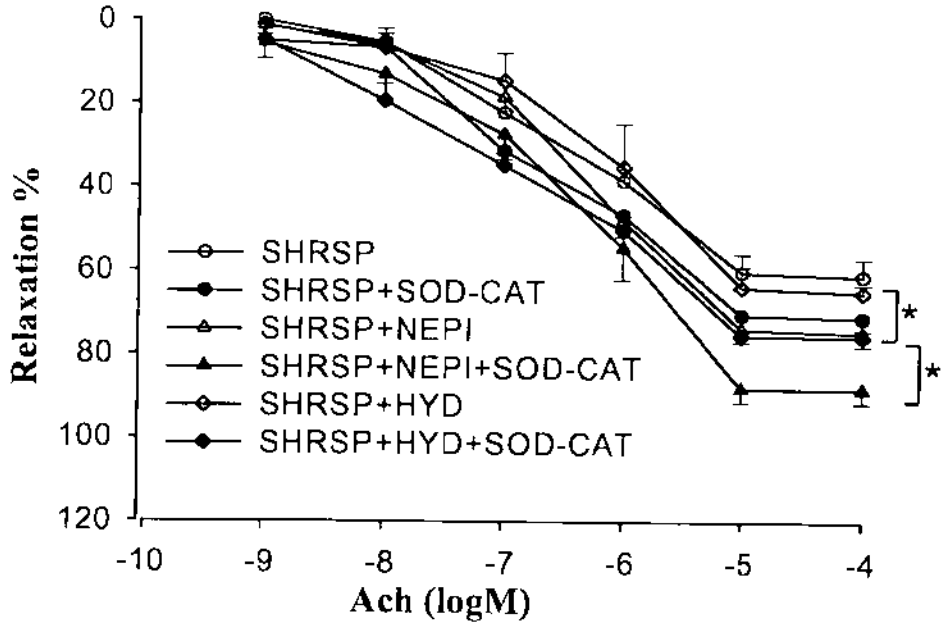
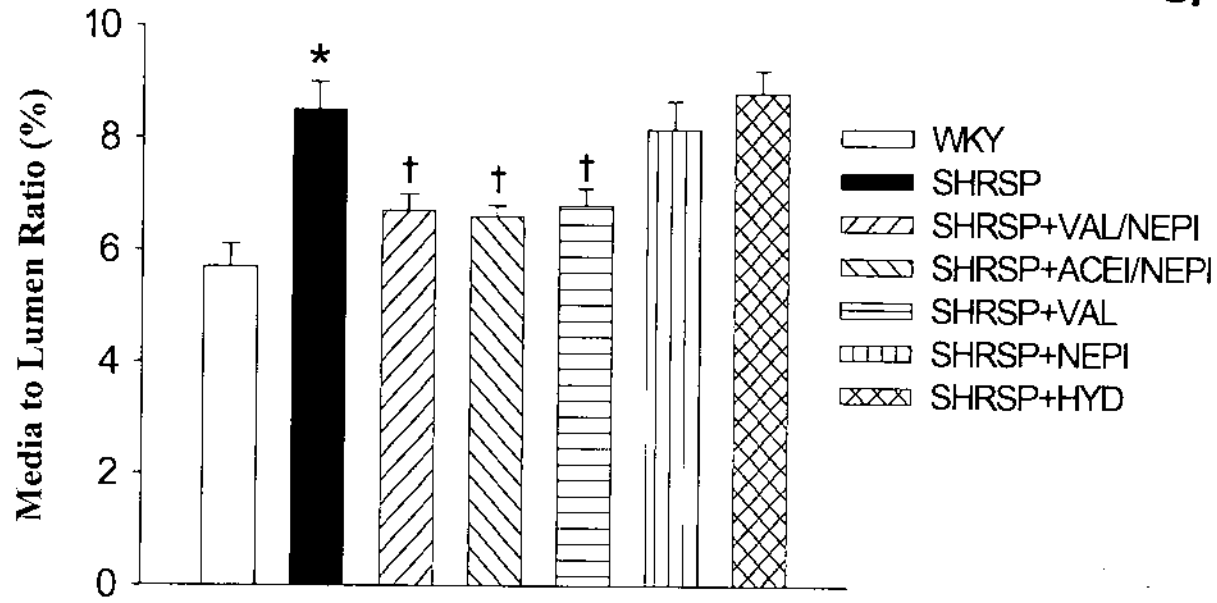


Figure 2

A.



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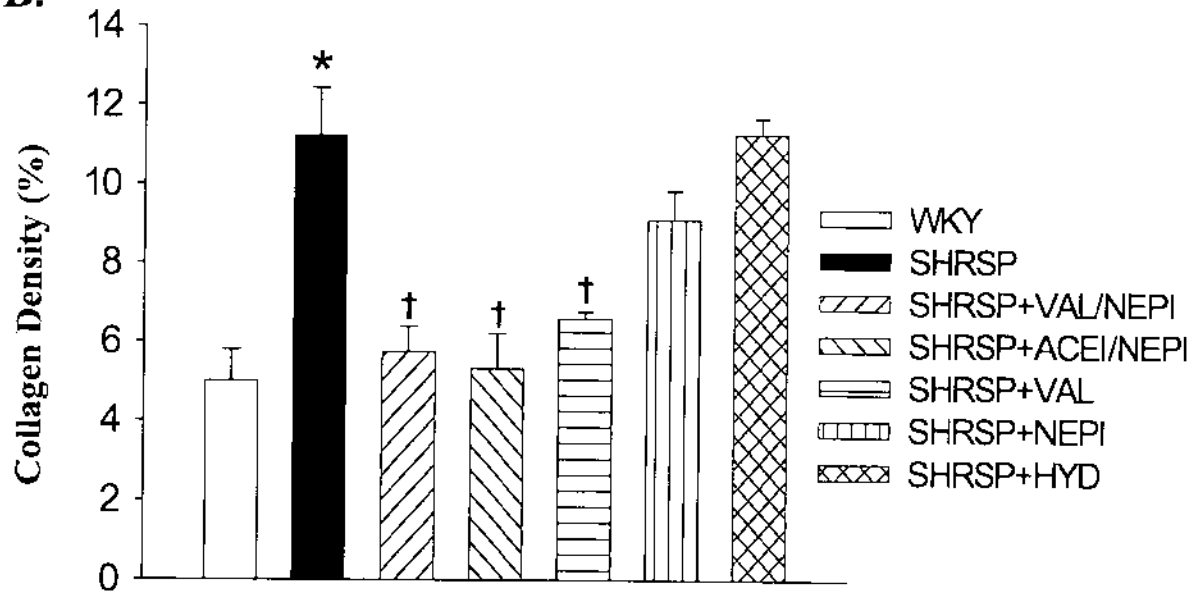


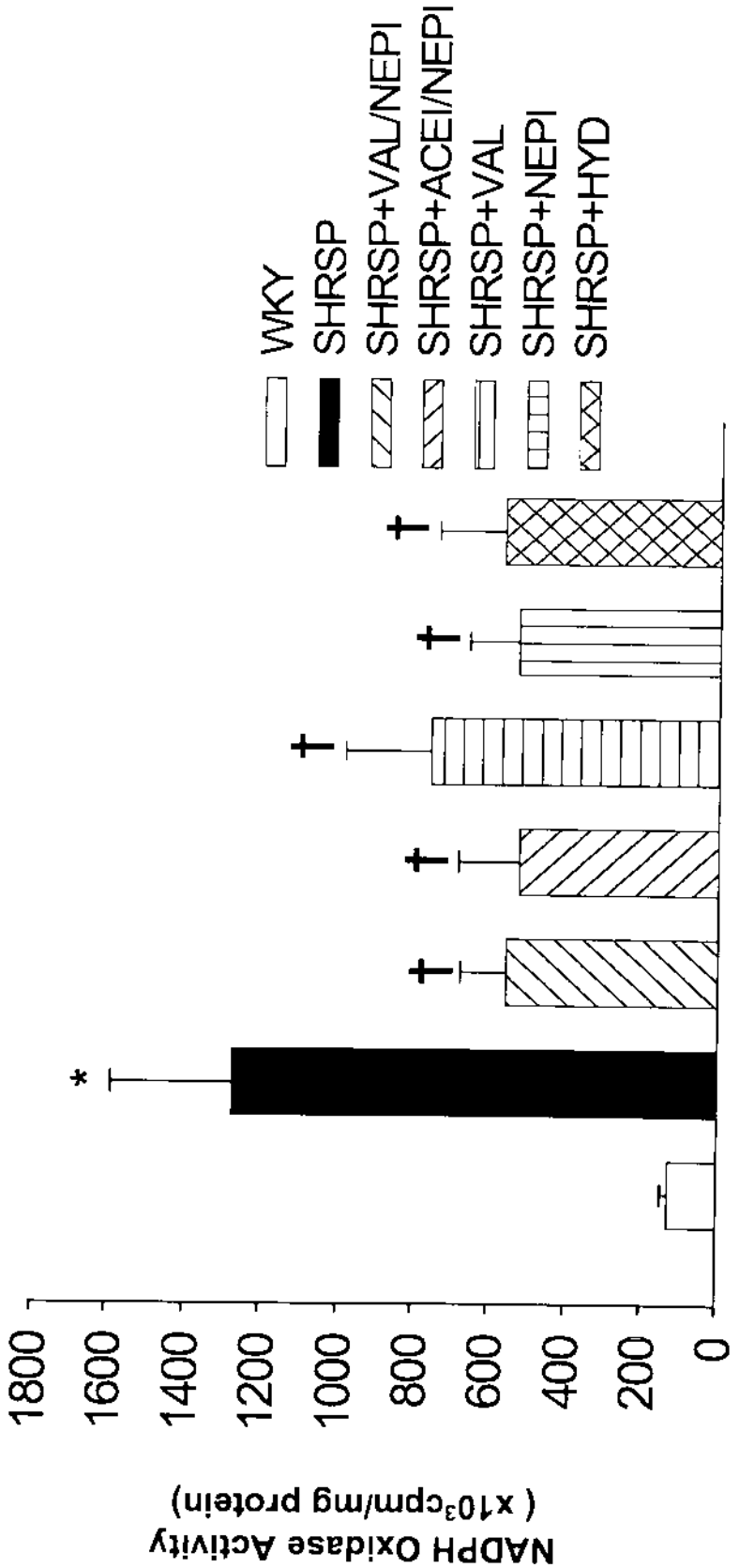
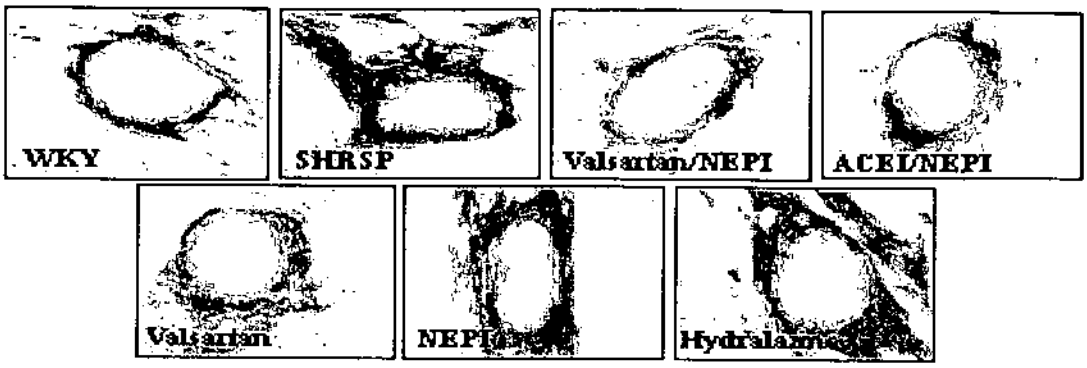
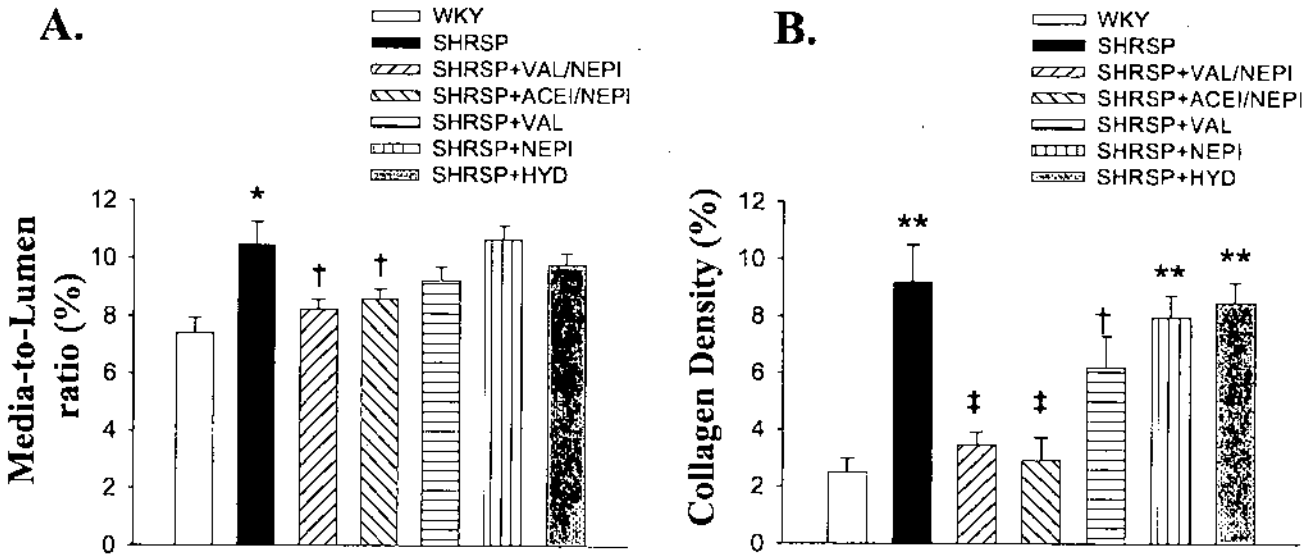


Figure 3

Figure 4





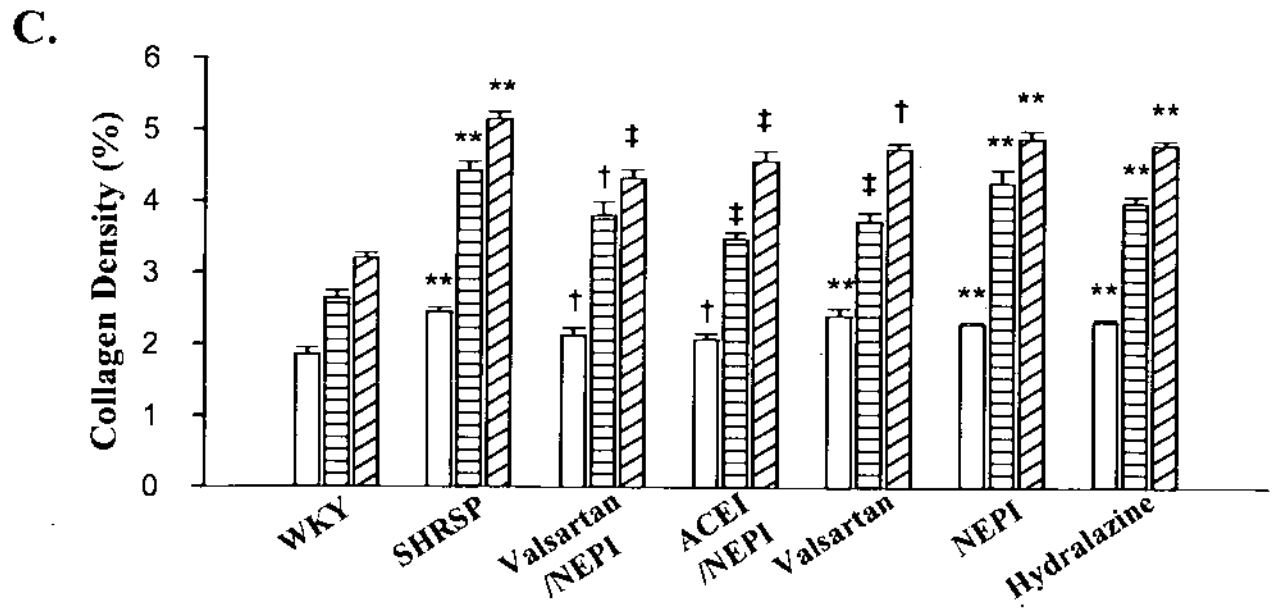


Figure 5

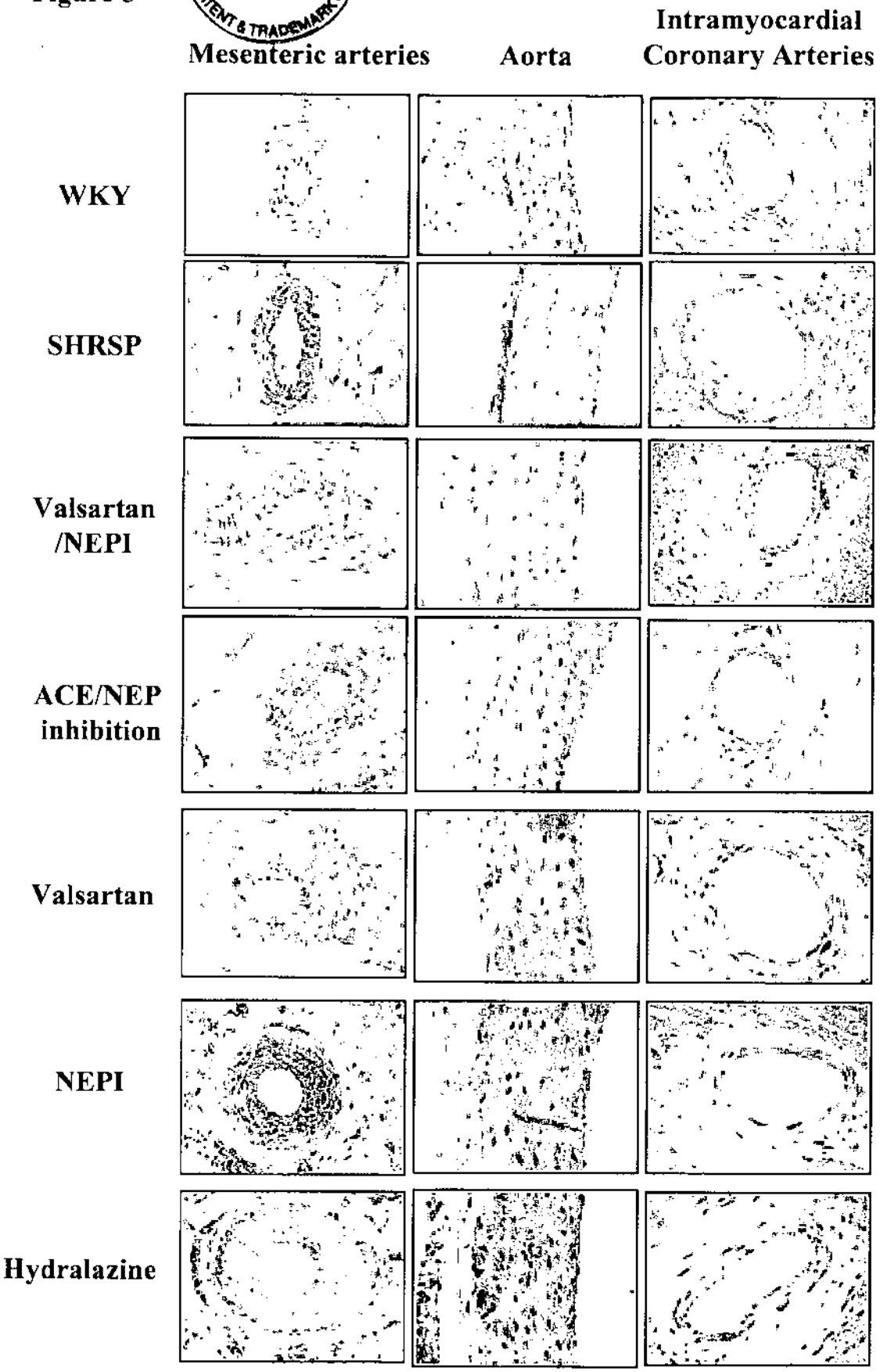
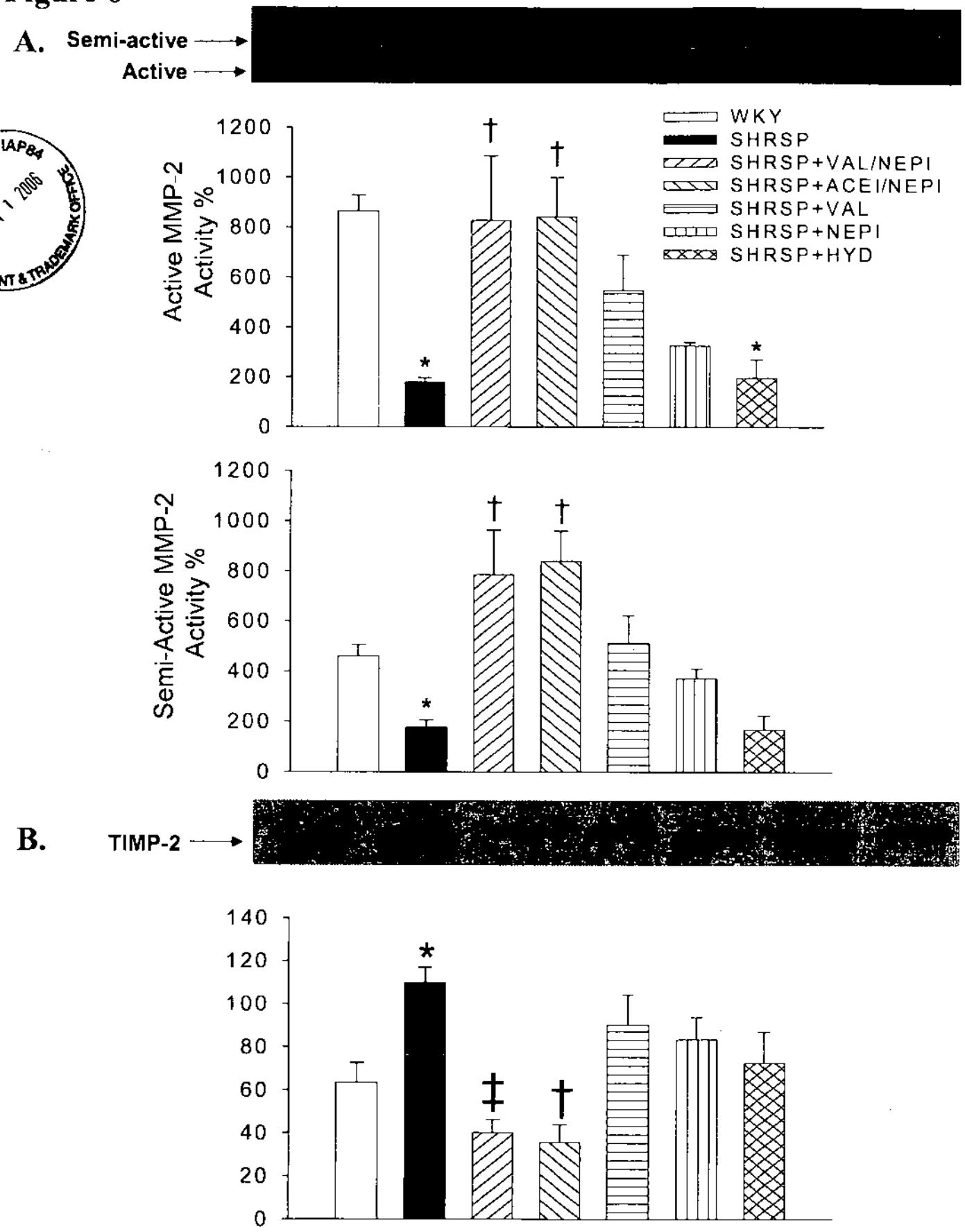


Figure 6



05-12-06 IFW 1617 #

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV824503415 US	May 11, 2006
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO: 10/341,868

FILED: JANUARY 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of January 12, 2006 has a shortened statutory time set to expire on April 12, 2006. A one-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $120 for payment of the extension fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

05/15/2006 FFANAEIA 00000015 190134 10341868
01 FC:1251 120.00 DA

Respectfully submitted,

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134
Phone No. (862) 778-7831

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Date: May 11, 2006

ARTIFACT SHEET

Enter artifact number below. Artifact number is application number + artifact type code (see list below) + sequential letter (A, B, C ...). The first artifact folder for an artifact type receives the letter A, the second B, etc..
Examples: 59123456PA, 59123456PB, 59123456ZA, 59123456ZB

10341868 CA

Indicate quantity of a single type of artifact received but not scanned. Create individual artifact folder/box and artifact number for each Artifact Type.

☐ CD(s) containing:
- computer program listing ☐
  Doc Code: Computer Artifact Type Code: P
- pages of specification and/or sequence listing and/or table ☐
  Doc Code: Artifact Artifact Type Code: S
- content unspecified or combined ☐
  Doc Code: Artifact Artifact Type Code: U

☒ Stapled Set(s) Color Documents or B/W Photographs
Doc Code: Artifact Artifact Type Code: C

☐ Microfilm(s)
Doc Code: Artifact Artifact Type Code: F

☐ Video tape(s)
Doc Code: Artifact Artifact Type Code: V

☐ Model(s)
Doc Code: Artifact Artifact Type Code: M

☐ Bound Document(s)
Doc Code: Artifact Artifact Type Code: B

☐ Confidential Information Disclosure Statement or Other Documents marked Proprietary, Trade Secrets, Subject to Protective Order, Material Submitted under MPEP 724.02, etc.
Doc Code: Artifact Artifact Type Code X

☐ Other, description: _____
Doc Code: Artifact Artifact Type Code: Z

March 8, 2004

PATENT APPLICATION FEE DETERMINATION RECORD
Effective January 1, 2003

Application or Docket Number: 10/341868

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	11	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	11 minus 20=	* 0
INDEPENDENT CLAIMS	5 minus 3 =	* 2
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	$375	OR	BASIC FEE	$750
X$ 9=		OR	X$18=	
X42=		OR	X84=	168
+140=		OR	+280=	
TOTAL		OR	TOTAL	918

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 9	Minus	** 20	* —
Independent	* 5	Minus	*** 5	* —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	—
X42=		OR	X84=	—
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	—

9-30-05

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* SAME	Minus	**	*
Independent	* SAME	Minus	***	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

		OR		
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

5-11-06

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 5	Minus	** 20	*
Independent	* 3	Minus	*** 5	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

1, 4, 5,

		OR		
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

1095 7590 07/25/2006

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/341,868	KSANDER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7* is/are pending in the application.

4a) Of the above claim(s) *5 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/4/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on May 11, 2005 have been received and entered into the application.

Action Summary

The rejection of claims 8-11 under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record is hereby expressly withdrawn in view of Applicant's amendment indicating cancellation of the claims.

The rejection of claims 1, 3 and 4 under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record and Buhlmayer et al. (U.S.Patent No. 5,399,578) is being maintained for the reasons stated in the previous Office Action.

Response to Arguments

Applicant's arguments filed May 11, 2005 have been fully considered but they are not persuasive. Applicants argues with respect to rejection under 35 U.S.C. 103(a) over Ksander and Buhlmayer et al. with the Declaration of Gary Ksander (as being one of ordinary skill) that one of ordinary skill in the art would not motivated to combined cited two patents to make the combination of the claimed invention. This is not persuasive

because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves. It is well settled in the law as stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

> It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

Further, the affidavit filed under 37 CFR 1.132, an expert's opinion on the ultimate legal issue must be supported by something more than a conclusory statement. *In re Brandstadter*, 484 F .2d 1395, 1405, 179 USPQ 286, 294 (CCPA 1973).

The Webb Declaration has been carefully reviewed and considered but the alleged unexpected result is not persuasive because each of the patent teaches the "effective amounts" to be employed to obtain antihypertensive effect, i.e. Buhlmayer et al. teach the effective amount of valsartan of about 30mg/kg. (column 7, lines 25-30); Ksander teach the effective amount of AHU377 of about 10mg and 100mg for a mammal of about 50 to 70kg (column 18, lines 59-64). It is noted that Applicants experiments showing synergistic, unexpected and surprising antihypertensive effect of a combination of valsartan at 30mg/kg/day and AHU 377 at 30mg/kg/day and the combination of valsartan at 100mg/kg/day and AHU377 at 30mg/kg/day, would be expected since these dosages are much higher than the effective dosage taught by the patents.

Therefore, Applicants recitation of the specification at page 7, line 17 that, "....a combination of valsartan and a NEP inhibitor **achieves greater therapeutic effect** than the administration of valsartan, ACE inhibitors or NEP inhibitors alone..." is expected upon administration of higher recommended dosage. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record and Buhlmayer et al. (U.S.Patent No. 5,399,578).

Ksander teaches a pharmaceutical composition comprising the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme (NEP) inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches ammonium salts, mono-, di- or tri-lower (**alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**) are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45).

Buhlmayer et al. teach valsartan is useful for an anti-hypertensive treatment. (abstract, claims).

The claims differ from the cited references in claiming a pharmaceutical composition comprising combination of the specific NEP inhibitor and valsartan. To employ combinations of specific NEP inhibitor and valsartan would have been obvious because all the components are well known individually for treating hypertension. One of ordinary skill in the art would have been motivated to combine specific NEP inhibitor and valsartan in a single composition in order to achieve an expected benefit of antihypertensive effect of the combination. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sreenivasan Padmanabhan
Supervisory Examiner
Art Unit 1617

Jmk
July 13, 2006

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. 4-32219A
APPLICATION NO. 10/341,868
APPLICANT KSANDER ET AL.
FILING DATE JANUARY 14, 2003
Group 1617

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA	US 4,610,816	09/09/86	Berger	549	452	06/15/84
	AB	US 4,722,810	02/02/88	Delaney et al.	260	402.5	08/13/86
	AC	US 4,740,499	04/26/88	Olins	514	13	07/28/86
	AD	US 4,749,688	06/07/88	Haslanger et al.	514	19	06/20/86
	AE	US 4,929,641	05/29/90	Haslanger et al.	514	506	05/11/88
	AF	US 5,217,996	06/08/93	Ksander	514	533	01/22/92
	AG	US 5,223,516	06/29/93	Delaney et al.	514	339	04/24/91
	AH	US 5,273,990	12/28/93	De Lombaert	514	381	09/03/92
	AI	US 5,294,632	03/15/94	Erion et al.	514	381	10/09/92
	AJ	US 5,399,578	03/21/95	Bühlmayer et al.	514	381	12/29/92
	AK	US 5,520,522	05/28/96	Rathore et al.	417	322	09/21/94
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM	EP 0 342 850	11/23/89	Europe			☐	☐
	AN	EP 0 343 911	11/29/89	Europe			☐	☐
	AO	EP 0 361 365	04/04/90	Europe			☐	☐
	AP	EP 0 443 983	08/28/91	Europe			☐	☐
	AQ	EP0636621B1	3/12/97	Europe			☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

AR	Almeida et al., "Clearance Function of Type C Receptors of Atrial Natriuretic Factor in Rats", *Am J Physiol*, Vol. 256, pp. R469-R475 (1989).
AS	Bazil, Krulan and Webb, "Telemetric Monitoring of Cardiovascular Parameteres in Conscious Spontaneously Hypertensive Rats", *J Cardiovasc Pharmacol*, Vol. 22, pp. 897-905 (1993).
AT	Consensus Trial Study Group, "Effects of Enalapril on Mortality in Severe Congestive Heart Failure", *N Eng J Med*, Vol. 316, No. 23, pp. 1429-1435 (1987).

EXAMINER [signature] DATE CONSIDERED 7/20/06

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

FORM PTO-1449 (REV. 7-85)
U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.
4-32219A
APPLICATION NO.
10/341,868
APPLICANT
KSANDER ET AL.
FILING DATE
JANUARY 14, 2003
Group
1617

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
✓	CA	EP 0 636 621	02/01/95	Europe			☐	☐
✓	CB	GB 2 218 983	11/29/89	United Kingdom			☐	☐
	CC	WO 90/09374	08/23/90	WIPO			☐	☐
	CD	WO 92/14706	09/03/92	WIPO			☐	☐
	CE	WO 93/09101	05/13/93	WIPO			☐	☐
	CF	WO 93/10773	06/10/93	WIPO			☐	☐
✓	CG	WO 94/15908	07/1/94	WIPO (English Abstract)			☐	☐
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EXAMINER [signature] DATE CONSIDERED 9/20/06

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

FORM PTO-1449 (REV. 7-85)

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FILING DATE
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Group
1617

EXAMINER INITIAL

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	DA	Stephenson et al., "The hydrolysis of a-human atrial natriuretic peptide by pig kindney microvillar membranes is initiated by endopeptidase-24.11 *Biochem J*, Vol. 243, pp. 183-187(1987).
	DB	Erdös, "Angiotensin I Converting Enzyme and the Changes in Our Concepts Through the Years" – Lewis K. Dahl Memorial Lecture, *Hypertension*, Vol. 16, No. 4, pp. 363-370 (1990).
	DC	Intengan, Park and Schiffrin, "Blood Pressure and Small Arteries in DOCA-Salt-Treated Genetically AVP-Deficient Rats", *Hypertension*, Vol. 34, No. 4, Part 2, pp. 907-913 (1999).
	DD	Intengan, Thibault, Li and Schiffrin, "Resistance Artery Mechanics, Structure, and Extracellular Components in Spontaneously Hypertensive Rats", *Circulation*, Vol. 100, No. 22, pp. 2267-2275 (1999).
	DE	Needleman et al., "The Biochemical Pharmacology of Atrial Peptides", *Annu Rev Pharm Tox*, Vol. 29, pp. 23-54 (1989).
	DF	Stephenson and Kenny, "Metabolism of Neuropeptides", *Biochem J*, Vol. 241, pp. 237-247 (1987).
	DG	Sybertz et al., "SCH 39370, a Neutral Metalloendopeptidase Inhibitor, Potentiates Biological Responses to Atrial Natriuretic Factor and Lowers Blood Pressure in Desoxycorticosterone Acetate-Sodium Hypertensive Rats", *J Pharmacol Exp Ther*, Vol. 250, No. 2, pp. 624-631 (1989).
	DH	Sybertz et al., "Atrial Natriuretic Factor-Potentiating and Antihypertensive Activity of SCH 34826", *Hypertension*, Vol. 15, No. 2, pp. 152-161 (1990).
	DI	Williford, Sharma, Korth and Sheu, "Spatial Heterogeneity of Intracellular Ca^{2+} Concentration in Nonbeating Guinea Pig Ventricular Myocytes", *Circ Res*, Vol. 66, No. 1, pp. 241-249 (1990).
	DJ	Zannad, "The Emerging Role of ACE Inhibitors in the Treatment of Cardiovascular Disease", *J Cardiovasc Pharmacol*, Vol. 15, Suppl. 2, pp. S1, S5 (1990).
	DK	CAPLUS Abstract AN 1986:573042 - Taub et al., f ZA8400670, 9/25//1985
	DL	CAPLUS Abstract AN 1995: 931230- Sugano et al., JP 07157459, 06/20/1995,
	DM	CAPLUS Abstract AN 1995:412660 – Yamada et al., JP 06234754, 8/23/1994
	DN	

EXAMINER	DATE CONSIDERED
	7/20/06

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/341,868	KSANDER ET AL	
Examiner	**Art Unit**	
Jennifer Kim	1617	

SEARCHED			
Class	Subclass	Date	Examiner
514	533	1/6/2006	JMK
514	381	1/6/2006	JMK
updated		7/20/06	JMK

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor search	1/6/2006	JMK
STN (medicine, registry); WEST	1/6/2006	JMK
STIC	12/15/2005	JMK
updated	7/20/06	JMK

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/341,868	KSANDER ET AL.
Examiner	**Art Unit**
Jennifer Kim	1617

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	+	Restricted	I	Interference	O	Objected

Claim		Date									
Final	Original	9/20/05	1/6/06	3/9/06							
	1	+	√	√							
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Interview Summary	Application No.	Applicant(s)	
	10/341,868	KSANDER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jennifer Kim*. (3) *Mr. Ferraro*. GF

(2) *Dr. Randy Lee Webb*. RLW (4)_____.

Date of Interview: *03 October 2006*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *Pending claims*.

Identification of prior art discussed: *Prior art of record (Buhlmayer et al., Ksander et al.(Us 5217996)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *General nature of the invention was discussed. Mr. Ferraro discussed synergistic effect of combination comprising valsartan and AHU 377. Exhibit 1 shows combination of Val:AHU377 in specific amounts showing significantly surprising and unexpected result. One dosage, valsartan and NEPi at 30:30 mg/kg/day is expressly disclosed in the cited references and others were implicitly disclosed.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

10/3/06
Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV 485023062US
Express Mail Label Number

11/20/06
Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M.

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

Sir:

Responsive to the Interview of October 3, 2006 and the outstanding action dated July 25, 2006, in the above-identified application, having a period for response set to expire November 27, 2006 (November 25, 2006 being a Saturday), due to the attached one-month petition for extension of time, Applicants respectfully request the following amendment be entered and the claims considered in light thereof.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

This listing of the claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof in a daily unit dose of about 20 mg to about 320 mg; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof in a daily unit dose of about 20 mg to about 800 mg and a pharmaceutically acceptable carrier.

2. (canceled)

3. (previously presented) The pharmaceutical composition of Claim 1, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. (currently amended) A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof in a daily unit dose of about 20 mg to about 800 mg and in a second container a pharmaceutical composition comprising valsartan in a daily unit dose of about 20 mg to about 320 mg.

5. (withdrawn) A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management

of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. (canceled)

7. (withdrawn) The method of Claim 5, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

8-11. (canceled)

REMARKS

Reconsideration of the above-identified application as amended is requested. Claims 1 and 4 have been amended. Claims 1, 3 and 4 remain in the application. No new matter has been added.

The Interview of October 3, 2006

Applicants thank the Examiner for the courtesy extended during the above Interview. Applicants agree with comments which were made a part of the Interview Summary prepared by the Examiner on October 3, 2006. For completeness, the exhibits provided to the Examiner during the interview are attached hereto.

Rejection of claims 1, 3 and 4 under 35 U.S.C. §103(a)

Claims 1, 3 and 4 were rejected under 35 U.S.C. §103(a) over Ksander U.S. Patent No. 5,217,996 ('996 patent) and Buhlmayer et al. U.S. Patent No. 5,399,578 ('578 patent). In response to the arguments and declarations previously submitted, the Examiner states that the Applicants' experiments showing synergistic, unexpected and surprising antihypertensive effect of a combination of valsartan at 30 mg/kg/day and AHU377 at 30 mg/kg/day and the combination of valsartan at 100 mg/kg/day and AHU377 at 30 mg/kg/day, would be expected since these dosages are much higher than the effective dosage taught by the patents. Applicants respectfully traverse this rejection insofar as it applies to the claims as amended.

The Examiner states that the Buhlmayer patent teaches the effective amount of valsartan of about 30 mg/kg/day and that the Ksander patent teaches the effective amount of AHU377 of about 10 mg and 100 mg for a mammal of about 50 to 70 kg. Applicants respectfully submit that the dosages for the tests in the Dahl salt-sensitive rat using 30 mg/kg valsartan and 30 mg/kg NEPi were, in fact, disclosed in the prior art. Buhlmayer discloses the 30 mg/kg valsartan dosage in a rat model that the Examiner cited at col. 7, lines 25-30, and Ksander also discloses a dosage of 30 mg/kg NEPi in a rat model at col. 11, lines 32-37. The section quoted in the Office Action ("about 10 mg and 100 mg for a mammal of about 50 to 70 kg") relates to dosages in humans, not rats.

Thus, because the dosages 30 mg/kg valsartan and 30 mg/kg NEPi for a rat are disclosed in the prior art, this test did not use "higher" than the effective dosages disclosed in prior art to yield synergistic results. For that reason alone, Applicants respectfully request that the rejection be withdrawn and the case allowed.

Further, for the tests combining the dosages of 100 mg/kg valsartan and 30 mg/kg NEPi in Dahl salt-sensitive rats, while the 100 mg/kg valsartan dosage was not expressly disclosed in the prior art, the test was fair and the results meaningful.

It is fair because the 100 mg/kg valsartan dosage in combination is compared with the same 100 mg/kg valsartan dosage as monotherapy. And the 30 mg/kg NEPi dosage is, as

shown above, disclosed. Testing at a dosage of 100 mg/kg valsartan is also meaningful to demonstrate efficacy over a range of fixed-dose combinations.

Moreover, the prior art does not limit the dosage to 30 mg/kg valsartan. The specification language with respect to valsartan dosages, "[i]t was possible to detect the pronounced antihypertensive effect from a dose of about 30 mg/kg p.o.", Buhlmayer col. 7, lines 15-18 and 27-29 (emphasis added), and "[t]he dose of the active ingredient depends on the species of warm blooded animal species, the age and the individual condition and on the manner of administration", Buhlmayer col. 27, lines 40-42 (emphasis added), is not limiting language.

Similarly, for the tests combining the dosages of 10 mg/kg valsartan and 100 mg/kg NEPi in the stroke prone spontaneously hypertensive rat (SHRsp), while the 100 mg/kg NEPi dosage was not expressly disclosed, the test was fair and the results meaningful. It is fair because the 100 mg/kg NEPi dosage in combination is compared with the same 100 mg/kg NEPi dosage as monotherapy. Testing at a dosage of 100 mg/kg NEPi is also meaningful to demonstrate efficacy over a range of fixed-dose combinations.

Moreover, the prior art does not limit the dosage to 30 mg/kg valsartan or NEPi. Again, the specification language with respect to valsartan dosages, "[i]t was possible to detect the pronounced antihypertensive effect from a dose of about 30 mg/kg p.o.", Buhlmayer col. 7, lines 15-18 and 27-29 (emphasis added), is not limiting language. Thus, testing at the lower 10 mg/kg valsartan dosage is meaningful.

The prior art language with respect to NEPi dosages, "[t]he dosage in vivo may range depending on the route of administration between about 0.01 and 50 mg/kg, advantageously between about 1.0 and 25 mg/kg", Ksander, col. 9, lines 27-30 and 36-39 (emphasis added), is also not limiting. Thus, testing at the higher 100 mg/kg NEPi dosage is meaningful.

In addition to the above and without admitting that a declaration is required to overcome the rejection, Applicants are attaching hereto a second declaration of Dr. Randy Webb. The second Webb Declaration establishes that the valsartan and AHU377 dosages in the rat studies were selected based on their ability to block the AT_1 receptor or inhibit the NEP enzyme, respectively, in the particular species, and that in humans, valsartan and AHU377 block the AT_1 receptor or inhibit the NEP enzyme at the dosages set forth in the amended claims. Accordingly, this establishes that testing at the dosages selected in the rat studies is predictive of the antihypertensive effect to be achieved in humans over the human dosage range of from about 20 mg to about 320 mg for valsartan and from about 20 mg to about 800 mg for NEP inhibitors (*see, e.g.*, page 16, lines 9-10 and 18 in the instant application).

Based on this, the combination of valsartan and AHU377 is expected to have the same synergistic, unexpected and surprising antihypertensive effect over monotherapy when administered in humans in the dosage ranges of from about 20 mg to about 320 mg of valsartan

and from about 20 mg to about 800 mg of AHU377 as was seen in the rats at the particular dosages administered.

Thus, since the human dosage ranges to which the amended claims are now directed would be expected to show synergy in humans, the obviousness rejection based on the cited art is overcome.

In view of the foregoing, Applicants submit that all rejections have been traversed and should be withdrawn and that the Application is now in condition for allowance and respectfully requests early notice to that effect.

Respectfully submitted,

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134

Date: 11/20/06

EXHIBIT 1:

Blood Pressure (BP) Results for Valsartan and Specific NEPi Monotherapy and Combination Therapy

Dahl salt-sensitive model:

	Dose mg/kg/day	Final BP mmHg	Improvement over Vehicle mmHg	Expected Improvement mmHg	**Improvement Factor mmHg**
Vehicle		193 ± 5			
Valsartan	30	191 ± 6	-2		
Valsartan	100	196 ± 7	+3		
AHU377	30	191 ± 5	-2		
AHU377	100	177 ± 5	-16		
Val:AHU377	**30:30**	**176 ± 6**	**-17**	**-4**	**-13**
Val:AHU377	**100:30**	**174 ± 5**	**-19**	**+1**	**-18**

SHRsp model :

Systolic Blood Pressure (SBP):

	Dose mg/kg/day	Final SBP mmHg	SBP Reduction	Expected Improvement mmHg	**Improvement Factor mmHg**
Vehicle		195 ± 6			
Valsartan	10	176 ± 6	-19		
AHU377	100	199 ± 6	+4		
Val:AHU377	**10:100**	**167 ± 5**	**-28**	**-15**	**-13**

Diastolic Blood Pressure (DBP):

	Dose mg/kg/day	Final DBP mmHg	DBP Reduction	Expected Improvement mmHg	**Improvement Factor mmHg**
Vehicle		142 ± 3			
Valsartan	10	137 ± 7	-4.6		
AHU377	100	151 ± 8	+9.5		
Val:AHU377	**10:100**	**118 ± 5**	**-23.8**	**+4.9**	**-28.7**

EXHIBIT 2:

Additional Therapeutic Benefits of Valsartan / Specific NEPi Combination

	Dosage (mg/kg/day)	Decreased Media/Lumen Ratio of Intramyocardial Coronary Arteries	Increased MMP-2 Activity; Decreased TIMP-2 Activation	Decreased Collagen Density of Intramyocardial Coronary Arteries	Decreased Vascular Macrophage Infiltration
Valsartan	10	No effect	No effect	Some effect	Some effect
AHU377 (NEPi)	100	No effect	No effect	No effect	Some effect
Combination	10 : 100	Effective	Effective	Most effective	Most effective

EXHIBIT 3:

Prior Art Disclosures of "Effective Amounts" of Valsartan and Specific NEPi

U.S. Patent No. 5,399,578 (Bühlmayer et al.) Valsartan	U.S. Patent No. 5,217,996 (Ksander) Specific NEPi
• "The antihypertensive activity of the compounds [of the invention] and their pharmaceutically acceptable salts may also be manifested in the renally hypertensive rat test model…It was possible to detect the pronounced antihypertensive effect from a dose of about **30 mg/kg p.o.**" [col. 7, lines 15-18 and 27-29 (emphasis added)]. • "The dose of the active ingredient depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration." [col. 27, lines 40-42].	• "The [diuretic, natriuretic, analgesic and antihypertensive] properties are demonstrable in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof…The dosage in vivo may range depending on the route of administration, between about 0.01 and 50 mg/kg, advantageously between about 1.0 and 25 mg/kg." [col. 9, lines 27-30 and 36-39]. • "Illustrative of the invention, [the specific NEPi] at a dose of **30 mg/kg p.o.** … produces a significant reduction in blood pressure in the DOCA-salt hypertensive rat model." [col. 11, lines 32-37 (emphasis added)]. • "A unit dosage for a mammal of about 50 to 70 kg may contain between about 10 and 100 mg of the active ingredient. The dosage of active compound is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration." [col. 18, lines 59-64].

11-21-06 RCE/ 1617

OIPE RECEIVED NOV 20 2006 PATENT & TRADEMARK OFFICE

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Subsection (b) of 35 U.S.C. § 132, effective on May 29, 2000, provides for continued examination of an utility or plant application filed on or after June 8, 1995.
See The American Inventors Protection Act of 1999 (AIPA).

Application Number	10/341,868
Filing Date	January 14, 2003
First Named Inventor	KSANDER ET AL.
Group Art unit	1617
Examiner Name	Kim, Jennifer M
Attorney Docket Number	4-32219A

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

NOTE: *37 C.F.R. § 1.114 is effective on May 29, 2000. If the above-identified application was filed prior to May 29, 2000, applicant may wish to consider filing a continued prosecution application (CPA) under 37 C.F.R. § 1.53 (d) (PTO/SB/29) instead of a RCE to be eligible for the patent term adjustment provisions of the AIPA. See Changes to Application Examination and Provisional Application Practice,* Interim Rule, 65 *Fed. Reg.* 14865 (Mar. 20, 2000), 1233 *Off. Gaz. Pat. Office* 47 (Apr. 11, 2000), which established RCE practice.

1. **Submission required under 37 C.F.R. § 1.114**

   a. ☐ Previously submitted
      i. ☐ Consider the amendment(s)/reply under 37 C.F.R. § 1.116 previously filed on _____
      (Any unentered amendment(s) referred to above will be entered).
      ii. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
   b. ☒ Enclosed
      i. ☒ Amendment/Reply
      ii. ☒ Affidavit(s)/Declaration(s) of Randy Webb
      iii. ☐ Information Disclosure Statement (IDS)
      iv. ☐ Other _____

2. **Miscellaneous**

   a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. § 1.17(i) **required**)
   b. ☐ Other _____

3. **Fees** The RCE fee under 37 C.F.R. § 1.17(e) is required by 37 C.F.R. § 1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 19-0134
      i. ☒ RCE fee required under 37 C.F.R. § 1.17(e)
      ii. ☒ Extension of time fee (37 C.F.R. §§ 1.136 and 1.17)
      iii. ☐ Other
   b. ☐ Check in the amount of $_____ enclosed
   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print/Type)	Gregory D. Ferraro	*Registration No. (Attorney/Agent)*	Reg. No. 36,134 Attorney for Applicants
Signature	Greg Ferraro	*Date*	11/20/06

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV 485023062US — Express Mail Label Number

11/20/06 — Date of Deposit

11/22/2006 DEMMANU1 00000004 190134 10341868

02 FC:1801 790.00 DA

CASE 4-32219A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander et al.
APPLICATION NO: 10/341,868
FILED: January 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M.

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Randy Lee Webb, being duly warned, hereby declare as follows:

1. I am the same Randy Lee Webb who submitted the Declaration under 37 C.F.R. §1.132 dated May 11, 2006 in the application identified in the caption above (which is referred to in this document as "the Application").

2. The experiments summarized in my previous Declaration involved administering valsartan and 4-[*N*-(3-carboxy-1-oxo-propyl)amino]-4-(*p*-phenylphenylmethyl)-3-methylbutanoic acid ethyl ester (AHU377) in combination and as monotherapy in the Dahl salt-sensitive rat, spontaneously hypertensive rat (SHR) and stroke prone male spontaneously hypertensive rat (SHRsp) models of hypertension.

3. Based on the results achieved in the animal models of hypertension, I would fully expect a combination of valsartan and AHU377 to have synergistic, unexpected and surprising antihypertensive effect and added therapeutic benefits in the treatment of hypertension over monotherapy when administered in humans in the daily unit dose ranges of from about 20 mg to about 320 mg of valsartan and from about 20 mg to about 800 mg of AHU377 (*see, e.g.*, page 16, lines 9-10 and 18 in the instant application).

4. I hereby declare that all statements made herein of my own knowledge are true

and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Nov. 16, 2006

Randy Lee Webb

Randy Lee Webb

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV 485023062US — Express Mail Label Number

11/20/06 — Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO: 10/341,868

FILED: JANUARY 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of July 25, 2006 has a shortened statutory time set to expire on October 25, 2006. A one-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $120 for payment of the extension fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Greg Ferraro

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134
Phone No. (862) 778-7831

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Date: 11/20/06

11/22/2006 DEMMANU1 00000004 190134 10341868
01 FC:1251 120.00 DA

PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

Application or Docket Number: 10/341868

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	minus 20=	*
INDEPENDENT CLAIMS	minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐ OR OTHER THAN SMALL ENTITY

RATE	FEE	OR	RATE	FEE
BASIC FEE	395.00	OR	BASIC FEE	790.00
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL		OR	TOTAL	790.00

CLAIMS AS AMENDED - PART II

AMENDMENT A — 12/1/04

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 5	Minus	** 20	*
Independent	* 3	Minus	*** 5	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY OR OTHER THAN SMALL ENTITY

RATE	ADDI-TIONAL FEE	OR	RATE	ADDI-TIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDI-TIONAL FEE	OR	RATE	ADDI-TIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDI-TIONAL FEE	OR	RATE	ADDI-TIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

1095 7590 02/05/2007

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/341,868	KSANDER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7* is/are pending in the application.

4a) Of the above claim(s) *5 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 20, 2006 has been entered.

Action Summary

The rejection of claims 1, 3 and 4 under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record and Buhlmayer et al. (U.S.Patent No. 5,399,578) is being maintained and the rejection is modified in this Office Action to address the newly added limitations in claims 1 and 4.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) and Buhlmayer et al. (U.S.Patent No. 5,399,578), both of record.

Ksander teaches a pharmaceutical composition comprising the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-

phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme (NEP) inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches ammonium salts, mono-, di- or tri-lower **(alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**) are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45). Ksander teaches units dosage for **warm blooded animal** weight **50 to 70 kg** may contain between about **10 and 100 mg of the active ingredient**. (column 18, lines 59-64). **These ranges overlap Applicants' range set forth in claims 1 and 4.**

Buhlmayer et al. teach valsartan is useful for an **anti-hypertensive** treatment. (abstract, claims). Buhlmayer et al. teach that the dose of the active ingredient as an approximate **daily dose** of about **10mg to about 250mg** is useful for oral administration for a patient weighing approximately 75kg for the warm-blooded animal species. (column 27, lines 40-46). **These ranges are within Applicants' ranges set forth in claims 1 and 4.**

The claims differ from the cited references that claiming a pharmaceutical composition comprising **combination** of the specific NEP inhibitor (N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) and valsartan in a single formulation with their effective amounts. To employ combinations of specific NEP inhibitor and valsartan with their effective amounts known in the each of the above references for treating hypertension in a single formulation would have been obvious because all the components and the amounts effective to treat hypertension

are well known individually. One of ordinary skill in the art would have been motivated to combine the specific NEP inhibitor (N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) and valsartan in a single composition in order to achieve an expected benefit of antihypertensive effect in warm-blooded animal species suffering from hypertension. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)).

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

Applicants' arguments filed November 20, 2006 have been fully considered but they are not persuasive. Applicants argue that the dosages for the tests in the Dahl salt-sensitive rat using **30mg/kg** valsartan and **30mg/kg** NEPi were disclosed in the prior art and that Buhlmayer discloses the 30mg/kg valsartan dosage in a rat model and that the section quoted in the Office Action ("about 10mg and 100mg for a mammal of

about 50 to 70kg") relates to dosages in humans, not rats and because the dosages **30mg/kg** valsartan and **30mg/kg** NEPi for a rat are disclosed in the prior art, this test did not use "higher" than the effective dosages disclosed in prior art to yield synergistic results. This is not persuasive because instant claims are drawn to a composition comprising daily dosages of Valsartan and NEPi. It is noted that each of the cited prior art teaches the daily dosages of each of the active agents within and/or overlapping with Applicants' dosages as claimed. Therefore, it would have been obvious to combine each of the active agents with known effective daily dosages in a single formulation for the treatment of hypertension for the warm-blooded animal suffering from hypertension. The declaration has been carefully considered, however, it is not persuasive because Ksander's dosages to be employed to warm-blooded animal is 10 and 100mg for about 50-70kg which is less than Applicants' mg/kg/day. Therefore, Applicants' data showing unexpected and surprising antihypertensive effect of a combination would be expected since the each of the prior art teaches daily dosages that are within/overlapping applicants' amounts and the comparison data shows much higher mg/kg/day dosages of NEPi. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Kim
Patent Examiner
Art Unit 1617

Jmk
January 31, 2007

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10341868	KSANDER ET AL.
	Examiner	Art Unit
	Kim, Jennifer	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/02/2007								
	1	✓								
	2	N								
	3	✓								
	4	✓								
	5	N								
	6	-								
	7	N								
	8	-								
	9	-								
	10	-								
	11	-								

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination
	10/341,868	KSANDER ET AL
	Examiner	Art Unit
	Jennifer Kim	1617

SEARCHED			
Class	Subclass	Date	Examiner
514	533	1/6/2006	JMK
514	381	1/6/2006	JMK
updated		7/20/06	JMK
updated		2/2/07	JMK

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor search	1/6/2006	JMK
STN (medicine, registry); WEST	1/6/2006	JMK
STIC	12/15/2005	JMK
updated	7/20/06	JMK
updated	2/2/07	JMK

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO: 10/341,868

FILED: JANUARY 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M.

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE

Sir:

Responsive to the outstanding action dated February 5, 2007, in the above-identified application, Applicants respectfully request consideration of the following remarks.

Remarks/Arguments begin on page 4 of this paper.

The claims have not been amended but are reproduced below for the Examiner's convenience. This listing of the claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (previously presented) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof in a daily unit dose of about 20 mg to about 320 mg; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof in a daily unit dose of about 20 mg to about 800 mg and a pharmaceutically acceptable carrier.

2. (canceled)

3. (previously presented) The pharmaceutical composition of Claim 1, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. (previously presented) A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof in a daily unit dose of about 20 mg to about 800 mg and in a second container a pharmaceutical composition comprising valsartan in a daily unit dose of about 20 mg to about 320 mg.

5. (withdrawn) A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary

renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. (canceled)

7. (withdrawn) The method of Claim 5, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

8-11. (canceled)

REMARKS

Claims 1, 3 and 4 remain in the application. Reconsideration of the above-identified application in light of the remarks that follow is respectfully requested.

Rejection of claims 1, 3 and 4 under 35 U.S.C. §103(a)

Claims 1, 3 and 4 stand rejected under 35 U.S.C. §103(a) over Ksander U.S. Patent No. 5,217,996 ('996 patent) and Buhlmayer et al. U.S. Patent No. 5,399,578 ('578 patent). As support for rejection, the Examiner maintains that (a) Ksander teaches that unit dosages for warm blooded animals weighing 50 to 70 kg may contain between about 10 and 100 mg of the [NEP inhibitor] active ingredient (b) Buhlmayer et al. teach that the dose of the [valsartan] active ingredient as an approximate daily dose of about 100 mg to about 250 mg is useful for oral administration for 75 kg warm-blooded animal species and (c) these ranges are within and/or overlap with Applicants' claimed ranges. The Examiner then concludes "[t]o employ combinations of specific NEP inhibitor and valsartan with their effective amounts known in each of the above references for treating hypertension in a single formulation would have been obvious because all the components and the amounts effective to treat hypertension are well known individually." Specifically, the Examiner alleges that the motivation for combining the components flows from their individually known common utility. In view of the evidence and argumentation submitted herein, Applicants respectfully traverse this rejection.

Without admitting the claimed invention is obvious, but in addressing the Examiner's allegation of *prima facie* obviousness, Applicants respectfully submit that the Examiner erred in dismissing Applicants' dispositive showing of unexpected superiority in treating hypertension.

"An analysis of obviousness of a claimed combination must include consideration of the results achieved by the combination." *Gillette Co. v. S.C. Johnson & Son Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990). Applicants have established factual evidence, via the Webb Declaration, that the claimed combination of valsartan and the specific NEPi produces a combined antihypertensive effect that is greater than expected, *i.e.*, greater than the sum of the antihypertensive effect produced by each component alone. Such showings of an unexpectedly superior property have long been held to rebut a *prima facie* case of obviousness. *See In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987) (a showing that an herbicide was unexpectedly superior in the property of selectivity it shared with prior art compounds was sufficient to rebut *prima facie* case of obviousness); *In re Orfeo*, 169 USPQ 487, 488-89 (CCPA 1971) (a showing that refrigerant mixture $CHF_3/CCIF_3$ exhibited a power requirement unexpectedly lower than that of known refrigerants CHF_3 and $CCIF_3$ individually was sufficient to rebut a *prima facie* case of obviousness).

In *In re Soni*, the Federal Circuit held that "when an applicant demonstrates substantially improved results, as Soni did here, and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." *In re Soni*, 34

USPQ2d 1684, 1688 (Fed. Cir. 1995). As evidence thereof, Applicants restate the evidence appearing in the Webb Declaration that the claimed combination of valsartan and specific NEPi produced an antihypertensive effect that was unexpected and "synergistic." *See Merck v. Biocraft Laboratories, Inc.*, 10 USPQ 1843, 1847 (Fed. Cir. 1989) ("when an inventor tries to distinguish his claims from the prior art by introducing evidence of unexpected 'synergistic' properties, the evidence should at least demonstrate 'an effect greater than the sum of the several parts taken separately.'")

Applicants respectfully submit that the Applicants' data, which follows, demonstrates the unexpectedly superior (*i.e.*, synergistic) results of the combination over valsartan or specific NEPi alone.

In the Tables on page 7 of the Webb Declaration, copies of which are presented below, the Applicants have provided results that establish the unexpectedly superior ability of the combination of valsartan and specific NEPi to lower blood pressure.

Table 1. Dahl Salt Sensitive Results for Valsartan and AHU377 Combination Therapy:

	Dose mg/kg/day	Final BP mmHg	Improvement over Vehicle mmHg	Expected Improvement mmHg	**Improvement Factor mmHG**
Vehicle		193 ± 5			
Val:AHU377	**30:30**	**176 ± 6**	**-17**	**-4**	**-13**
Val:AHU377	30:100	179 ± 6	-14	-18	+4
Val:AHU377	**100:30**	**174 ± 5**	**-19**	**+1**	**-18**
Val:AHU377	100:100	182 ± 8	-11	-13	+2

Table 2. SHRsp Model Results for Valsartan and AHU377 Monotherapy and Combination Therapy for Systolic Blood Pressure (SBP):

	Dose mg/kg/day	Final BP mmHg	SBP Reduction	Expected Improvement mmHg	**Improvement Factor mmHG**
SHRsp		195 ± 6			
Valsartan	10	176 ± 6	-19		
AHU377	100	199 ± 6	+4		
Val:AHU377	**10:100**	**167 ± 5**	**-28**	**-15**	**-13**

Table 3. SHRsp Model Results for Valsartan and AHU377 Monotherapy and Combination Therapy for Diastolic Blood Pressure (DBP):

	Dose mg/kg/day	Final BP mmHg	SBP Reduction	Expected Improvement mmHg	**Improvement Factor mmHG**
SHRsp		142 ± 3			
Valsartan	10	137 ± 7	-4.6		
AHU377	100	151 ± 8	+9.5		
Val:AHU377	**10:100**	**118 ± 5**	**-23.8**	**+4.9**	**-28.7**

The protocol for the above experiments is described in the Webb Declaration in detail at pages 4-5. The data in Table 1 reports the blood pressure effect of a combination of valsartan and specific NEPi as measured by improvement over vehicle in the Dahl Salt Sensitive rat. Table 1, col. 4, reports that the bolded combinations of valsartan and specific NEPi had -17 mmHg and -19 mmHg improvements respectively relative to vehicle. If the combined effect of

valsartan and NEPi were merely cumulative, one would expect cumulative improvements of -4 and +1 respectively (Table 1, col. 5). Instead of the predicted – 4 and +1 effects on blood pressure, Applicants found unexpected -13 and -18 mmHg improvements respectively over these predicted values for the claimed combination (Table 1, col. 6).

The data in Table 2 reports the systolic blood pressure effect of a combination of valsartan and specific NEPi as measured by improvement over the SHRsp rat model. Table 2, col. 4, reports that the combination of valsartan and specific NEPi had -28 mmHg improvement relative to vehicle. If the combined effect of valsartan and NEPi were merely cumulative, one would expect a cumulative improvement of -15 mmHg (Table 2, col. 5). Instead of the predicted -15 mmHg improvement, Applicants found an unexpected -13 mmHg improvement over the predicted value for the claimed combination (Table 2, col. 6).

The data in Table 3 reports the diastolic blood pressure effect of a combination of valsartan and specific NEPi as measured by improvement over the SHRsp rat model. Table 3, col. 4, reports that the combination of valsartan and specific NEPi had -23.8 mmHg improvement relative to vehicle. If the combined effect of valsartan and NEPi were merely cumulative, one would expect a cumulative detriment of +4.9 mmHg. Instead of the predicted +4.9 mmHg detriment, Applicants found an unexpected -28.7 mmHg improvement over the predicted value for the claimed combination.

As further evidence that the combination of the claimed invention is not obvious, the Webb Declaration provides evidence that the combination of the present invention has other unexpected therapeutic benefits in the treatment of hypertension. The Webb Declaration provides evidence that the combination of the present invention provides an overall improvement of endothelial function, cardiac fibrosis and cardiac vascular remodeling and fibrosis of intramyocardial coronary arties in SHRsp rat model as compared to monotherapy with valsartan or specfic NEPi.

Applicants respectfully submit that the dosages of the individual components disclosed in the prior art are immaterial to the test results evidenced in the Webb Declaration because the dosages tested in combination were compared against the same dosages in monotherapy. Even though the tested combination dosages may have overlapped with or were higher than the component dosages in the prior art, the combination still provided greater than additive results over the monotherapy tested at the same dosages.

For these reasons, Applicants submit that they have presented sufficient factual data of an unexpectedly superior result to rebut any *prima facie* case of obviousness made out by the Examiner.

In view of the foregoing, Applicants submit that all rejections have been traversed and should be withdrawn and that the Application is now in condition for allowance and respectfully requests early notice to that effect.

Respectfully submitted,

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Reg. No. 36,134

Date: 3/8/07

Electronic Acknowledgement Receipt

EFS ID:	1579412
Application Number:	10341868
International Application Number:	
Confirmation Number:	8865
Title of Invention:	Methods of treatment and pharmaceutical composition
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Gregory David Ferraro./Monika Van Houten
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	4-32219A
Receipt Date:	09-MAR-2007
Filing Date:	14-JAN-2003
Time Stamp:	14:23:48
Application Type:	Utility

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Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1		US32219Re2-5-07.pdf	201978	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment - After Non-Final Rejection	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	7
Warnings:			
Information:			
	Total Files Size (in bytes):	201978	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

Application or Docket Number: 10/341868

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	minus 20= *	
INDEPENDENT CLAIMS	minus 3 = *	
MULTIPLE DEPENDENT CLAIM PRESENT	☐	

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐	RATE	FEE	OR	OTHER THAN SMALL ENTITY	RATE	FEE
	BASIC FEE	395.00	OR		BASIC FEE	790.00
	X$ 25=		OR		X$50=	
	X100=		OR		X200=	
	+180=		OR		+360=	
	TOTAL		OR		TOTAL	790.00

CLAIMS AS AMENDED - PART II

AMENDMENT A — 12/1/06

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 5	Minus	** 20	*
Independent	* 3	Minus	*** 5	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY	RATE	ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY	RATE	ADDITIONAL FEE
	X$ 25=		OR		X$50=	
	X100=		OR		X200=	
	+180=		OR		+360=	
	TOTAL ADDIT. FEE		OR		TOTAL ADDIT. FEE	

3/9/07

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	*
Independent	*	Minus	***	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	*
Independent	*	Minus	***	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 25=		OR	X$50=	
X100=		OR	X200=	
+180=		OR	+360=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

1095 7590 05/31/2007

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/341,868	KSANDER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3/9/2007.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,3-5 and 7 is/are pending in the application.

4a) Of the above claim(s) 5 and 7 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3,4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed March 9, 2007 have been received and entered into the application. No amendments have been made. Accordingly, claims 1, 3-5 and 7 remain pending, among which claims 5 and 7 have been withdrawn from consideration and claims 1, 3 and 4 are being examined on the merits.

Action Summary

The rejection of claims 1, 3 and 4 under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record and Buhlmayer et al. (U.S.Patent No. 5,399,578) is being maintained for the reasons stated in the previous Office Action.

Response to Arguments

1. Applicants' arguments filed March 15, 2007 have been fully considered but they are not persuasive. Applicants argue that Applicants have established factual evidence, via the Webb Declaration that the claimed combination of valsartan and the specific NEPi produces a combined antihypertensive effect that is greater than expected, i.e., greater than the sum of the antihypertensive effect produced by each component alone.

The Webb Declaration have been reviewed and carefully considered. This is not persuasive because the evidence is clearly not commensurate in scope with what is claimed herein. The Examiner particularly refers to the data reported in Tables 1, 2 and 3, wherein the claimed combination of compounds of Valsartan and AHU377 in their specific amounts gives surprising and unexpected results. The "synergistic" combination testing reported by the Webb Declaration is limited to data for these two specific combinations with the specific amounts shown in Tables 1, 2 and 3. Thus the comparative testing is very specific whereas none of the instant claims are so limited. It is well established that a showing of unexpected results generally must be commensurate in scope with the breadth of the claims sought to be patented. See, inter alia, (1) In re Greenfield, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978); (2) In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); and (3) In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (showing of unexpected results must be commensurate in scope with breadth of claim). Applicants argue that the data in Table 1 reports that the effect on blood pressure of a combination of valsartan and specific NEPi as measured in the Dahl Salt Sensitive rat was found to unexpectedly be –13 and –18 mmHg respectively less than the predicted values for the claimed combination; the data in Table 2 reports the effect of systolic blood pressure on a combination of valsartan and specific NEPi, as measured in the SHRsp rat, resulted in an unexpected 13mmHg reduction over the predicted value for the claimed combination; and the data in Table 3 reports the effect on diastolic blood pressure of a combination of valsartan and specific NEPi as measured in the SHRsp rat, resulted in

an unexpected –28.7 mmHg reduction over the predicted value for the claimed combination. It is noted that the results in Tables 1, 2 and 3 for specific amounts show surprising and unexpected results of the claimed combination of compounds of Valsartan and AHU377. The "synergistic" results reported by the Webb Declaration are limited to the specific amounts shown in Tables 1, 2 and 3. Thus the comparative testing is very specific whereas none of the instant claims are so limited. Applicants argue that the Webb Declaration provides evidence that the combination of the present invention has other unexpected therapeutic benefits in the treatment of hypertension and an overall improvement of endothelial function, cardiac fibrosis and cardiac vascular remodeling, and fibrosis of intramyocardial coronary arteries in the SHRsp rat as compared to monotherapy with valsartan or specific NEPi. This is not persuasive because, again, these results only represent the specific combination with the specific amounts tested, but the instant claims are not limited to what is shown by the data. Applicants argue that the dosages of the individual components disclosed in the prior art are immaterial to the test results in the Webb Declaration because the dosages tested in combination in the Declaration were compared against the same dosages in monotherapy and that even though the tested combination dosages may have overlapped with or were higher than the component dosages in the prior art, the combination still provided greater than additive results over the monotherapy tested at the same dosages. This is not persuasive because the dosages of the individual components disclosed in the prior art teaches the usual daily dosage of valsartan and the NEPi for the treatment of hypertension. Therefore, these dosages are pertinent to

the determination of prima facie obviousness for the combining of the each of the active agents as instantly claimed. The Webb Declaration in Tables 2 and 3, demonstrate the unobvious result when the specific combination at specific amounts in the therapy lowered systolic and diastolic blood pressure. However, the data showing unobviousness must be commensurate in scope with the invention being claimed. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

In view of the above Office Action of February 5, 2007 is deemed proper and asserted with full force and effect herein to obviate applicants' claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) and Buhlmayer et al. (U.S.Patent No. 5,399,578), both of record.

Ksander teaches a pharmaceutical composition comprising the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme (NEP) inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches that ammonium salts including, mono-, di- or tri-lower (**alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**), are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45).

Ksander teaches that unit dosage forms for **warm blooded animals** weighing **50 to 70 kg** may contain between about **10 and 100 mg of the active ingredient**. (column 18, lines 59-64). **These ranges overlap Applicants' range set forth in claims 1 and 4.**

Buhlmayer et al. teach valsartan is useful for an **anti-hypertensive** treatment. (abstract, claims). Buhlmayer et al. teach that the dose of the active ingredient in an approximate **daily dosage range** of about **10mg to about 250mg** is useful for oral administration for a patient weighing approximately 75kg for warm-blooded animal species. (column 27, lines 40-46). **These ranges are within Applicants' ranges set forth in claims 1 and 4.**

The claims differ from the cited references by claiming a pharmaceutical composition comprising a **combination** of the specific NEP inhibitor (N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) and valsartan in a single formulation with their effective amounts. To employ combinations of a specific NEP inhibitor and valsartan with effective amounts taught in each of the above references for treating hypertension in a single formulation would have been obvious because all the components and the amounts effective to treat hypertension are well known individually. One of ordinary skill in the art would have been motivated to combine the specific NEP inhibitor (N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) and valsartan in a single composition in order to achieve an expected added benefit of antihypertensive effect in warm-blooded animal species suffering from hypertension. The motivation for

combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)).

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

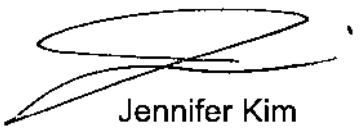
None of the claims are allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Jennifer Kim
Patent Examiner
Art Unit 1617

Jmk
May 23, 2007

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10341868	KSANDER ET AL.
	Examiner	Art Unit
	Kim, Jennifer	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/02/2007	05/24/2007							
	1	✓	✓							
	2	-	-							
	3	✓	✓							
	4	✓	✓							
	5	N	N							
	6	-	-							
	7	N	N							
	8	-	-							
	9	-	-							
	10	-	-							
	11	-	-							

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/341,888	KSANDER ET AL
Examiner	**Art Unit**
Jennifer Kim	1617

SEARCHED

Class	Subclass	Date	Examiner
514	933	1/6/2006	JMK
514	381	1/6/2006	JMK
updated		7/10/06	
updated		2/2/07	
	updated	5/29/07	

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
Inventor search	1/6/2006	JMK
STN (medicine, registry); WEST	1/6/2006	JMK
STIC	12/15/2005	JMK
updated	7/10/06	
updated	2/2/07	
updated	5/29/07	

Response Under 37 CFR §1.116
Expedited Procedure
Examining Group 1617

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER FINAL REJECTION

Sir:

Responsive to the outstanding action dated May 31, 2007, in the above-identified application, having a period for response set to expire October 31, 2007, Applicants respectfully request the following amendment be entered and the claims considered in light thereof.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

This listing of the claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof ~~in a daily unit dose of about 20 mg to about 320 mg~~; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof ~~in a daily unit dose of about 20 mg to about 800 mg~~,

wherein the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) the NEP inhibitor *N* -(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered in combination achieve a greater therapeutic effect than the sum of the therapeutic effects achievable with the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt administered alone and (ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone, and a pharmaceutically acceptable carrier.

2. (canceled)

3. (previously presented) The pharmaceutical composition of Claim 1, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. (currently amended) A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof ~~in a daily unit dose of~~

~~about 20 mg to about 800 mg~~ and in a second container a pharmaceutical composition comprising valsartan or a pharmaceutically acceptable salt thereof ~~in a daily unit dose of about 20 mg to about 320 mg~~ wherein the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts and valsartan or a pharmaceutical acceptable salt thereof administered in combination achieve a greater therapeutic effect than the sum of the therapeutic effects achievable with the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone and valsartan or a pharmaceutically acceptable salt thereof administered alone.

5. (withdrawn) A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. (canceled)

7. (withdrawn) The method of Claim 5, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

8-11. (canceled)

REMARKS

Reconsideration of the above-identified application as amended is requested. Claims 1, 3 and 4 remain in this application. Claims 1 and 4 have been amended. Support for these amendments can be found at page 8, first full paragraph.

Applicants would like to thank the Examiner for the courtesy extended during the recent communications in which the Examiner agreed to review a draft copy of the above amended claims prior to their submission herein.

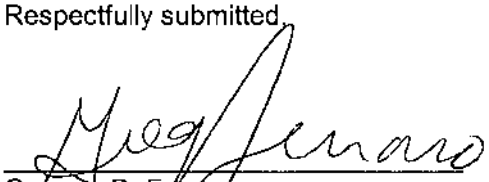
Rejection of claims 1, 3 and 4 under 35 U.S.C. §103(a)

The rejection of Claims 1, 3 and 4 under 35 U.S.C. §103(a) over Ksander U.S. Patent No. 5,217,996 ('996 patent) and Buhlmayer et al. U.S. Patent No. 5,399,578 ('578 patent) has been maintained by the Examiner in the May 31, 2007 office action. In response to the arguments and declarations previously submitted, the Examiner stated that the Applicants' experiments showing synergistic, unexpected and surprising antihypertensive effects were not commensurate in scope with the claimed invention. In this response, Applicants have amended the claims so that they are now commensurate in scope with the data showing unobviousness, as indicated by the Examiner after a review of a fax copy of the claims. Therefore, it is Applicant's position that the claims as presented herein are allowable. Based on this, Applicants respectfully traverse this rejection insofar as it applies to the claims as amended.

The claims have been amended such that they are directed to pharmaceutical compositions comprising valsartan and the specifically claimed NEPi (and salts thereof of both actives) wherein the amounts of these actives when administered in combination achieves a greater therapeutic effect than the sum of the therapeutic effects achievable with the amounts of these two actives administered alone. Accordingly, the data showing unobviousness in now commensurate in scope with the invention being claimed and, therefore, the claims patentably distinguish over the state of the art as represented by the cited references. Based on this, the rejection under 35 U.S.C. §103(a) has been traversed and should be withdrawn.

In view of the foregoing, Applicant submits the Application is now in condition for allowance and respectfully requests early notice to that effect.

Respectfully submitted,



Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134

Date: October 23, 2007

Electronic Patent Application Fee Transmittal

Application Number:	10341868
Filing Date:	14-Jan-2003
Title of Invention:	Methods of treatment and pharmaceutical composition
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Gregory David Ferraro./Monika Van Houten
Attorney Docket Number:	4-32219A

Filed as Large Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	460	460

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**460**

Electronic Acknowledgement Receipt

EFS ID:	2356569
Application Number:	10341868
International Application Number:	
Confirmation Number:	8865
Title of Invention:	Methods of treatment and pharmaceutical composition
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Gregory David Ferraro./Monika Van Houten
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	4-32219A
Receipt Date:	23-OCT-2007
Filing Date:	14-JAN-2003
Time Stamp:	14:26:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$460
RAM confirmation Number	7241
Deposit Account	190134
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219ROA.pdf	237963 f9f87b0a278afae7cd6c2f3587a2de8fcff58c58	yes	6

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Extension of Time	1	1
Amendment After Final	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8161 e94c61bc8dbe526d9cb4dde1f9eca14b4e7059a1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	246124		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of May 31, 2007 has a shortened statutory time set to expire on August 31, 2007. A two-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $460 for payment of the extension fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134
Phone No. (862) 778-7831

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Date: October 23, 2007

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/341,868	Filing Date 01/14/2003	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	10/23/2007	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 5	Minus	** 20	= 0	X $ =		OR	X $50=	0
AMENDMENT	Independent (37 CFR 1.16(h))	* 1	Minus	***5	= 0	X $ =		OR	X $210=	0
AMENDMENT	☐ Application Size Fee (37 CFR 1.16(s))									
AMENDMENT	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
AMENDMENT	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
AMENDMENT	☐ Application Size Fee (37 CFR 1.16(s))									
AMENDMENT	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
TIFFIANY n. TABB

Response Under 37 CFR §1.116
Expedited Procedure
Examining Group 1617

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER FINAL REJECTION

Sir:

Responsive to the outstanding action dated May 31, 2007, in the above-identified application, having a period for response set to expire October 31, 2007, Applicants respectfully request the following amendment be entered and the claims considered in light thereof.

Do not enter
10/26/07

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

1095 7590 11/01/2007

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
11/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/341,868	**Applicant(s)** KSANDER ET AL.	
	Examiner Jennifer Kim	**Art Unit** 1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 October 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3 and 4*.
   Claim(s) withdrawn from consideration: *5 and 7*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Jennifer Kim
Primary Examiner
Art Unit: 1617

Continuation of 3. NOTE: The proposed amendment of amounts of active agents require new search..

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Subsection (b) of 35 U.S.C. § 132, effective on May 29, 2000, provides for continued examination of an utility or plant application filed on or after June 8, 1995.
See The American Inventors Protection Act of 1999 (AIPA).

Application Number	10/341,868
Filing Date	January 14, 2003
First Named Inventor	KSANDER ET AL.
Group Art unit	1617
Examiner Name	Kim, Jennifer M
Attorney Docket Number	4-32219A

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

NOTE: *37 C.F.R. § 1.114 is effective on May 29, 2000. If the above-identified application was filed prior to May 29, 2000, applicant may wish to consider filing a continued prosecution application (CPA) under 37 C.F.R. § 1.53 (d) (PTO/SB/29) instead of a RCE to be eligible for the patent term adjustment provisions of the AIPA. See Changes to Application Examination and Provisional Application Practice*, Interim Rule, 65 *Fed. Reg.* 14865 (Mar. 20, 2000), 1233 *Off. Gaz. Pat. Office* 47 (Apr. 11, 2000), which established RCE practice.

1. **Submission required under 37 C.F.R. § 1.114**

   a. ☐ Previously submitted
      i. ☐ Consider the amendment(s)/reply under 37 C.F.R. § 1.116 previously filed on _____
      (Any unentered amendment(s) referred to above will be entered).
      ii. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
   b. ☒ Enclosed
      i. ☒ Amendment/Reply
      ii. ☐ Affidavit(s)/Declaration(s)
      iii. ☐ Information Disclosure Statement (IDS)
      iv. ☐ Other _____

2. **Miscellaneous**

   a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. § 1.17(i) **required**)
   b. ☐ Other _____

3. **Fees** The RCE fee under 37 C.F.R. § 1.17(e) is required by 37 C.F.R. § 1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 19-0134
      i. ☒ RCE fee required under 37 C.F.R. § 1.17(e)
      ii. ☒ Extension of time fee (37 C.F.R. §§ 1.136 and 1.17) (2 month Extension of time was previously paid)
      iii. ☐ Other _____
   b. ☐ Check in the amount of $_____ enclosed
   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name ***(Print/Type)***	Gregory D. Ferraro	*Registration No. (Attorney/Agent)*	Reg. No. 36,134 Attorney for Applicants
Signature	Gregory Ferraro	*Date*	11/6/07

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the:
Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450

Type or print name	Signature	Date

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO: 10/341,868

FILED: JANUARY 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The period for filing a Notice of Appeal has a shortened statutory time set to expire on August 31, 2007. A three-month extension is hereby requested pursuant to 37 CFR §1.136(a).

A two-month extension was previously requested and paid for, making the extension fee due at this time $590 ($1050 less the previously paid amount of $460).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $590 for payment of the extension fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Novartis

Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Date: 11/6/07

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134
Phone No. (862) 778-7831

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
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Respectfully submitted,

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One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Date: 11/6/07

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134
Phone No. (862) 778-7831

CASE 4-32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

Responsive to the outstanding action dated May 31, 2007, in the above-identified application, Applicants respectfully request the following amendment be entered and the claims considered in light thereof.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

This listing of the claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof ~~in a daily unit dose of about 20 mg to about 320 mg~~; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof ~~in a daily unit dose of about 20 mg to about 800 mg~~,

wherein the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) the NEP inhibitor *N* -(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered in combination achieve a greater therapeutic effect than the sum of the therapeutic effects achievable with the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt administered alone and (ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone, and a pharmaceutically acceptable carrier.

2. (canceled)

3. (previously presented) The pharmaceutical composition of Claim 1, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. (currently amended) A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof ~~in a daily unit dose of about 20 mg to about 800 mg~~ and in a second container a pharmaceutical composition

comprising valsartan or a pharmaceutically acceptable salt thereof ~~in a daily unit dose of about 20 mg to about 320 mg~~ wherein the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts and valsartan or a pharmaceutical acceptable salt thereof administered in combination achieve a greater therapeutic effect than the sum of the therapeutic effects achievable with the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone and valsartan or a pharmaceutically acceptable salt thereof administered alone.

5. (withdrawn) A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. (canceled)

7. (withdrawn) The method of Claim 5, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

8-11. (canceled)

REMARKS

Claims 1, 3 and 4 remain in this application. Claims 1 and 4 have been amended. Support for these amendments can be found at page 8, first full paragraph.

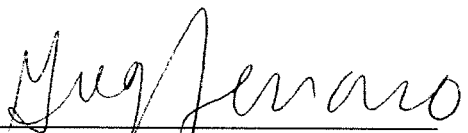
Rejection of claims 1, 3 and 4 under 35 U.S.C. §103(a)

The rejection of Claims 1, 3 and 4 under 35 U.S.C. §103(a) over Ksander U.S. Patent No. 5,217,996 ('996 patent) and Buhlmayer et al. U.S. Patent No. 5,399,578 ('578 patent) has been maintained by the Examiner in the May 31, 2007 office action. In response to the arguments and declarations previously submitted, the Examiner stated that the Applicants' experiments showing synergistic, unexpected and surprising antihypertensive effects were not commensurate in scope with the claimed invention. In this response, Applicants have amended the claims so that they are now commensurate in scope with the data showing unobviousness, as indicated by the Examiner after a review of a fax copy of the claims. Therefore, it is Applicant's position that the claims as presented herein are allowable. Based on this, Applicants respectfully traverse this rejection insofar as it applies to the claims as amended.

The claims have been amended such that they are directed to pharmaceutical compositions comprising valsartan and the specifically claimed NEPi (and salts thereof of both actives) wherein the amounts of these actives when administered in combination achieves a greater therapeutic effect than the sum of the therapeutic effects achievable with the amounts of these two actives administered alone. Accordingly, the data showing unobviousness in now commensurate in scope with the invention being claimed and, therefore, the claims patentably distinguish over the state of the art as represented by the cited references. Based on this, the rejection under 35 U.S.C. §103(a) has been traversed and should be withdrawn.

In view of the foregoing, Applicant submits the Application is now in condition for allowance and respectfully requests early notice to that effect.

Respectfully submitted,



Gregory D. Perraro
Attorney for Applicants
Reg. No. 36,134

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831

Date: November 6, 2007

Electronic Patent Application Fee Transmittal

Application Number:	10341868
Filing Date:	14-Jan-2003
Title of Invention:	Methods of treatment and pharmaceutical composition
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Gregory David Ferraro./Monika Van Houten
Attorney Docket Number:	4-32219A

Filed as Large Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $460 paid	1253	1	590	590

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**1400**

Electronic Acknowledgement Receipt

EFS ID:	2431807
Application Number:	10341868
International Application Number:	
Confirmation Number:	8865
Title of Invention:	Methods of treatment and pharmaceutical composition
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Gregory David Ferraro./Monika Van Houten
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	4-32219A
Receipt Date:	06-NOV-2007
Filing Date:	14-JAN-2003
Time Stamp:	16:01:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1400
RAM confirmation Number	1209
Deposit Account	190134
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219RCE2.pdf	83668 70695cd24ac2facfd6c13482245a2fcf0c2a9c99	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Request for Continued Examination (RCE)	1	1
Extension of Time	2	3
Amendment After Final	4	4
Claims	5	6
Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	8322 039d3639c40a15ba3b64b0784a5bb9ea05d32fdd	no	2

Warnings:

Information:

Total Files Size (in bytes):	91990

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☒ To be Mailed
10/341,868	01/14/2003	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/06/2007	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 5	Minus	** 20	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***5	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
GOIGA N. DUCKETT

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO: 10/341,868

FILED: JANUARY 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT

Sir:

Applicants respectfully request the following amendment be entered and the claims considered in light thereof.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

This listing of the claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof,

wherein the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) the NEP inhibitor *N* -(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered in combination achieve a greater ~~therapeutic~~ anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt administered alone and (ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone, and a pharmaceutically acceptable carrier.

2. (canceled)

3. (previously presented) The pharmaceutical composition of Claim 1, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. (currently amended) A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and in a second container a pharmaceutical composition comprising valsartan or a pharmaceutically acceptable salt thereof

wherein the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts and valsartan or a pharmaceutical acceptable salt thereof administered in combination achieve a greater ~~therapeutic~~ anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone and valsartan or a pharmaceutically acceptable salt thereof administered alone.

5. (withdrawn) A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. (canceled)

7. (withdrawn) The method of Claim 5, wherein *N*-(3-carboxy-1-oxopropyl)-

(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

8-11. (canceled)

REMARKS

Consideration of the above-identified application as amended is requested. Claims 1, 3 and 4 remain in this application. Claims 1 and 4 have been amended. Support for these amendments can be found at page 9, first full paragraph.

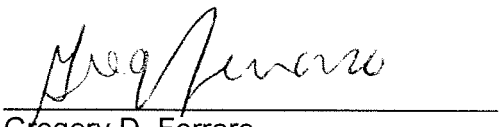
Rejection of claims 1, 3 and 4 under 35 U.S.C. §103(a)

The rejection of Claims 1, 3 and 4 under 35 U.S.C. §103(a) over Ksander U.S. Patent No. 5,217,996 ('996 patent) and Buhlmayer et al. U.S. Patent No. 5,399,578 ('578 patent) has been maintained by the Examiner in the May 31, 2007 office action. In response to the arguments and declarations previously submitted, the Examiner stated that the Applicants' experiments showing synergistic, unexpected and surprising antihypertensive effects were not commensurate in scope with the claimed invention. In this Supplemental Amendment, Applicants have amended the claims to better define Applicants invention. Therefore, it is Applicant's position that the claims as presented herein are allowable. Based on this, Applicants respectfully traverse this rejection insofar as it applies to the claims as amended.

The claims have been amended such that they are directed to pharmaceutical compositions comprising valsartan and the specifically claimed NEPi (and salts thereof of both actives) wherein the amounts of these actives when administered in combination achieves a greater anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of these two actives administered alone.

In view of the foregoing, Applicant submits the Application is now in condition for allowance and respectfully requests early notice to that effect.

Respectfully submitted,



Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831

Date: January 14, 2008

CASE 32219A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL. Examiner: Jennifer M. Kim

APPLICATION NO: 10/341,868

FILED: JANUARY 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed within three months of the filing date of the application. Therefore, no fees are required. If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449 and also of the co-pending application number 11/722,360.

A copy of the reference is enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134

Date: 1/15/08

FORM PTO-1449 (REV. 7-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.
32219A
APPLICATION NO.
10/341,868
APPLICANT
KSANDER ET AL.
FILING DATE
JANUARY 14, 2003

Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM						☐	☐
	AN						☐	☐
	AO						☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	Matsumoto et al., "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopeptidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in conscious dogs", JASN, Hemodynamics and Vascular Regulation, page 517, September 1993).
	AS	
	AT	

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

Electronic Acknowledgement Receipt

EFS ID:	2719031
Application Number:	10341868
International Application Number:	
Confirmation Number:	8865
Title of Invention:	Methods of treatment and pharmaceutical composition
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Gregory David Ferraro./Monika Van Houten
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	4-32219A
Receipt Date:	15-JAN-2008
Filing Date:	14-JAN-2003
Time Stamp:	15:36:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		US32219upamend.pdf	111012 14aa74be987e9c6a89cf4592b98af1750dfaa3b3	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment - After Non-Final Rejection	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	5
	Information Disclosure Statement Letter	6	7
	Information Disclosure Statement (IDS) Filed	8	8
	NPL Documents	9	9

Warnings:	
Information:	
Total Files Size (in bytes):	111012

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/341,868	01/14/2003	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/15/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 5	Minus	** 20	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***5	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/CAROLYN E. THOMAS/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

1095 7590 02/01/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
02/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/341,868	KSANDER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/6/2007 & 1/15/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7* is/are pending in the application.

4a) Of the above claim(s) *5 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/15/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 6, 2007 and January 15, 2008 have been entered.

Action Summary

The rejection of claims 1, 3 and 4 under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) and Buhlmayer et al. (U.S.Patent No. 5,399,578) is being maintained for the reasons stated in the previous Office Action.

Upon further consideration following objection has been made:

Specification

The disclosure is objected to because of the following informalities: There is an imbalanced parenthesis in the chemical name of the compound. (e.g. page 6,line 5-6).

Appropriate correction is required.

Claim Objections

Claims 1, 3 and 4 are objected to because of the following informalities: There is an imbalanced parenthesis in the chemical name of the first compound. Appropriate correction is required.

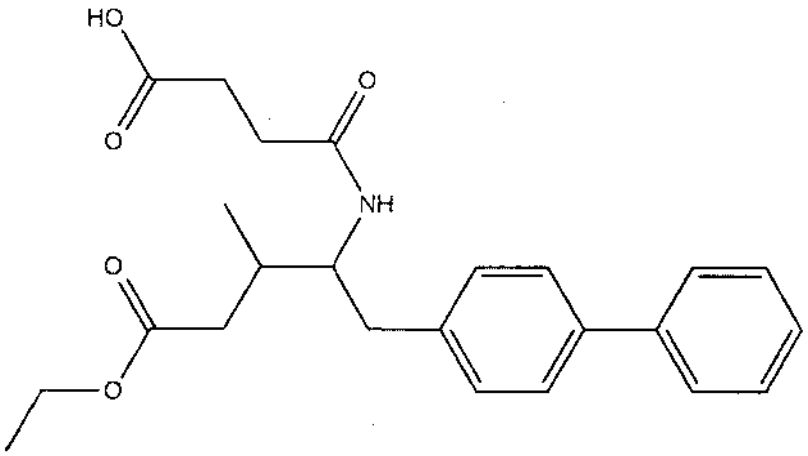
Response to Arguments

1. Applicants' arguments filed March 15, 2007 have been fully considered but they are not persuasive. Applicants argue that Applicants have amended claims such that they are directed to pharmaceutical composition comprising valsartan and the **specifically** claimed NEPi (and salts thereof of both actives) as shown in the Webb Declaration that the claimed combination of valsartan and the specific NEPi produces a combined antihypertensive effect that is greater than expected, i.e., greater than the sum of the antihypertensive effect produced by each component alone. The Webb Declaration (May 11, 2006) have been reviewed and carefully considered. This is not persuasive because the evidence is clearly not commensurate in scope with what is claimed herein. The Examiner particularly refers to the data reported in Tables 1, 2 and

3, wherein the claimed combination of compounds of Valsartan and AHU377 in their specific amounts gives surprising and unexpected results.

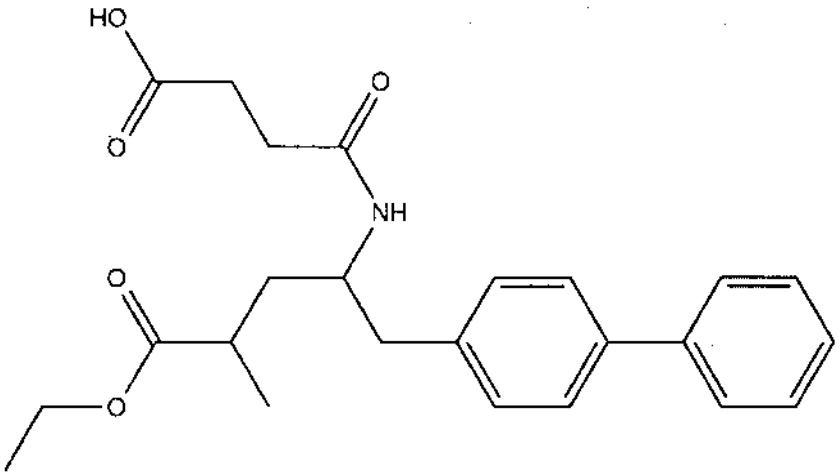
2. It is noted that the tested compound AHU377 (4-[N-3-carboxy-1-oxo-propyl)amino-4-(p-phenylphenylmethyl)-**3-methyl**butanoic acid ethyl ester) (see page 2 paragraph #5 and results) differs from the compound currently claimed.

3. The structure of the AHU377 is depicted below:



4-[n-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-3-methylbutanoic acid ethyl ester

4. The structure of the instantly claimed compound is depicted below:



4-[n-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester

5. The data showing unobviousness must be commensurate in scope with the invention being claimed. It is well settled in the patent practice that unexpected result must be established by factual evidence. No factual evidence is presented in support of the greater than sum of the therapeutic agents instantly claimed gives a greater therapeutic effects than the sum of the therapeutic effects achievable with the amount of each of the active agents administered alone. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

In view of the above Office Action of May 31, 2007 is deemed proper and asserted with full force and effect herein to obviate applicants' claims.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) and Buhlmayer et al. (U.S.Patent No. 5,399,578), both of record.

Ksander teaches a pharmaceutical composition comprising the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme (NEP) inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches that ammonium salts including, mono-, di- or tri-lower (**alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**), are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45). Ksander teaches that unit dosage forms for **warm blooded animals** weighing **50 to 70 kg** may contain between about **10 and 100 mg of the active ingredient**. (column 18, lines 59-64).

Buhlmayer et al. teach valsartan is useful for an **anti-hypertensive** treatment. (abstract, claims). Buhlmayer et al. teach that the dose of the active ingredient in an approximate **daily dosage range** of about **10mg to about 250mg** is useful for oral

administration for a patient weighing approximately 75kg for warm-blooded animal species. (column 27, lines 40-46).

The claims differ from the cited references by claiming a pharmaceutical composition comprising a **combination** of the specific NEP inhibitor (N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) and valsartan in a single formulation with their effective amounts. To employ combinations of a specific NEP inhibitor and valsartan with effective amounts taught in each of the above references for treating hypertension in a single formulation would have been obvious because all the components and the amounts effective to treat hypertension are well known individually. One of ordinary skill in the art would have been motivated to combine the specific NEP inhibitor (N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) and valsartan in a single composition in order to achieve an expected added benefit of antihypertensive effect in warm-blooded animal species suffering from hypertension. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)).

With respect to claimed combination achieves a greater antihypertensive effect than the sum of the therapeutic effects achievable with the amounts of each of the active agents administered alone is mere conjecture absent a showing.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Kim
Primary Examiner
Art Unit 1617

Jmk
January 30, 2008

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. 32219A
APPLICATION NO. 10/341,868
APPLICANT KSANDER ET AL.
FILING DATE JANUARY 14, 2003
Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM						☐	☐
	AN						☐	☐
	AO						☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	Matsumoto et al., "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopeptidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in conscious dogs", JASN, Hemodynamics and Vascular Regulation, page 517, September 1993).
	AS	
	AT	

EXAMINER [signature] DATE CONSIDERED 1/29/08

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/341,688	KSANDER ET AL
Examiner	**Art Unit**
Jennifer Kim	1617

SEARCHED

Class	Subclass	Date	Examiner
514	533	1/6/2006	JMK
514	381	1/6/2006	JMK
updated		7/10/06	
updated		2/2/07	
	updated	5/29/07	
	updated	11/29/08	

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
Inventor search	1/6/2006	JMK
STN (medicine, registry); WEST	1/6/2006	JMK
STIC	12/15/2005	JMK
updated	7/10/06	
updated	2/2/07	
updated	5/29/07	
updated	11/29/08	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10341868	KSANDER ET AL.
	Examiner	Art Unit
	Kim, Jennifer	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/02/2007	05/24/2007	01/30/2008						
	1	✓	✓	✓						
	2	-	-	-						
	3	✓	✓	✓						
	4	✓	✓	✓						
	5	N	N	N						
	6	-	-	-						
	7	N	N	N						
	8	-	-	-						
	9	-	-	-						
	10	-	-	-						
	11	-	-	-						

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER ET AL.
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

In response to the February 1, 2008 Office Action, for which the time to respond extends to and includes May 1, 2008, Applicants respectfully request the following amendment be entered and the claims considered in light thereof.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the claims are reflected in the listing of claims which begins on page 6 of this paper.

Remarks/Arguments begin on page 9 of this paper.

Amendments to the Specification:

Please replace the first full paragraph on page 6, with the following amended paragraph:

NEP inhibitors within the scope of the present invention also include the compounds disclosed in U.S. Patent No. 5,217,996, particularly, N-(3-carboxy-1-oxopropyl)-(4S)-[p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; the compounds disclosed in EP 00342850, particularly (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; the compounds disclosed in GB 02218983, particularly 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; the compounds disclosed in WO 92/14706, particularly N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; the compounds disclosed in EP 00343911; the compounds disclosed in JP 06234754; the compounds disclosed in EP 00361365, particularly 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; the compounds disclosed in WO 90/09374, particularly 3-[1-(Cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; the compounds disclosed in JP 07157459, particularly N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; the compounds disclosed in WO 94/15908 particularly N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; the compounds disclosed in U.S. Patent No. 5,273,990 particularly (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; the compounds disclosed in U.S. Patent No. 5,294,632 particularly (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; the compounds disclosed in U.S. Patent No. 5,250,522, particularly β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; the compounds disclosed in EP 00636621, particularly N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; the compounds disclosed in WO 93/09101, particularly 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; the compounds disclosed in EP 00590442 particularly ((L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N--[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine, N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropy]amino]-

cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; and the compounds disclosed in WO 93/10773 particularly N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester.

Please replace the second full paragraph on page 7, with the following amended paragraph:

With respect to N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, preferred salts include the sodium salt disclosed in U.S. Patent No. 5,217,996, the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt. Preparation of the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt may be carried out as follows:

Please replace the third full paragraph on page 7, with the following amended paragraph:

Triethanolamine

To N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (349 mg, 0.848 mmol) is added 5 ml of ethyl ether and 0.113 mL (0.848 mmol) of triethanolamine in 1 mL of ethyl acetate. The solid was collected and dried melting at 69-71 °C.

Please replace the first full paragraph on page 8, with the following amended paragraph:

Tris(hydroxymethyl) aminomethane

To N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (3.2 g, 7.78 mmol) is added 32 ml of ethyl acetate and 940 mg (7.78 mmol) *tris*(hydroxymethyl)aminomethane. The suspension is diluted with 45 ml of ethyl acetate and refluxed overnight (~20 hours). The reaction is cooled to 0°C, filtered, solid washed with ethyl acetate and dried melting at 114-115 °C.

Please replace the third full paragraph on page 9, with the following amended paragraph:

Representative studies are carried out with a combination of valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, e.g. applying the following methodology:

Please replace the last full paragraph on page 11, with the following amended paragraph:

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during, and after drug administration. All measurements are performed in unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months. For studies of this duration, rats are dosed orally (1-3 mL/kg vehicle), no more than twice daily or drug is administered via the drinking water or mixed with food. For studies of a shorter duration, that is, up to 8 weeks, drugs are given via s.c. implanted osmotic minipumps. Osmotic minipumps are selected based on drug delivery rate and time. Valsartan dosages range from 1-10 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester range from 10-50 mg/kg/day.

Please replace the first full paragraph on page 12, with the following amended paragraph:

Additionally, SHRs are utilized to study the effects of valsartan in combination with N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the renin angiotensin system (RAS) or chronic salt depletion to activate the RAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the various test substances. Experiments performed in SHRs are supplied by Taconic Farms, Germantown, New York (Tac:N(SHR)fBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul, MN) is implanted into the lower abdominal aorta of all test animals between the ages of 14-16 weeks of age. All SHRs are allowed to recover from the surgical implantation procedure for at least two weeks prior to the initiation of the experiments. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24-hour period

and are made up of the 144-10 minute samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24-hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12-hour light dark cycle.

Please replace the last full paragraph on page 12, with the following amended paragraph:

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is measured five times per week. Valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water, and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days. Typical dosages for valsartan in drinking water range from 3-30 mg/kg/day whereas the dosage of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is highly dependent upon the specific agent used. In most situations, a daily dose will not exceed 50 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1-30 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy.

Please replace the first full paragraph on page 13, with the following amended paragraph:

When drugs are administered by oral gavage, the dose of valsartan ranges from 1-50 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester does not exceed 100 mg/kg/day.

This listing of the claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof,

wherein the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered in combination achieve a greater anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt administered alone and (ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone, and a pharmaceutically acceptable carrier.

2. (canceled)

3. (currently amended) The pharmaceutical composition of Claim 1, wherein *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. (currently amended) A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and in a second container a pharmaceutical composition comprising valsartan or a pharmaceutically acceptable salt thereof

wherein the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts and valsartan or a pharmaceutical acceptable salt thereof administered in combination achieve a greater anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone and valsartan or a pharmaceutically acceptable salt thereof administered alone.

5. (withdrawn) A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester or (2*R*,4*S*)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. (canceled)

7. (withdrawn) The method of Claim 5, wherein *N*-(3-carboxy-1-oxopropyl)-

(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

8-11. (canceled)

REMARKS

Consideration of the above-identified application as amended is requested. Claims 1, 3 and 4 remain in this application. Claims 1, 3 and 4 have been amended. No new matter has been added.

Objections to Specification and Claims 1, 3 and 4

The specification has been objected to because of imbalanced parentheses in the chemical name of the compound. Applicants have searched the specification and inserted a parenthesis in the appropriate place in all occurrences of the chemical name of the compound. Claims 1, 3 and 4 were objected to for the same reason and the claims were similarly corrected. Accordingly, these objections have been overcome and should be withdrawn.

Rejection of claims 1, 3 and 4 under 35 U.S.C. §103(a)

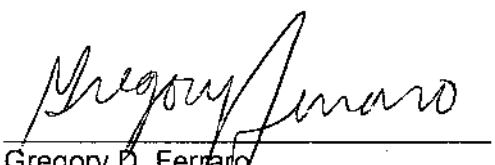
The rejection of Claims 1, 3 and 4 under 35 U.S.C. §103(a) over Ksander U.S. Patent No. 5,217,996 ('996 patent) and Buhlmayer et al. U.S. Patent No. 5,399,578 ('578 patent) has been maintained by the Examiner. The Examiner states that the tested compound as set forth in the Webb Declaration differs from the compound currently claimed.

Based on the attached February 13, 2008 Declaration of Randy Webb, Applicants submit that the compound used in the testing, as referred to in the May 11, 2006 and November 16, 2006 Webb Declarations, and the compound currently claimed are the same compound. As shown in the attached Webb Declaration, the tested compound was inadvertently set forth with a ... 3-methyl... where a ...2-methyl... was intended.

Since the compound tested and claimed are the same, the data showing unobviousness is commensurate in scope with the invention being claimed. This data is sufficient to distinguish the claimed invention over the state of the art as represented by the cited references.

In view of the foregoing, Applicant submits the Application is now in condition for allowance and respectfully requests early notice to that effect.

Respectfully submitted,



Gregory D. Ferraro
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Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
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(862) 778-7831
Date: February 13, 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander et al.
APPLICATION NO: 10/341,868
FILED: January 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M.

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Randy Lee Webb, being duly warned, hereby declare as follows:

1. I am the same Randy Lee Webb who submitted the Declarations under 37 C.F.R. § 1.132 dated May 11, 2006 and November 16, 2006, attached hereto, in the application identified in the caption above (which is referred to in this document as "the Application").

2. I have read and understand the February 1, 2008 Office Action issued in the Application.

3. The experiments described in both Declarations identified above were carried out using 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester (AHU377) and valsartan as claimed in the Application.

4. The description of AHU in my May 11, 2006 and November 16,2006 Declarations should have read 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester. The insertion of "...2-methyl..." instead of "...3-methyl..." would have been correct. This error was inadvertent and unintended. This was a mistake and was not noticed by me upon my review of the Declarations prior to signing.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2-13-2008

Randy Lee Webb

Randy Lee Webb

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Ksander et al.

APPLICATION NO: 10/341,868

FILED: January 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M.

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Randy Lee Webb, being duly warned, hereby declare as follows:

1. I am a citizen of the United States of America, residing at 17 Honeymoon Lane, Flemington, New Jersey 08822.

2. I am a named inventor of the invention presently claimed in U.S. application Serial No. 10/341,868 identified in the caption above (which is referred to in this document as "the Application").

3. I received a Ph.D. in Pharmacology from the University of Iowa in 1984. I have carried out research in the area of hypertension and cardiovascular disease for 30 years, including 21 years at Ciba/Novartis and I have published 64 papers and 3 book chapters on my research in this area. Presently, I am at Novartis Inc., where I am head of Hypertension Research and conduct research in the identification of novel therapeutic targets for hypertension and the development of new antihypertensive drugs. My background is presented in more detail in my *Curriculum Vitae*, which is attached to this Declaration as EXHIBIT 1.

4 I have read and understand the January 12, 2006 Office Action issued in the Application and the Ksander (U.S. Patent No. 5,217,996) and Buhlmayer et al. (U.S. Patent No. 5,399,578) references cited therein

5. The experiments summarized in the paragraphs below were carried out by me or under my direction and supervision, or by collaborators with my full participation and understanding. The experimental results, as explained below, provide evidence that the pharmaceutical combination of 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-3-methylbutanoic acid ethyl ester (AHU377) and valsartan as claimed in the Application (the combination of the present invention), has (i) synergy in lowering mean arterial pressure in animal models of hypertension as compared to monotherapy with either active agent alone and that this synergy is an unexpected and surprising blood pressure lowering effect which would not be expected by one of ordinary skill in the art and (2) has added therapeutic benefits in the treatment of hypertension compared to valsartan monotherapy and AHU377 monotherapy.

6. As described in greater detail below, the experiments show that : (1) administration of a combination of valsartan at 30 mg/kg/day and AHU377 at 30 mg/kg/day to Dahl salt sensitive rats provides a synergistic, unexpected and surprising antihypertensive effect and the combination of valsartan at 100 mg/kg/day and AHU377 at 30 mg/kg/day also elicited a synergistic, unexpected and surprising antihypertensive effect, even though in Dahl salt sensitive rats valsartan alone has no discernable effect and AHU377 only has an effect at a 100 mg/kg/day dose; (2) administration of a combination of the claimed invention to stroke prone male spontaneously hypertensive rats (SHRsp) had a synergistic, unexpected and surprising antihypertensive effect, even though the combination of valsartan and AHU377 did not significantly reduce blood pressure in SHR; and (3) the combination of the claimed invention has the added therapeutic benefits in the treatment of hypertension of improved cardiac fibrosis and vascular remodeling and fibrosis of mesenteric and intramyocardial coronary arteries thereby reducing hypertension by decreasing media/lumen ratio of intramyocardial coronary arteries as compared to valsartan monotherapy and AHU377 monotherapy. In summary, the experiments show that the combination of valsartan and AHU377 has a synergistic, unexpected and surprising antihypertensive effect and has added therapeutic benefits in the treatment of hypertension.

7. The experiments on the SHR and Dahl salt-sensitive animal models of hypertension were performed to assess and compare the efficacy on hypertension of the combination of the Application with valsartan and AHU377 administered as monotherapy. In the experiments

performed on the SHRsp rats, the objective was to assess the efficacy on hypertension, oxidative stress, endothelial function and vascular remodeling of the combination of the claimed invention with a combined angiotensin converting enzyme inhibitor and neutral endopeptidase inhibitor (ACE/NEP inhibitor), valsartan monotherapy, AHU377 monotherapy and hydralazine monotherapy.

8. The experiments on the SHR model of hypertension were carried out as follows: Procedure: All SHR were implanted with radiotransmitters between the ages of 15 to 16 weeks old according to the procedures described previously in Webb and Yao, Novartis Study Report, PKF-99-00909. Rats were allowed a minimum of 7-10 days to recover from surgery prior to the start of experimentation. SHR were allocated to four treatment groups depending upon baseline blood pressure measurements and with the goal of having similar group mean blood pressure values at the start of the study. Baseline blood pressure represents the overall average blood pressure recorded over 3 consecutive days. Blood pressure was collected for 10 seconds every 10 minutes throughout the day and thus, 144 pressure measurements were recorded every 24 hours. All treatments commenced in SHR between 17-18 weeks of age. Drugs were administered by oral gavage, once daily to conscious SHR in four separate groups as follows:

Drug Treatment

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Group 1	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle
Group 2	Vehicle	Vehicle	Val 3	Val 10	Val 30	Val 100
Group 3	NEPI 30	NEPI 30	NEPI 30 Val 3	NEPI 30 Val 10	NEPI 30 Val 30	NEPI 30 Val 100
Group 4	NEPI 30	NEPI 100	NEPI 100 Val 3	NEPI 100 Val 10	NEPI 100 Val 30	NEPI 100 Val 100

Treatments: Vehicle, 3% cornstarch; NEPI, AHU377 ; Val, valsartan. Valsartan was administered in ascending dosages of 3, 10, 30 and 100 mg/kg/day on a background of either vehicle, AHU377 at 30 mg/kg/day or AHU377 at 100 mg/kg/day. Each dose of valsartan was given for a period of one week.

Starting at week 3, valsartan was given at 3, 10, 30 and 100 mg/kg/day in one week intervals, either alone or adjunctively with NVP-AHU377-AB. Results in the SHR were analyzed by a mixed effects model (MEM) using the average weekly blood pressure and secondly, the average weekly slope of the blood pressure effect (Brown and Prescott, 1999). This analysis is similar to an analysis of variance but generally considered to be more efficient and sensitive since missing data due to an animal death does not have to be excluded. The daily observations of blood pressure (24 hr averages) and heart rate are repeated throughout the study protocol. All values were considered significant when $P < 0.05$.

9. The experiments on the Dahl salt sensitive rats were carried out as follows:

Procedure: Radiotransmitters were implanted into Dahl salt-sensitive rats at 7 weeks of age. All animals were placed on a high salt diet (8%) between 7 and 8 weeks of age (approximately 12 days prior to the start of the study) and maintained on this regimen for the duration of the study. Drug treatment was initiated at 9 weeks of age and was continued for 3 weeks. Drugs were administered once daily by oral gavage. The effects of valsartan alone and in combination with AHU377 were assessed using a 3 X 3 factorial design as follows:

Protocol design for the 3 X 3 factorial study in Dahl salt-sensitive Rats

Vehicle n = 8	Val 30 n = 8	Val 100 n = 8
NEPI 30 n = 8	Val 30 + NEPI 30 n = 8	Val 100 + NEPI 30 n = 8
NEPI 100 n = 7	Val 30 + NEPI 100 n = 8	Val 100 + NEPI 100 n = 8

NEPI 30 and 100 represent AHU377 administered by oral gavage at a dose of 30 and 100 mg/kg/day, respectively. Val 30 and 100 depict valsartan given at a dose of 30 and 100 mg/kg/day, respectively. Vehicle was 3% cornstarch given at 2 ml/kg body weight.

10. The experiments on the SHRsp were carried out as follows:

Animal Experiments: Male SHRSP were obtained from a colony originally acquired from the National Institutes of Health (NIH), and maintained locally. Rats were housed at 22°C and 60% humidity under a 12-hour light/dark cycle. Starting at 10 weeks of age, SHRSP were fed powdered diet (Agribrands Purina, Drummondville, QC, Canada) containing the combined valsartan (10mg/kg/day)/AHU377 (100mg/kg/day, NEPI), CGS 30440 (10mg/kg/day, a combined ACEI/NEPI), valsartan alone (10mg/kg/day), AHU377 (100mg/kg/day), or hydralazine (25mg/kg/day). Wistar-Kyoto rats (WKY) served as normotensive controls. Systolic blood pressure (BP) was measured initially by the tail-cuff method under slight restraint and was monitored weekly for the last 5 weeks by radio-telemetry as previously described (Amiri F, et al., *Circulation.* 2004;110:2233-2240). After 10 weeks of treatment, rats were killed humanely.

Preparation and Study of Mesenteric Resistance Arteries: Third-order branch of the mesenteric vasculature was isolated and mounted on a pressurized myograph as described previously (Savoia C, et al., *J Hypertens.* 2005;23:1037-1045.). Endothelium-dependent and independent relaxations

were assessed in norepinephrine (10^{-5}mol/L) pre-contracted vessels with acetylcholine and sodium nitroprusside, respectively. Lumen and media dimensions were measured while intraluminal pressure maintained at 45mmHg upon vessel deactivation with 10mmol/L EGTA (Virdis A, et al., *Hypertension.* 2002;40:504-510). Thereafter, vessels were fixed with 4% paraformaldehyde for histology.

Measurement of NADPH Oxidase Activity: Vascular NADPH oxidase activity was measured in aortic segments and mesenteric arteries by lucigenin chemiluminescence (5µmol/L), using NADPH (100µmol/L) as substrate, as previously described ((Virdis A, et al., *Hypertension.* 2002;40:504-510)). Lucigenin signal specificity was tested by adding both diphenylene iodinium, a flavoprotein inhibitor, and tempol, a superoxide dismutase mimetic.

Histology and Immunohistochemistry: Four animals per group were perfused with 4% paraformadehyde *in vivo*. Once mesenteric arteries were removed, heart and aorta were embedded in paraffin, and serially sectioned (5µm) for histological and immunohistochemical studies. As previously described (Pu Q, et al., *Am J Hypertens.* 2001;14:1067-1072.), severity of vascular and cardiac fibrosis was evaluated with Sirius red staining and analyzed by image analysis system (Northern Eclipse 5.0, EMPIX Imaging Inc., Mississauga, ON, Canada), by an investigator unaware of the experimental group examined. Collagen density was defined as the ratio of the area stained to the total tissue area and expressed as percentage. Macrophage infiltration was assessed by immunostaining with a monoclonal antibody against rat monocytes/macrophages (ED-1, Serotec, Raleigh, NC) as previously described (Pu Q, et al., *J Hypertens.* 2005;23:401-409).

Preparation of Vascular Tissue for Western Blotting: Samples were extracted (Amiri F, et al., *Circulation.* 2004;110:2233-2240) and expression of nitric oxide synthase (NOS) was assessed with endothelial NOS (eNOS) antibody (BD Biosciences, San Jose, CA) as previously described (Javeshghani D, et al., *Hypertension.* 2003;42:761-767). Signals were revealed with chemiluminescence and visualized autoradiographically. Subsequently membranes were stripped (Pierce Biotechnology, Rockford, IL) and re-probed with beta-actin (Sigma Chemicals, Mississauga, ON, CAN) to verify equal loading. Optical density of bands was quantified by ImageQuant 5.0 (Molecular Dynamics, Sunnyvale, CA), and expressed as arbitrary units.

Gelatin Zymography and Reverse Zymography: Protein was extracted from frozen aorta by homogenization as previously described (Brassard P, et al., *Hypertension.* 2005; 46:598-606), while latent and activated gelatinases were detected with SDS-PAGE gelatin zymography (Galis ZS, et al., *Circ Res.* 1994;75:181-189; Brassard P, et al., *Hypertension.* 2005; 46:598-606). After gel staining, MMPs were identified based on gelatin lysis at 62kDa and 82kDa for activated MMP-2 and MMP-9, respectively. Gelatinolytic bands were quantified using ImageQuant software 5.0. Reverse zymography was performed as previously described (Brassard P, et al., *Hypertension.*

2005; 46:598-606) where stained bands represent gelatinase inhibitory activity corresponding to TIMPs.

Data Analysis: Data are presented as mean±SEM and analyzed by repeated measures ANOVA followed by Newman-Keuls *post-hoc* test. $P<0.05$ was considered significant.

11. SHR Results:

Blood Pressure (mmHg)

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Group 1	146 ± 2	147 ± 1	148 ± 1	149 ± 1	149 ± 2	148 ± 2
Group 2	149 ± 3	150 ± 4	146 ± 3	142 ± 4	135 ± 4	120 ± 5
Group 3	148 ± 2	148 ± 2	145 ± 2	143 ± 4	137 ± 3	124 ± 2
Group 4	146 ± 5	145 ± 4	138 ± 5	136 ± 5	128 ± 4	117 ± 5

12. Dahl Salt Sensitive Results for Valsartan Monotherapy:

	Dose mg/kg/day	Final BP mmHg	Improvement over vehicle mmHg
Vehicle		193 ± 5	
Valsartan	30	191 ± 6	-2
Valsartan	100	196 ± 7	+3

13. Dahl Salt Sensitive Results for AHU377 Monotherapy:

	Dose mg/kg/day	Final BP mmHg	Improvement over vehicle mmHg
Vehicle		193 ± 5	
AHU377	30	191 ± 5	-2
AHU377	100	177 ± 5	-16

14. Dahl Salt Sensitive Results for Valsartan and AHU377 combination therapy:

	Dose mg/kg/day	Final BP mmHg	Improvement over vehicle mmHg	Expected Improvement mmHg	Improvement Factor mmHg
Vehicle		193 ± 5			
Vals:AHU377	30:30	176 ± 6	-17	-4	-13
Vals:AHU377	30:100	179 ± 6	-14	-18	+4
Vals:AHU377	100:30	174 ± 5	-19	+1	-18
Vals:AHU377	100:100	182 ± 8	-11	-13	+2

15. SHRsp Model Results for Valsartan and AHU377 monotherapy and combination therapy for Systolic Blood Pressure (SBP):

	Dose mg/kg/day	Final SBP mmHg	SBP Reduction	Expected Improvement mmHg	Improvement Factor mmHg
SHRsp		195 ± 6			
Valsartan	10	176 ± 6	-19		
AHU377	100	199 ± 6	+4		
Vals:AHU377	10:100	167 ± 5	-28	-15	-13
ACE/NEP inhibitor	10	152 ± 2	-43		

SHRsp Model Results for Valsartan and AHU377 monotherapy and combination therapy for Diastolic Blood Pressure (DBP)

	Dose mg/kg/day	Final SBP mmHg	SBP Reduction	Expected Improvement mmHg	Improvement Factor mmHg
SHRsp		142±3			
Valsartan	10	137±7	-4.6		
AHU377	100	151±8	+9.5		
Vals:AHU377	10:100	118±5	-23.8	+4.9	-28.7
ACE/NEP inhibitor	10	108±3	-34		

16. Based on the above, the combination therapy of the claimed invention was clearly shown to demonstrate synergism with respect to blood pressure lowering, for both the Dahl study at 30:30 and 100:30 (Valsartan to NVP-AHU377-AB, respectively (mg/kg/day)); and in the SHRsp study. This synergy is illustrated by the improvement factors reported in the preceding table, where the improvement factors are calculated by subtracting the expected additivity of independent events from the combination therapy. In paragraphs 14 and 15 above, synergy is shown by the negative number set forth in the "Improvement Factor" column. This number is the actual blood pressure lowering effect of the combination of the present invention beyond that which is expected from the combination based on the results of monotherapy. The demonstrated synergism was both unexpected and surprising. The only exception is the SHR study, which does not show synergy. This is explained by the fact that the SHR hypertensive animal model is one in which the BP is generally stable over extended periods of time, that is, it will rise with age but does so more gradually than many other experimentally-induced models of hypertension in the rat. Additionally, it is known that angiotensin receptor blockers (ARBs) work to lower BP in these animals due to an underlying contribution of the renin angiotensin system in these animals. Blockade of the renin angiotensin system in the SHR, especially chronically, will result in blood pressure lowering. Further, NEPi, which does not block the renin angiotensin system, are known not to be effective in the SHR animal model. Therefore, combinations of valsartan and AHU did not lower BP significantly more than valsartan alone in the SHR model.

17. This makes the Dahl and SHRsp data even more unexpected. The animals in this model rapidly become moribund due to a progressive malignant hypertension, that if left untreated would result in mortalilty in one hundred percent of the animals. Therefore, the fact that the combination had synergistic effects in these models, when not having synergistic effects in the stable SHR model, is therefore even more unexpected and surprising.

18. As shown in Figure 1, attached hereto as EXHIBIT 2, experiments performed on SHRsp shows that the combination of the present invention, the dual ACEi/NEPi compound and valsartan alone normalized maximal acetylcholine relaxation responses, whereas AHU377 and hydralazine were ineffective. This shows that of the combination of the present invention has the added therapeutic value of exerting protective effects on the endothelium and thereby reducing endothelial dysfunction. Reduction of endothelial dysfunction improves vascular function and therefore helps treat hypertension. The combination of the present invention is more beneficial with respect to endothelial dysfunction than AHU377 alone although it is similar to valsartan alone.

19. As shown in Figure 2, attached hereto as EXHIBIT 3, experiments performed on SHRsp shows that the combination of the present invention, the dual ACEi/NEPi compound and valsartan alone significantly decreased media/lumen ration and collagen deposition, whereas AHU377 and hydralazine were ineffective. This is indicative of therapeutic vascular remodeling of the endothelium by the combination of the present invention. The combination of the present invention is more beneficial with respect to vascular remodeling than AHU377 alone, although it is similar to valsartan alone.

20. As shown in Figure 3, attached hereto as EXHIBIT 4, experiments performed on SHRsp shows that the combination of the present invention, the dual ACEi/NEPi compound, valsartan alone, AHU377 alone and hydralazine all decreased vascular NADPH oxidase activity significantly in SHRsp. The increased activity of NADPH oxidase seen in the SHRsp results in increased oxidative stress (reduction in reactive oxygen species) within the vessel wall. The significant reduction in NADPH oxidase activity will minimize vessel wall damage due to oxidant stress and improve vascular function.

21. As shown in Figure 4, attached hereto as EXHIBIT 5, experiments performed on SHRsp shows that the combination of the present invention and the dual ACEi/NEPi compound improved media/lumen ratio and interstitial collagen density better than valsartan alone, whereas AHU377 and hydralazine were ineffective. These effects on small arteries may be of importance in the treatment of hypertensive patients, wherein these patients have detrimental small artery remodeling in the myocardium or in other organs which may contribute to cardiovascular events. Animals treated with the combination of the present invention show a collagen density closer to the control animal (WKY) than either monotherapy with valsartan or AHU377.

22. As shown in Figure 5, attached hereto as EXHIBIT 6, experiments performed on SHRsp shows that the combination of the present invention and the dual ACEi/NEPi compound were more effective than valsartan alone, AHU377 alone or hydralazine in decreasing vascular macrophage infiltration. Vascular macrophage infiltration is a marker of inflammation and leads to vascular damage and diminished vessel wall function such as reduced vasorelaxant capacity.

23. As shown in Figure 6, attached hereto as EXHIBIT 7,SHRsp exhibited reduced MMP-2 activity with concurrent increase in TIMP-2 activation, thus resulting in increased cardiac and vascular collagen deposition due to a reduction in collagen degradation. The combination of the present invention as well as dual ACEI/NEPI increased MMP-2 activity and decreased TIMP-2

activity, whereas valsartan or NEPI alone had no effect. Therefore, the combination of the present invention shows an added therapeutic value in the protection of the vessel wall and in the treatment of hypertension not shown by monotherapy.

24. In summary, based on my expertise and experience and on my evaluation of the results set forth above, it is my opinion that the combination of the present invention unexpectedly and surprisingly lowers blood pressure as compared to the monotherapy and shows an added therapeutic value in the treatment of hypertension as compared to monotherapy of valsartan or NVP-AHU377-AB.

25. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 11, 2006

Randy Lee Webb

Randy Lee Webb

Curriculum Vitae

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Tel. No. (908) 806-6032

Education

Rutgers University, New Brunswick, NJ, **B.S. Biology** - 1976
Fairleigh Dickinson University, Teaneck, NJ, **M.S. Physiology** - 1979
University of Iowa, Iowa City, Iowa, **Ph.D. Pharmacology** - 1984
NIH Predoctoral Trainee - University of Iowa, 1979-1983
NRSA Postdoctoral Fellowship - Medical College of Wisconsin, 1984

Appointments and Honors

Co-chairman – ANF: Metabolism and Receptors, FASEB, Las Vegas, NV, May, 1988.

Scientific Advisory Board and session chairman - Fourth International Conference on Endothelin, London, England, April 23-26, 1995.

Research Peer Review Committee, American Heart Association, New Jersey Affiliate and Northeast Affiliate Consortium Group 3 Reviewer, 1997-2001.

Discipline Expert and member of the Novartis Scientific Council on Pharmacology (1999)

International Council within Novartis Research consisting of 16 members with quarterly meetings (Basel), review policies within Research, establish guidelines for Research efforts across disciplines, organize workshops, prepare position papers, etc.

Member of the Novartis Global CV Council (2001-2004)

Represent CV Research and serve on a panel with 7 International CV experts to provide feedback to Novartis on trends, controversies, opportunities for optimizing current products and to make recommendations regarding CV portfolio strategy.

Member - Novartis Metabolic/Cardiovascular Franchise Board (2002-2004)

Management team includes members from Research, Clinical Development, Marketing and Business Development and Licensing. Board members review on a monthly basis all Metab/CV programs/products within Franchise to set development and commercial strategy and to ensure alignment within the Novartis portfolio. Evaluate in-licensing opportunities and acquisitions.

Inventor – U.S. Patent 6,204,281 (2001)
Inventor – U.S. Patent 6,395,728 (2002)

Employment Experience

2003-present	Executive Director, Cardiovascular Research, Novartis Institutes for BioMedical Research
2002-2003	Executive Director, Cardiovascular Disease Pharmacology, Metabolic and Cardiovascular Diseases, Novartis Pharma.
2000-2001	Principal Fellow, Novartis Pharma.
1997-1999	Senior Fellow, Novartis Pharma.
1995-1996	Senior Research Fellow I, Ciba Pharma.
1991-1994	Staff Scientist, Ciba Geigy Pharma.
1988-1990	Senior Research Scientist, Ciba Geigy Pharma.
1984-1987	Senior Scientist, Ciba Geigy Pharma., Summit, NJ
1976-1979	Pharmacologist, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ

Team Membership

2000-2001	Research Representative – Diovan International Project Team Roles/Responsibilities – Coordinate all preclinical (External/Internal Investigators) studies, review and critique scientific aspects and align with IPT strategy for Product Lifecycle Management, oversee financial support for external collaborations, represent Research on all matters pertaining to product, attend monthly team meetings, various conferences with investigators, serve as a scientific consultant to the Diovan Brand Team and prepare/present lectures for Novartis International Scientific Symposia.
1998	Research Representative - Diovan Life Cycle Management Team Cardioprotection Task Force – member
1997	International Project Team Member, International Clinical Team Member (CGP 60536B, renin inhibitor) and Preclinical Research Coordinator
1993-1995	Valsartan (Angiotensin II Antagonist) Project Team Member
1989-1993	Project Team Member, Preclinical Research Coordinator - Benazepril/Amlodipine (LOTREL™)

Leadership Skills

2004-	Fully Integrated Program (FIP) Head for hypertension

Roles/Responsibilities – oversight of all hypertension projects, including setting project/program strategy, review of progress, resource allocation, project prioritization. Also, responsible for coordinating compound progression up to entry of compounds into Phase I.

2000 Program Team Leader – VPI program

Roles/Responsibilities – supervise multi-disciplinary team consisting of approximately 20 team members (chemistry, pharmacology, pharmacokinetics, cellular biology; MDs, PhDs, MS and BS level), identify, evaluate and recommend compounds for further development

1999- Cardioprotection/CHF/Hypertension Indication Team Leader

Roles/Responsibilities – 6 PhD Research team members, review all in-licensing opportunities related to Cardioprotection (hypertension, post-MI, CHF, ischemia/reperfusion), make recommendations to Metabolic and Cardiovascular Diseases Therapeutic Area Board, propose novel targets/mechanisms for new programs within therapeutic area

1995-1996 Chairman, International Strategic Alignment Committee (Renal Disease)

Roles/Responsibilities – 9 member task force consisting of MDs and PhDs from Clinical, DRA, Marketing, Research + 2 external consultants (nephrologists), prepared strategic proposal/documentation for initiating therapeutic programs in kidney disease and presented to Global Head of Pharmaceutical Division

1991-1995 Co-Leader - Endothelin Receptor Antagonists

1988-1991 Co-Leader - Adenosine

1986-1988 Deputy Project Leader - Adenosine

Organizational Skills

Organized and Chaired International Renal Advisory Board Meeting, December, 1995, San Diego, CA.

One-day CIBA workshop consisting of 8 International Opinion Leaders on Kidney Disease; incorporated recommendations for novel targets, research approaches, etc. into a Renal Strategic Proposal for CIBA senior management.

Organized and Chaired Novartis International Hypertension Workshop – March 20-21, 2000

Two day workshop with internal participants from various line functions and 5 International Consultants and consisted of a series of seminars and a roundtable discussion covering all aspects of Hypertension Research. A final report was prepared with specific recommendations and conclusions and was presented to management at the Annual Portfolio Review.

IND/NDA/IB Preparation

Ismelin (guanethidine) - "orphan IND" Section 6A/IND

CGS 14831 (benazeprilat, ACE inhibitor) Section 6A/IND

Lotensin HCT™ (Benazepril/Hydrochlorothiazide) NDA Submission

Lotensin™ (Benazepril) - Biology Compound Sponsor - 1989-present,

Summary Basis of Approval, 1990

LOTREL™ (Benazepril/Amlodipine) - NDA Submission (1993); Summary Basis of Approval (1994); FDA Advisory Board Meeting, invited guest, NIH Campus, June, 1994; Investigators' Brochure, June, 2003.

Diovan™(Valsartan) - Hypertension NDA Submission, December, 1995.

Diovan-HCT™ (Valsartan/Hydrochlorothiazide) - Hypertension NDA Submission, March, 1997

Diovan™ (Valsartan) – Heart Failure sNDA Submission (Preclinical report) and European Dossier for Heart Failure Submission (Preclinical Expert Report), April 2001, FDA Cardio-renal Advisory Committee Meeting, designated Novartis participant, October 11, 2001, Investigator's Brochure Edition 13, May, 2001.

Diovan™ - valsartan/simvastatin preclinical summary IND filed September, 2001.

Invited Conference Participant/Lecturer

1. Neural Control of the Circulation, FASEB Summer Conference, Saxtons River, VT, July 1982.

2. Vasopressin Conference, Aspen, Colorado, August 1984.

3. Cardiovascular Residency Program, Georgetown University Medical School, April 27-29, 1987.

4. "Identification of adenosine A_2-selective agonists: Novel antihypertensive agents?" Ciba Geigy Ltd., Basel, Switzerland, June 27, 1991.

5. "Highly selective adenosine A_2 agonists: Cardiovascular actions during acute and chronic administration." Presented at Purines '92, University of Milan, Milan, Italy, June 21-24, 1992.

6. Data Sciences, Inc., Experimental Biology Telemetry Tutorial, "Pharmacological evaluations using radiotelemetry n conscious rats", Anaheim, CA., April, 1994.

7. "Therapeutic potential of AT_1 receptor antagonists in chronic renal disease", Valsartan Diabetic Nephropathy Advisory Meeting, Short Hills, NJ, June 5, 1994.

8. "Telemetric monitoring of cardiovascular parameters in conscious rats." Tri-Branch AALAS Conference, Philadelphia, PA, June 7-8, 1994.

9. "Role of ET_B receptors in cardiovascular and renal function." Endothelin Inhibitors: Advances in Therapeutic Application and Development, IBC Conference, Philadelphia, PA., June 9-10, 1994.

10. "Long-term monitoring of cardiovascular parameters in conscious rats using radiotelemetry. International Congress of Pharmacology (IUPHAR), Telemetry Tutorial, Montreal, Canada, July 23-28, 1994.

11. Session Chairman, "Pathophysiology of Endothelin", Fourth International Conference on Endothelin, London, UK, April 23-26, 1995.

12. "Lotrel: Logical antihypertensive therapy." Lotrel Advisory Meeting, New York City, NY, May 16, 1995.

13. "Preclinical overview of benazepril/amlodipine results in experimental models of cardiovascular disease." Lotrel Investigators Meeting, San Diego, CA, July 13-16, 1995.

14. "Overview of benazepril/amlodipine results in experimental models of cardiovascular disease." Lotrel Speakers Training Meeting, Colorado Springs, CO, August 17-20, 1995.

15. "Overview of benazepril/amlodipine results in experimental models of cardiovascular disease." Lotrel Speakers Training Meeting, Phoenix, AZ, October 12-15, 1995.

16. "Inhibitors of the renin angiotensin system: Novel therapeutics for renal disease." Ciba International Advisory Meeting on Kidney Disease, San Diego, CA, November 8, 1995.

17. "Preclinical profile of the novel renin inhibitor CGP 60536B." Novartis Advisory Meeting, New York, NY, August 6-7, 1997.

18. "Chronic antihypertensive effects of combination therapy in telemetered-spontaneously hypertensive rats." American Association for Laboratory Animal Science, 49th National Meeting, Cincinnati, Ohio, October 19, 1998.

19. DIOVAN® "Preclinical research profiling in cardiovascular and renal disease" National Advisory Board Meeting, Atlanta, GA, January 22, 1999.

20. DIOVAN® "New basic science initiatives with the angiotensin II antagonist, valsartan", Heart Failure Investigators Meeting, Prague, The Czech Republic, December 2-3, 2000.

21. DIOVAN® " New Basic Science Initiatives with the Angiotensin II Antagonist, Valsartan", International Symposium "Selective Angiotensin Receptor Blockade: Treatment Strategies along the Cardiovascular Continuum", May 12-13, 2001, Paris, France (1000 participants from 45 countries).

22. DIOVAN® "Update of Preclinical Results with Diovan", ARB/RAS Vascular Advisory Meeting, New York City, December 14-16, 2001.

23. "Preclinical results with the new renin inhibitor, aliskiren", Aliskiren Advisory Board Meeting, Zurich, Switzerland, March 4, 2002.

24. Aliskiren Advisory Board Meeting, New York City, NY, September 23, 2002.

25. Aliskiren Nephrology Advisory Board Meeting and Aliskiren Global Advisory Board Meeting, Boston, MA, April 2-3, 2004. "Preclinical evidence of efficacy and safety".

26. Diovan Lifecycle Planning Meeting, New Orleans, LA, November 10, 2004. "Development Candidates for Hypertension – Preclinical Review".

27. Novartis Metabolic Syndrome Advisory Board Meeting. London, UK, February 28-March 2, 2005.

28. Panelist at The 4th Annual Waterbury Forum, "State of the Heart: The Future of Cardiac Care in Connecticut", Post University, Waterbury, CT, April 14, 2005.

29. ARB/RAS Vascular Advisory Board: International Summit, Budapest, Hungary, May 20-21, 2005. "ARB/NEPI Combination Development", "Aliskiren: Preclinical Overview and Development Plan" and "Is Aldosterone a Target for Improving Intervention?".

Society Membership

Physiological Society of Philadelphia, 1986-1993.
The American Society of Hypertension, 1988 -
The New York Academy of Sciences, 1989 -
ASPET, 1993 -
Council for High Blood Pressure Research, 1998 -

Teaching Experience

Advanced Cardiovascular Pharmacology: Drug Development, New York Medical College, Valhalla, NY
Fall Semester 1994, 1996; Therapeutic Potential of the Endothelin System
Fall Semester 2002; ACE/NEP Inhibitors

Spring Semester 2005, Class #1088; The Discovery and Development of Renin Inhibitors

Scientific Journal Referee

Journal of Pharmacology and Experimental Therapeutics
Hypertension – 1996, 1997, 1998
Cardiovascular Drug Reviews
Canadian Journal of Physiology and Pharmacology – 1996
American Journal of Physiology: Heart and Circulatory – 1997, 1998
Life Sciences - 1998

Extra-curricular Activities

Judge (Team Captain - Health and Medicine) - New Jersey Regional Science Fair (High School Competition) - March 14-15, 1997 Morris County Community College; March 12-13, 1999, Morris County Community College, NJ.

Supervisory Responsibility

Executive Director (2002-) CV Pharmacology – supervision of 5 Ph.D. and 14 BS/MS scientists; direct lab reports - 1 MS scientist.

Group Leader (1991-1994) CV Pharmacology Unit – supervision of 3 Ph.D., 1 MD and 6 BS/MS scientists.

Post-doctoral trainee, Michelle Bazil, 1990-1992.

Publications

Manuscripts

1. K.H. Berecek, K.W. Barron, **R.L. Webb** and M.J. Brody. Vasopressin central nervous system interactions in the development of DOCA hypertension. Hypertension 4(Suppl. II):II131-II137, 1982.

2. K.H. Berecek, K.W. Barron, **R.L. Webb** and M.J. Brody. Relationship between vasopressin and the anteroventral third ventricle region in deoxycorticosterone/salt hypertension. (Brattleboro Rat Model). Ann. New York Acad. Sci. 394: 392-397, 1982.

3. K.H. Berecek, K.W. barron, **R.L. Webb** and M.J. Brody. Vasopressin projections and central control of cardiovascular function. (Brattleboro Rat Model). Ann. New York Acad. Sci. 394: 729-734, 1982.

4. K.H. Berecek, **R.L. Webb** and M.J. Brody. Evidence for a central role for vasopressin in cardiovascular regulation. Am. J. Physiol. 244: H852- H859, 1983.

5. S.P. Americ, S.A. Chow, R.K. Bhatnagar, **R.L. Webb**, L.J. Fisher and J.P. Long. Evidence that central dopamine receptors modulate sympathetic neuronal activity to the adreanl medulla to alter glucoregulatory mechanisms. Neuropharmacology 23: 137-147, 1984.

6. M.J. Brody, **R.L. Webb**, M.L. Mangiapane, J.P. Porter, A.C. Bonham and A.J. Trapani. Comparative central and peripheral antihypertensive mechanisms of urapidil and prazosin. Am. J. Med. 77(4A): 74-80, 1984.

7. J.P. Porter, A.C. Bonham, M.L. Mangiapane, **R.L. Webb** and M.J. Brody. Central and peripheral cardiovascular effects of indoramin in conscious rats. Eur. J. Pharmacol. 109: 9-17, 1985.

8. A.W. Cowley, Jr., J.F. Liard, M.M. Skelton, E.W. Quillen, Jr., J.W. Osborn, Jr. and **R.L. Webb**. Vasopressin-neural interactions in the control of cardiovascular function. In: *Vasopressin*, ed. by R.W. Schrier. Raven Press, New York, 1985, pp. 1-10.

9. R.W. Lappe, **R.L. Webb** and M.J. Brody. Selective destruction of renal afferent versus efferent nerves in rat. Am. J. Physiol. 249: R634-R637, 1985.

10. **R.L. Webb**, R. Della Puca, J. Manniello, R.D. Robson, M.B. Zimmerman and R.D. Ghai. Dopaminergic mediation of the diuretic and natriuretic effects of ANF in the rat. Life Sci. 38: 2319-2327, 1986.

11. **R.L. Webb**, G.R. Ghai, B.W. Barclay, R.D. Ghai and M.B. Zimmerman. A comparison of the vasorelaxant and hemodynamic properties of synthetic atriopeptins. In: *Biologically Active Atrial Peptides*, ASH Symposium Series, ed. by J. Laragh, Raven Press, New York, 1987, pp. 335-338.

12. **R.L. Webb**, J.W. Osborn, Jr. and A.W. Cowley, Jr. Cardiovascular actions of vasopressin: baroreflex modulation in the conscious rat. Am. J. Physiol. 251: H1244-H1251, 1986.

13. **R.L. Webb** and M.J. Brody. Functional identification of the central projections of afferent renal nerves. Clin. Exp. Hyperten. (Theory and Practice), A9 (Suppl. 1): 47-57, 1987.

14. E.F. Smith, III, J.W. Egan, F.R. Goodman, M.B. Zimmerman, **R.L. Webb** and L.G.T. Ribeiro. Effects of two non-sulfhydryl angiotensin converting enzyme inhibitors, CGS 14831 and CGS 16617, on myocardial damage and left ventricular hypertrophy following coronary artery occlusion in the rat. Pharmacology, 37: 254-263, 1988.

15. L.P. Wennogle, R.D. Ghai, C. McMartin, **R.L. Webb**, M. Erion, J. Gilligan, H.H. Oei and M.B. Zimmerman. Multiple mechanisms mediate disappearance of ANF from the vascular compartment in the rat. In: *Biological and Molecular Aspects of Atrial Factors*, ed. by P. Needleman. Alan R. Liss, Inc., New York, 1988, pp. 13-27.

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55. B. Pilz, E. Shagsaduren, M. Wellner, A. Fiebeler, R. Dechend, P. Gratzer, S. Meiners, D. L. Feldman, **R. L. Webb**, F.C. Luft, and D.N. Muller. Aliskiren, a human renin inhibitor, reverses angiotensin II-induced renal and cardiac damage in dTGR in a regression study design. Submitted to the American Society of Nephrology, May, 2004.

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Figure 1

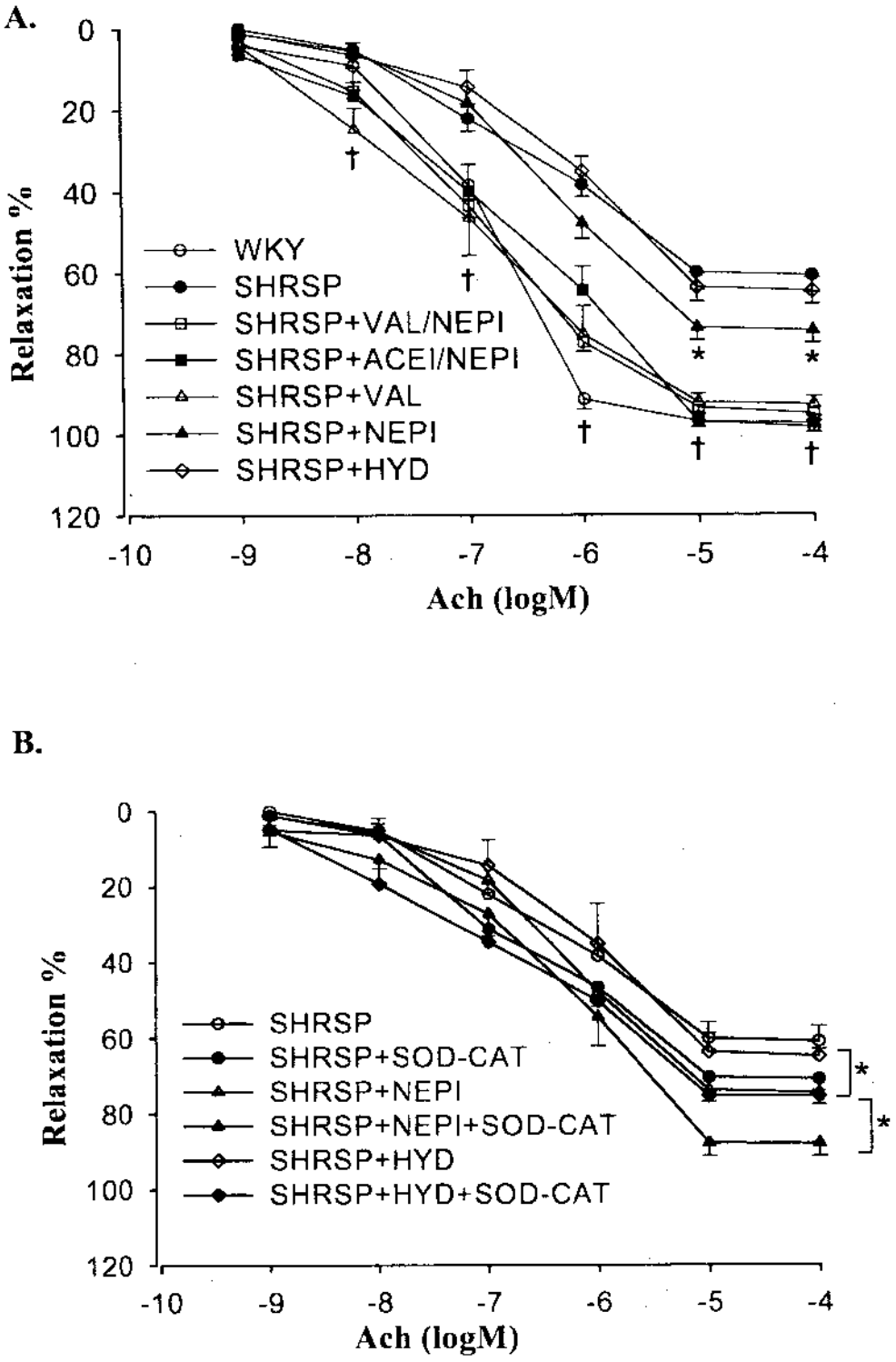

A.
Relaxation %
0
20
40
60
80
100
120
-10
-9
-8
-7
-6
-5
-4
Ach (logM)
WKY
SHRSP
SHRSP+VAL/NEPI
SHRSP+ACEI/NEPI
SHRSP+VAL
SHRSP+NEPI
SHRSP+HYD
†
*
B.
Relaxation %
SHRSP
SHRSP+SOD-CAT
SHRSP+NEPI
SHRSP+NEPI+SOD-CAT
SHRSP+HYD
SHRSP+HYD+SOD-CAT
*
*
Ach (logM)

Figure 2

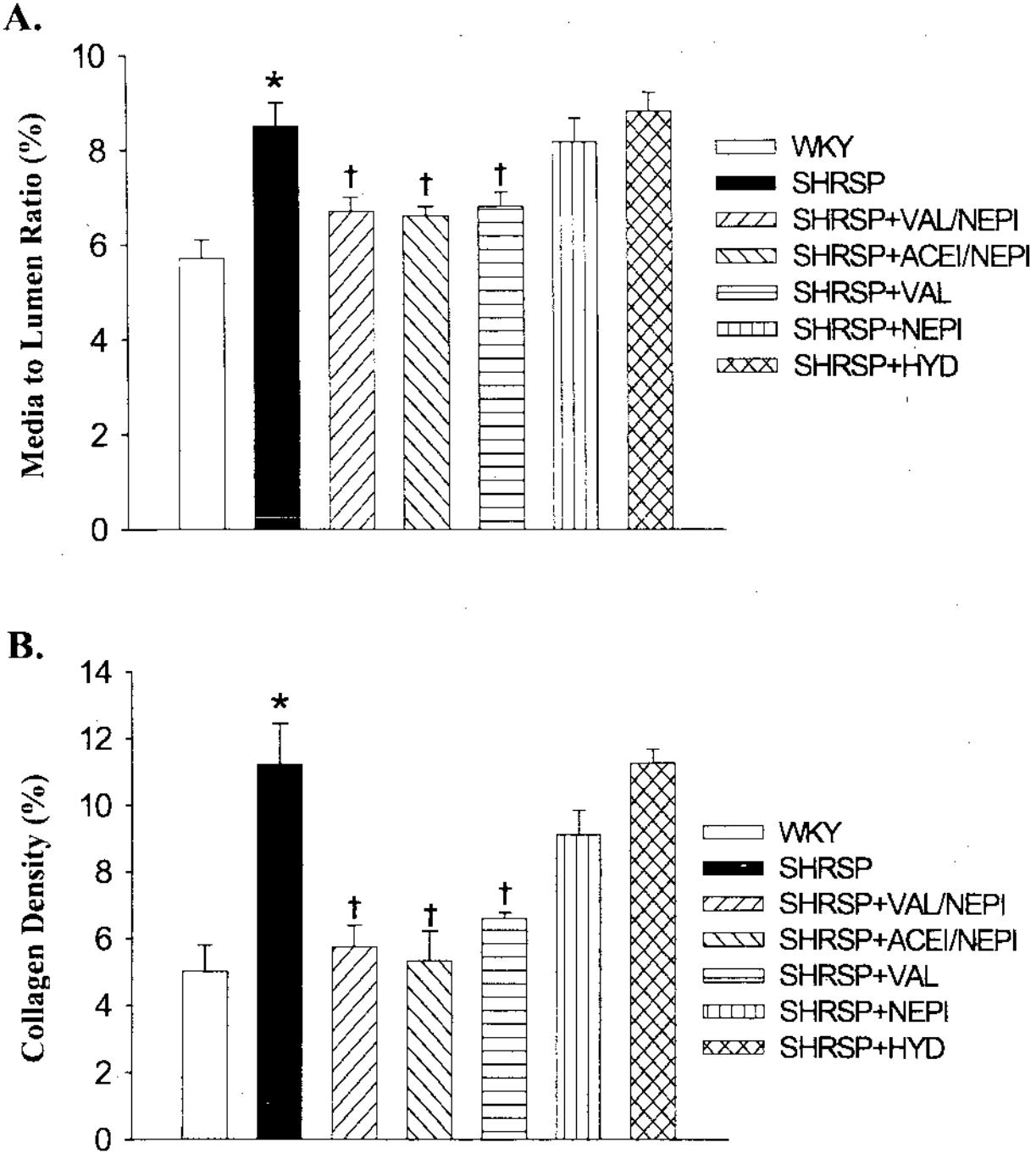

A.
Media to Lumen Ratio (%)
10
8
6
4
2
0
*
†
†
†
WKY
SHRSP
SHRSP+VAL/NEPI
SHRSP+ACEI/NEPI
SHRSP+VAL
SHRSP+NEPI
SHRSP+HYD
B.
Collagen Density (%)
14
12
10
8
6
4
2
0
*
†
†
†
WKY
SHRSP
SHRSP+VAL/NEPI
SHRSP+ACEI/NEPI
SHRSP+VAL
SHRSP+NEPI
SHRSP+HYD

Figure 3

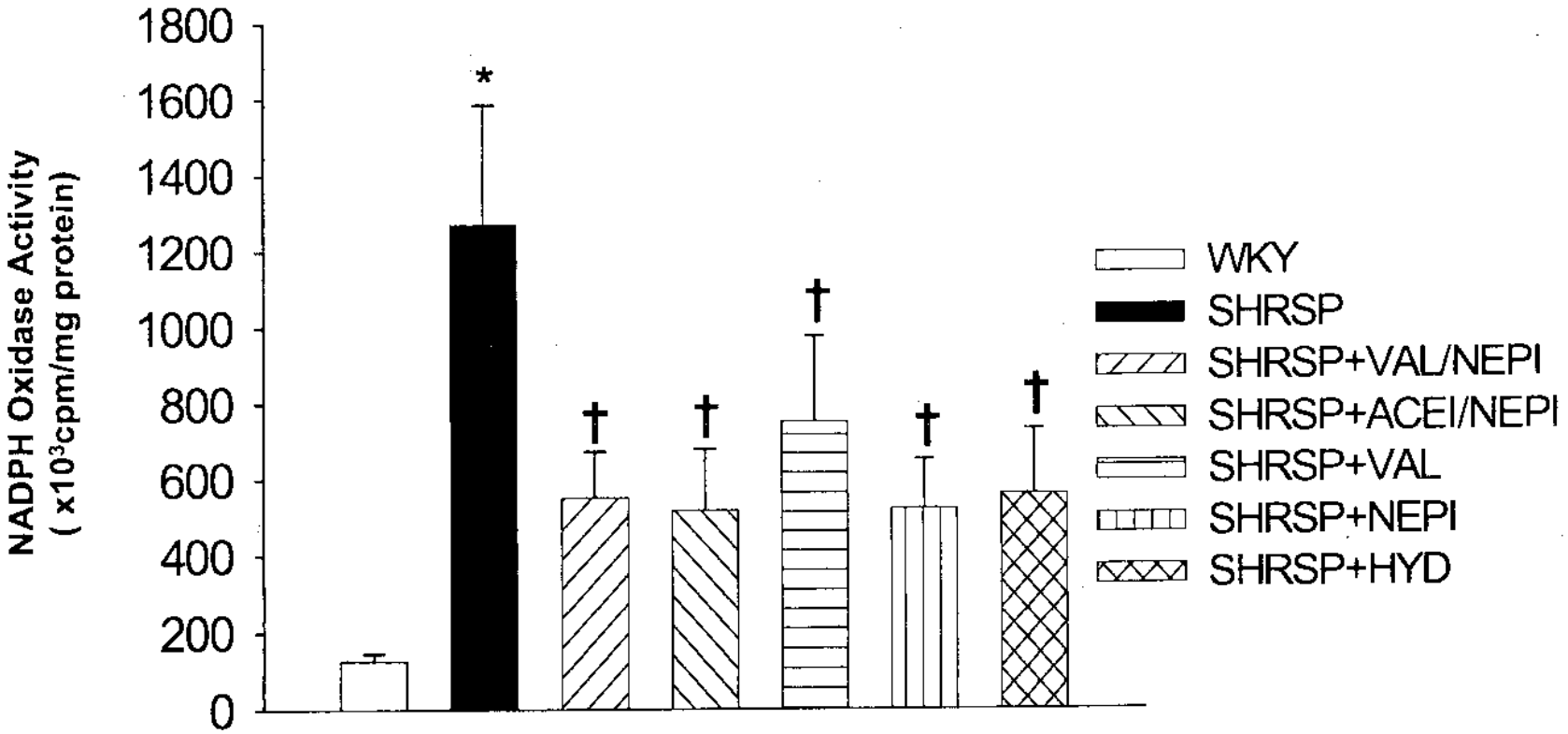
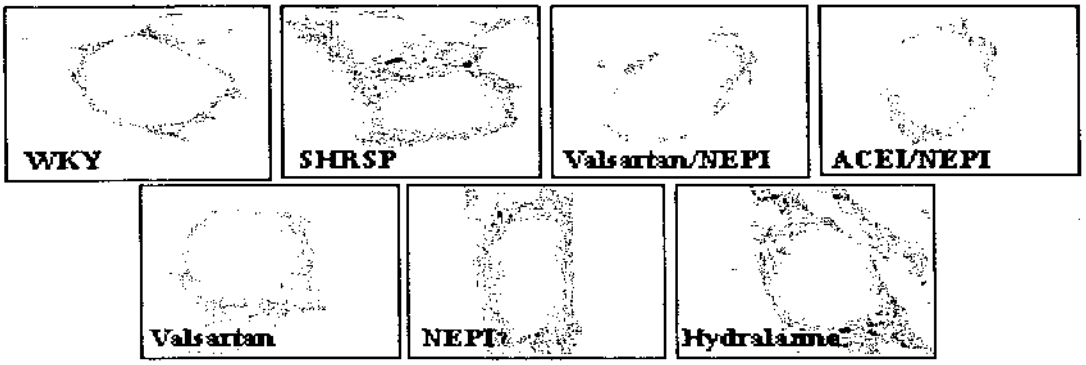
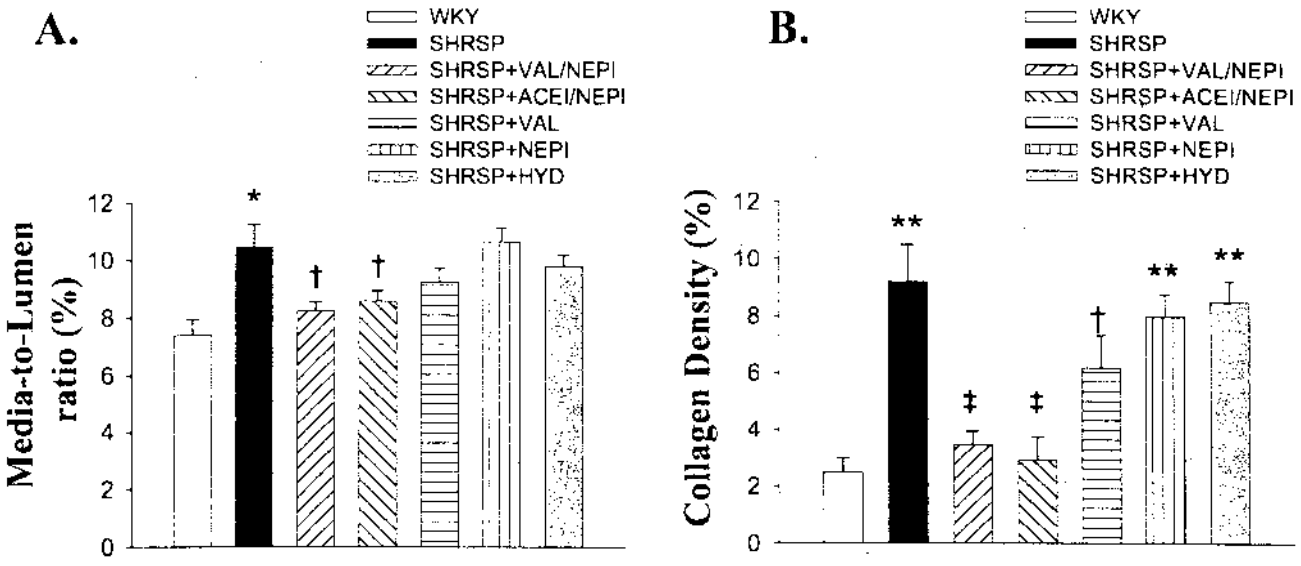


Figure 4


WKY
SHRSP
Valsartan/NEPI
ACEI/NEPI
Valsartan
NEPI
Hydralazine


A.
WKY
SHRSP
SHRSP+VAL/NEPI
SHRSP+ACEI/NEPI
SHRSP+VAL
SHRSP+NEPI
SHRSP+HYD
Media-to-Lumen ratio (%)
0
2
4
6
8
10
12
B.
Collagen Density (%)

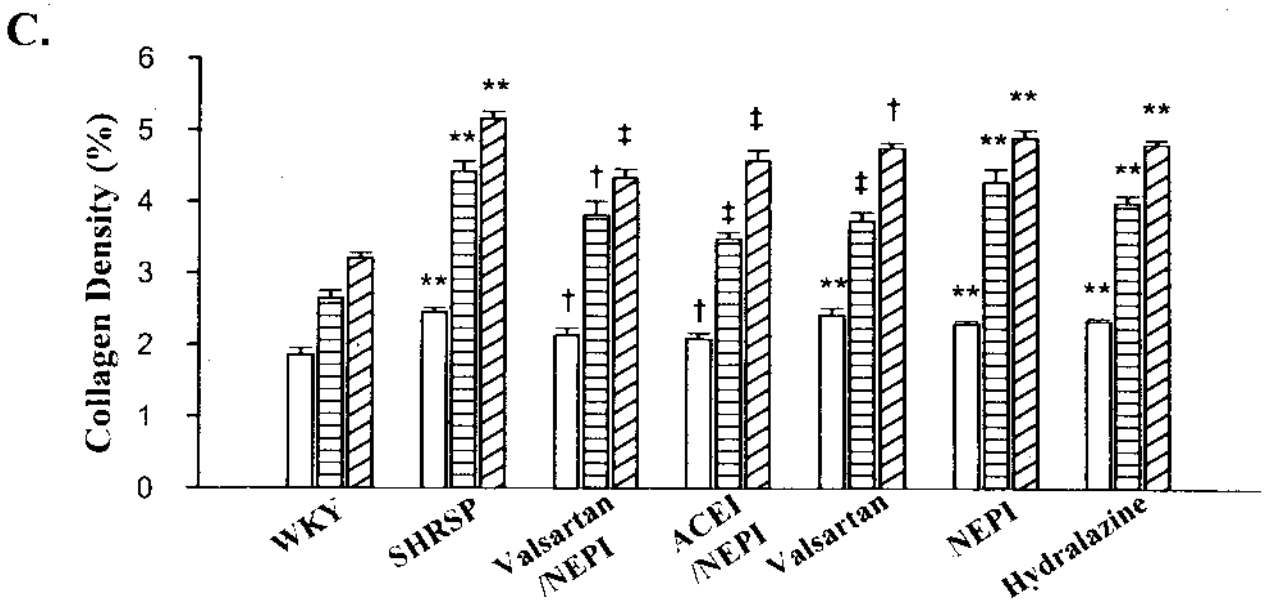

C.
Collagen Density (%)
0
1
2
3
4
5
6
WKY
SHRSP
Valsartan /NEPI
ACEI /NEPI
Valsartan
NEPI
Hydralazine

Figure 5

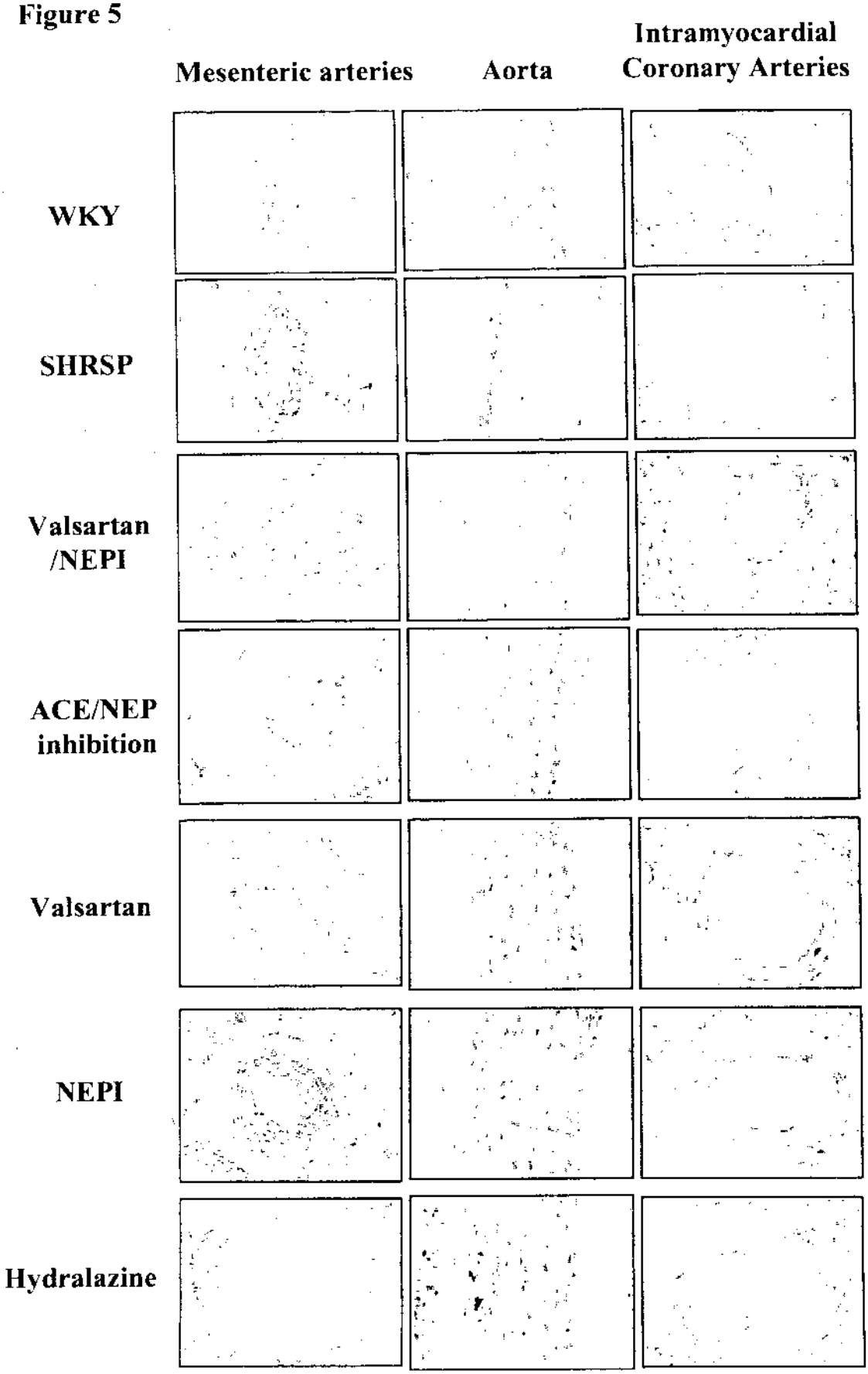
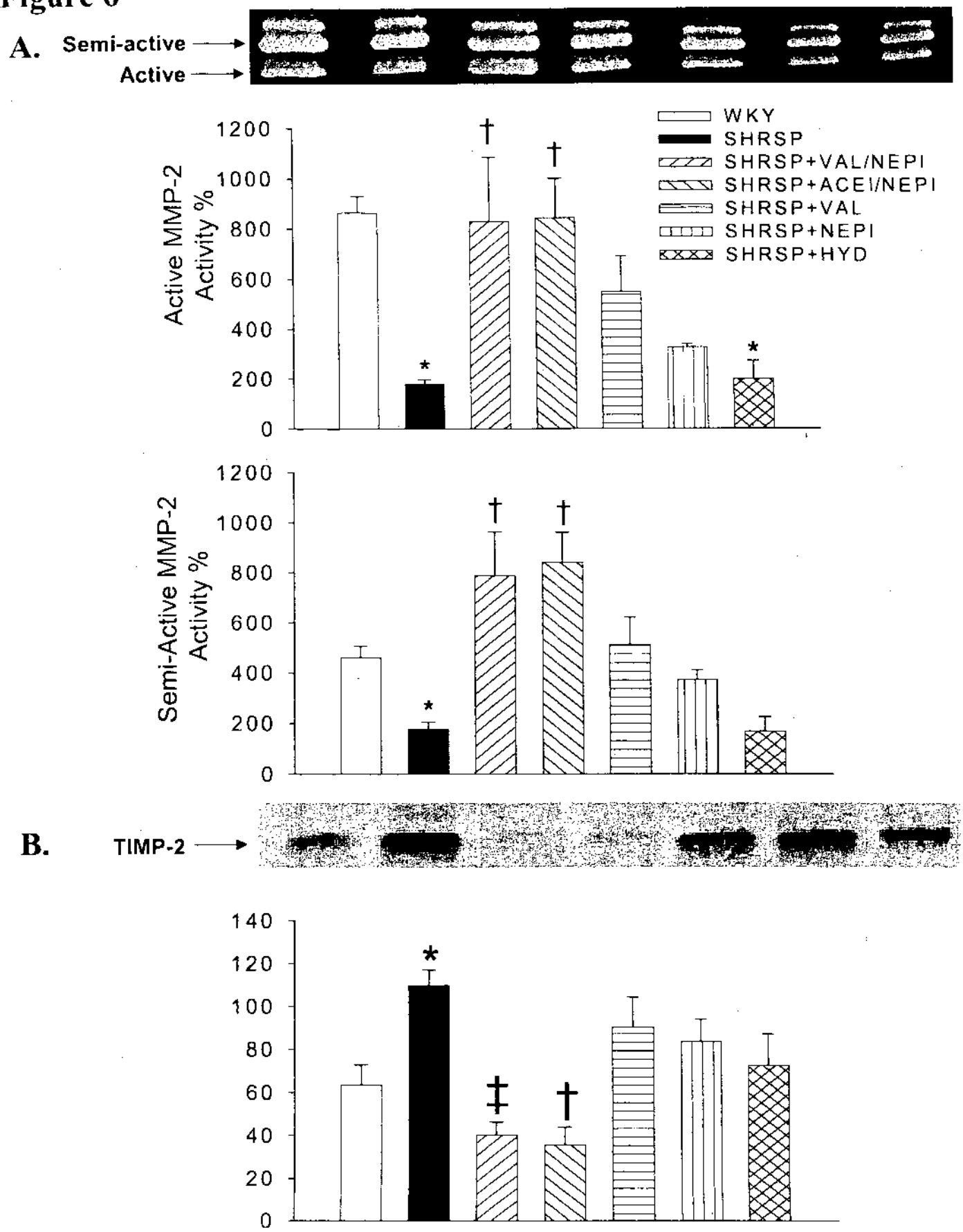

Mesenteric arteries
Aorta
Intramyocardial Coronary Arteries
WKY
SHRSP
Valsartan /NEPI
ACE/NEP inhibition
Valsartan
NEPI
Hydralazine

Figure 6


A.
Semi-active
Active
WKY
SHRSP
SHRSP+VAL/NEPI
SHRSP+ACEI/NEPI
SHRSP+VAL
SHRSP+NEPI
SHRSP+HYD
Active MMP-2 Activity %
Semi-Active MMP-2 Activity %
0
200
400
600
800
1000
1200
B.
TIMP-2
0
20
40
60
80
100
120
140

CASE 4-32219A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Ksander et al.

APPLICATION NO: 10/341,868

FILED: January 14, 2003

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617

Examiner: Kim, Jennifer M.

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Randy Lee Webb, being duly warned, hereby declare as follows:

1. I am the same Randy Lee Webb who submitted the Declaration under 37 C.F.R. §1.132 dated May 11, 2006 in the application identified in the caption above (which is referred to in this document as "the Application").

2. The experiments summarized in my previous Declaration involved administering valsartan and 4-[*N*-(3-carboxy-1-oxo-propyl)amino]-4-(*p*-phenylphenylmethyl)-3-methylbutanoic acid ethyl ester (AHU377) in combination and as monotherapy in the Dahl salt-sensitive rat, spontaneously hypertensive rat (SHR) and stroke prone male spontaneously hypertensive rat (SHRsp) models of hypertension.

3. Based on the results achieved in the animal models of hypertension, I would fully expect a combination of valsartan and AHU377 to have synergistic, unexpected and surprising antihypertensive effect and added therapeutic benefits in the treatment of hypertension over monotherapy when administered in humans in the daily unit dose ranges of from about 20 mg to about 320 mg of valsartan and from about 20 mg to about 800 mg of AHU377 (*see, e.g.,* page 16, lines 9-10 and 18 in the instant application).

4. I hereby declare that all statements made herein of my own knowledge are true

and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Nov. 16 2004

Randy Lee Webb

Electronic Acknowledgement Receipt

EFS ID:	2858404
Application Number:	10341868
International Application Number:	
Confirmation Number:	8865
Title of Invention:	Methods of treatment and pharmaceutical composition
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Gregory David Ferraro./Cindy Klepacky
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	4-32219A
Receipt Date:	14-FEB-2008
Filing Date:	14-JAN-2003
Time Stamp:	10:53:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219.pdf	2370807 fcbcaaa762b20c9b9cde54ed0f307d459772506e	yes	49

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment - After Non-Final Rejection	1	5
	Claims	6	8
	Applicant Arguments/Remarks Made in an Amendment	9	9
	Miscellaneous Incoming Letter	10	49
Warnings:			
Information:			
	Total Files Size (in bytes):	2370807	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/341,868	01/14/2003	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	02/14/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 5	Minus	** 20	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/NICOLE LOVE HENSLEY/

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NOTICE OF ALLOWANCE AND FEE(S) DUE

1095 7590 04/16/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/16/2008

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

TITLE OF INVENTION: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	07/16/2008

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 04/16/2008

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

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nonprovisional	NO	$1440	$300	$0	$1740	07/16/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
KIM, JENNIFER M	1617	514-533000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1_____

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2_____ 3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

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❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

1095 7590 04/16/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/16/2008

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 459 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 459 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	10/341,868	KSANDER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *2/14/2008 & 4/9/2008*.

2. ☒ The allowed claim(s) is/are *1, 3, and 4 (renumbered as 1, 2 and 3)*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Gregory D. Ferraro on April 9th 2007.

The application has been amended as follows:

IN THE CLAIMS:

Claims 5 and 7 have been canceled without prejudice.

Remarks

The above amendment places this case in condition for allowance.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

The claims are allowable over the cited prior art because the prior art does not teach, disclose nor make obvious the claimed pharmaceutical composition comprising valsartan and the specific NEP inhibitor set forth in claim 1 wherein the sum of the therapeutic effects of combination achieve a greater anti-hypertensive effect than the sum of the therapeutic effects achievable with the amount of each of the active agents administered alone.

Applicants presented the experimental data showing that the combination of valsartan and the specific NEP inhibitor (AH377) has a synergistic, unexpected and surprising antihypertensive effect which is not taught or obvious from the cited prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
April 14, 2008

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
10341868	KSANDER ET AL.
Examiner	**Art Unit**
Jennifer Kim	1617

ORIGINAL		INTERNATIONAL CLASSIFICATION												
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED							
514	533	A	6	1	K	31 / 235 (2006.01.01)								
CROSS REFERENCE(S)		A	6	1	K	31 / 41 (2006.01.01)								
		A	6	1	K	31 / 195 (2006.01.01)								

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	381	561	563		

NONE (Assistant Examiner) (Date)		**Total Claims Allowed:** 3
/Jennifer Kim/ (Primary Examiner)	4/14/2008 (Date)	O.G. Print Claim(s) 1 / O.G. Print Figure 0

U.S. Patent and Trademark Office

Part of Paper No. 20080410

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10341868	KSANDER ET AL.
	Examiner	**Art Unit**
	Jennifer Kim	1617

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**
514	533, 381, 561, 563	4/14/2008	jmk

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
Updated	4/14/2008	jmk

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**
514	533, 381, 561, 563	4/14/2008	jmk

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10341868	KSANDER ET AL.
	Examiner	Art Unit
	Kim, Jennifer	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/02/2007	05/24/2007	01/30/2008	04/14/2008					
1	1	✓	✓	✓	=					
	2	-	-	-	-					
2	3	✓	✓	✓	=					
3	4	✓	✓	✓	=					
	5	N	N	N	-					
	6	-	-	-	-					
	7	N	N	N	-					
	8	-	-	-	-					
	9	-	-	-	-					
	10	-	-	-	-					
	11	-	-	-	-					

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 8865

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/341,868	01/14/2003	514	1617	4-32219A

APPLICANTS

Gary Michael Ksander, Amherst, NH;
Randy Lee Webb, Flemington, NJ;

**** CONTINUING DATA ***************************

This appln claims benefit of 60/386,792 06/07/2002
and claims benefit of 60/349,660 01/17/2002

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

03/03/2003

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JENNIFER MYONG M KIM/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NH	0	11	5

ADDRESS

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080
UNITED STATES

TITLE

Methods of treatment and pharmaceutical composition

FILING FEE RECEIVED		
1048	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 04/16/2008

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ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	01/14/2003	Gary Michael Ksander	4-32219A	8865

TITLE OF INVENTION: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	07/16/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
KIM, JENNIFER M	1617	514-533000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Gregory D. Ferraro
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Novartis AG
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Basel, Switzerland

Assignment recorded:
June 4, 2008
Reel/Frame:
021038/0682

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 19-0134 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Gregory Ferraro Date 6/10/08

Typed or printed name Gregory D. Ferraro Registration No. 36,134

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	10341868
Filing Date:	14-Jan-2003
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Gregory David Ferraro./Maureen McGee
Attorney Docket Number:	4-32219A

Filed as Large Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1440	1440
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1740**

Electronic Acknowledgement Receipt

EFS ID:	3432222
Application Number:	10341868
International Application Number:	
Confirmation Number:	8865
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Gregory David Ferraro./Maureen McGee
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	4-32219A
Receipt Date:	10-JUN-2008
Filing Date:	14-JAN-2003
Time Stamp:	15:45:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1740
RAM confirmation Number	1093
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	32219fee.pdf	47356 656aa57226912db7d1466de37b55d1b155c5a10b	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8316 f50194e8a9532cbdbbb7f86f2ded83677fd35b18	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	55672		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CASE 4-32219A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
GARY MICHAEL KSANDER
APPLICATION NO: 10/341,868
FILED: JANUARY 14, 2003
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITIOIN

Art Unit: 1617
Examiner: Kim, Jennifer M.

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

COMMUNICATION REGARDING "INITIAL" PATENT TERM ADJUSTMENT

Sir:

It is believed that the "initial" Patent Term Adjustment indicated by the PTO is incorrect, i.e., extra days of patent term have been credited to the Applicants. In this connection, it is believed that the PTO overlooked the fact that the RCE filed on November 20, 2006 was submitted later than the three months allotted under 37 C.F.R. 1.704(b), thereby resulting in a debit of 26 days. Accordingly, the correct "initial" Patent Term Adjustment should be 433 days (i.e., 555-122 days).

No fee is believed to be necessitated by this Communication. However, if a fee is required, the Commissioner is hereby authorized to charge said fee to Deposit Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Greg Ferraro

Gregory D. Ferraro
Attorney for Applicant
Reg. No. 36,134

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831
Date: June 10, 2008

Electronic Acknowledgement Receipt

EFS ID:	3432402
Application Number:	10341868
International Application Number:	
Confirmation Number:	8865
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Gregory David Ferraro./Maureen McGee
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	4-32219A
Receipt Date:	10-JUN-2008
Filing Date:	14-JAN-2003
Time Stamp:	15:56:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	32219comm.pdf	7352 a2bc1c644560288c3eba5226ff1a93326b053767	no	1

Warnings:	
Information:	

Total Files Size (in bytes):	7352

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER NJ 07936-1080

COPY MAILED

NOV 21 2008

OFFICE OF PETITIONS

In re Application of	:	
KSANDER et al.	:	LETTER REGARDING
Application No. 10/341,868	:	PATENT TERM ADJUSTMENT
Filed: January 14, 2003	:	
Attorney Docket No. 4-32219A	:	

This letter is in response to the "COMMUNICATION REGARDING INITIAL PATENT TERM ADJUSTMENT," filed June 10, 2008. Pursuant to applicants' duty of good faith and candor to the Office, applicants request that the determination of patent term adjustment under 35 U.S.C. 154(b) be reviewed for accuracy.

The request for review of the determination of patent term adjustment is **GRANTED** to the extent indicated herein.

The Office has updated the PAIR screen to reflect that the correct Patent Term Adjustment (PTA) determination at the time of the mailing of the notice of allowance is **363 days.** A copy of the updated PAIR screen, showing the correct determination, is enclosed.

On April 16, 2008, the Office mailed the Determination of Patent Term Adjustment under 35 U.S.C. 154(b) in the above-identified application. The Notice stated that the patent term adjustment to date is 459 days. On June 10, 2008, applicants submitted the instant comment.

Applicants state that the initial patent term adjustment should be corrected to 433 days (555 days of Office delay - 122 days of applicant delay). Applicants assert that they should have been assessed a reduction of 26 days for filing a Request for

Continued Examination on November 20, 2006, in excess of the three-month period from the mailing date of the final Office action pursuant to 37 CFR 1.704(b).

The application history has been reviewed and it has been determined that the number days of applicant delay is incorrect.

A final Office action was mailed on July 25, 2006. Applicants filed their response in the form of a RCE and submission on November 20, 2006, in excess of the three-month period from the mailing date of the final Office action. See 37 CFR 1.704(b). Thus, applicants failed to engage in reasonable efforts to conclude prosecution of this application. The period of adjustment should have been reduced by 26 days, the number of days in the period beginning on the day after the date that is three months after the date of mailing of the final Office action, October 26, 2006, ending on the date the reply was filed, November 20, 2006. See 37 CFR 1.704(b). Accordingly, a period of reduction of 26 days will be entered.

Additionally, applicants should have been assessed a delay under 37 CFR 1.704(c)(8) for submission of a supplemental reply or paper after a reply had been filed without the express request of the examiner.

Pursuant to 37 CFR 1.704(c)(8):

> Submission of a supplemental reply or other paper, other than a supplemental reply or other paper expressly requested by the examiner, after a reply has been filed, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date the initial reply was filed and ending on the date that the supplemental reply or other such paper was filed[.]

On January 15, 2008, applicants submitted a Supplement Amendment and an Information Disclosure Statement (IDS) after filing a reply on November 6, 2007. The record does not support a conclusion that the examiner expressly requested the filing of the Supplemental Amendment or IDS. Further, a review of the IDS, filed January 15, 2008, reveals that applicants did not

include a statement under 37 CFR 1.704(d).[1] Accordingly, the period of adjustment should be reduced by 70 days, the number of days beginning on the day after the date the reply was filed, November 7, 2007, and ending on the date that the Supplemental Amendment and IDS were filed, January 15, 2008.

It is noted that the filing of the Supplemental Amendment and the filing of the IDS on January 15, 2008, are two separate acts, each of which constitutes a failure to engage in reasonable efforts to conclude prosecution of the application. Since the periods of reduction for the filing of the Supplemental Amendment and the filing of the IDS completely overlap, only one period of reduction of 70 days is being entered.

In view thereof, the correct patent term adjustment at the time of the mailing of the notice of allowance is **363 days** (555 days of Office delay - 192 days of applicant delay).

As this letter was submitted as an advisement to the Office of an error in applicants' favor, the Office will not assess the $200.00 fee as set forth in 37 CFR 1.18(e). The Office thanks applicants for applicants' good faith and candor in bringing this to the attention of the Office.

Applicants are reminded that any delays by the Office pursuant to 37 CFR 1.702(a)(4) and 1.702(b) and any applicant delays under 37 CFR 1.704(c)(10) will be calculated at the time of the issuance of the patent and applicants will be notified in the Issue Notification letter that is mailed to applicants approximately three weeks prior to issuance.

---

[1] Pursuant to 37 CFR 1.704(d):

> A paper containing only an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section if it is accompanied by a statement that each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement. This thirty-day period is not extendable.

The Office of Data Management has been advised of this decision. This matter is being referred to the Office of Data Management for issuance of the patent.
Telephone inquiries regarding this matter should be directed to Christina Tartera Donnell, Senior Petitions Attorney, at (571) 272-3211.

Nancy Johnson
Senior Petitions Attorney
Office of Petitions

Enclosure: Copy of updated PAIR screen

PTA Calculations for Application: 10/341868			
Application Filing Date:	01/14/2003	PTO Delay (PTO):	555
Issue Date of Patent:		Three Years:	0
Pre-Issue Petitions:	0	Applicant Delay (APPL):	96
Post-Issue Petitions:	0	Total PTA (days):	363
PTO Delay Adjustment:	-96		

File Contents History

Number	Date	Contents Description	PTO	APPL	START
100	11/19/2008	ADJUSTMENT OF PTA CALCULATION BY PTO		26	
99	11/19/2008	ADJUSTMENT OF PTA CALCULATION BY PTO		70	
88	04/16/2008	MAIL NOTICE OF ALLOWANCE			
87	04/14/2008	ISSUE REVISION COMPLETED			
86	04/14/2008	DOCUMENT VERIFICATION			
85	04/14/2008	NOTICE OF ALLOWANCE DATA VERIFICATION COMPLETED			
84	04/14/2008	CASE DOCKETED TO EXAMINER IN GAU			
83	04/14/2008	EXAMINER'S AMENDMENT COMMUNICATION			
82	04/14/2008	NOTICE OF ALLOWABILITY			
74	02/14/2008	AFFIDAVIT(S) (RULE 131 OR 132) OR EXHIBIT(S) RECEIVED			
73	03/12/2008	DATE FORWARDED TO EXAMINER			
72	02/14/2008	RESPONSE AFTER NON-FINAL ACTION			
70	01/15/2008	AMENDMENT CROSSED IN MAIL			
69	02/01/2008	MAIL NON-FINAL REJECTION			
68	01/31/2008	NON-FINAL REJECTION			
67	01/15/2008	INFORMATION DISCLOSURE STATEMENT CONSIDERED			
65	01/15/2008	INFORMATION DISCLOSURE STATEMENT (IDS) FILED			
64	11/29/2007	DATE FORWARDED TO EXAMINER			
63	11/06/2007	AMENDMENT SUBMITTED/ENTERED WITH FILING OF CPA/RCE			
62	11/29/2007	DATE FORWARDED TO EXAMINER			
61	11/06/2007	REQUEST FOR CONTINUED EXAMINATION (RCE)		67	50

60	11/29/2007	DISPOSAL FOR A RCE/CPA/129 (EXPRESS ABANDONMENT IF CPA)			
59	11/06/2007	WORKFLOW - REQUEST FOR RCE - BEGIN			
58	11/01/2007	MAIL ADVISORY ACTION (PTOL - 303)			
57	10/29/2007	ADVISORY ACTION (PTOL-303)			
56	10/24/2007	DATE FORWARDED TO EXAMINER			
55	10/23/2007	AMENDMENT AFTER FINAL REJECTION			
54	10/23/2007	REQUEST FOR EXTENSION OF TIME - GRANTED			
50	05/31/2007	MAIL FINAL REJECTION (PTOL - 326)			
49	05/29/2007	FINAL REJECTION			
48	03/15/2007	DATE FORWARDED TO EXAMINER			
47	03/09/2007	RESPONSE AFTER NON-FINAL ACTION			
46	02/05/2007	MAIL NON-FINAL REJECTION			
45	02/02/2007	NON-FINAL REJECTION			
44	12/01/2006	DATE FORWARDED TO EXAMINER			
43	11/20/2006	REQUEST FOR CONTINUED EXAMINATION (RCE)			
42	12/01/2006	DISPOSAL FOR A RCE/CPA/129 (EXPRESS ABANDONMENT IF CPA)			
41	11/20/2006	REQUEST FOR EXTENSION OF TIME - GRANTED			
40	11/20/2006	WORKFLOW - REQUEST FOR RCE - BEGIN			
39	10/03/2006	EXAMINER INTERVIEW SUMMARY RECORD (PTOL - 413)			
38	07/25/2006	MAIL FINAL REJECTION (PTOL - 326)			
37	07/21/2006	FINAL REJECTION			
36	04/04/2006	INFORMATION DISCLOSURE STATEMENT CONSIDERED			
35	05/11/2006	NEW OR ADDITIONAL DRAWING FILED			
34	05/11/2006	AFFIDAVIT(S) (RULE 131 OR 132) OR EXHIBIT(S) RECEIVED			
33	05/22/2006	DATE FORWARDED TO EXAMINER			
32	05/11/2006	RESPONSE AFTER NON-FINAL ACTION		29	28
31	05/11/2006	REQUEST FOR EXTENSION OF TIME - GRANTED			
30	04/04/2006	REFERENCE CAPTURE ON IDS			
29.7	04/04/2006	INFORMATION DISCLOSURE STATEMENT (IDS) FILED			
29	04/04/2006	INFORMATION DISCLOSURE STATEMENT (IDS)			

		FILED			
28	01/12/2006	MAIL NON-FINAL REJECTION			
27	01/09/2006	NON-FINAL REJECTION			
26	06/01/2004	INFORMATION DISCLOSURE STATEMENT CONSIDERED			
25	11/05/2003	INFORMATION DISCLOSURE STATEMENT CONSIDERED			
24	11/02/2005	DATE FORWARDED TO EXAMINER			
23	09/30/2005	RESPONSE TO ELECTION / RESTRICTION FILED			
22	09/20/2005	MAIL RESTRICTION REQUIREMENT	555		-1
21	09/19/2005	REQUIREMENT FOR RESTRICTION / ELECTION			
20	08/29/2005	MAIL MISCELLANEOUS COMMUNICATION TO APPLICANT			
19	08/29/2005	MISCELLANEOUS COMMUNICATION TO APPLICANT - NO ACTION COUNT			
18	08/15/2005	MISCELLANEOUS INCOMING LETTER			
17	01/19/2005	CASE DOCKETED TO EXAMINER IN GAU			
16	11/30/2004	PRELIMINARY AMENDMENT			
15	11/30/2004	WORKFLOW INCOMING AMENDMENT IFW			
14	10/04/2004	MISCELLANEOUS INCOMING LETTER			
13.7	06/01/2004	INFORMATION DISCLOSURE STATEMENT (IDS) FILED			
13	06/01/2004	INFORMATION DISCLOSURE STATEMENT (IDS) FILED			
12	03/09/2004	IFW TSS PROCESSING BY TECH CENTER COMPLETE			
11	11/05/2003	REFERENCE CAPTURE ON IDS			
10.7	11/05/2003	INFORMATION DISCLOSURE STATEMENT (IDS) FILED			
10	11/05/2003	INFORMATION DISCLOSURE STATEMENT (IDS) FILED			
9	03/09/2004	CASE DOCKETED TO EXAMINER IN GAU			
7	03/26/2003	APPLICATION DISPATCHED FROM OIPE			
6	03/26/2003	APPLICATION IS NOW COMPLETE			
5	03/10/2003	ADDITIONAL APPLICATION FILING FEES			
4	03/10/2003	A STATEMENT BY ONE OR MORE INVENTORS SATISFYING THE REQUIREMENT UNDER 35 USC 115, OATH OF THE APPLIC			
3	03/03/2003	NOTICE MAILED--APPLICATION INCOMPLETE--FILING DATE ASSIGNED			

2	01/22/2003	IFW SCAN & PACR AUTO SECURITY REVIEW			
1	01/14/2003	INITIAL EXAM TEAM NN			

Search Another: Application# Search

EXPLANATION OF PTA CALCULATION

EXPLANATION OF PTE CALCULATION

To go back, right click here and select Back. To go forward, right click here and select Forward. To refresh, right click here and select Refresh.

Back to OASIS | Home page

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/341,868	12/23/2008	7468390	4-32219A	8865

1095 7590 12/03/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 317 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Gary Michael Ksander, Amherst, NH;
Randy Lee Webb, Flemington, NJ;

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
EV724612505US Express Mail Label Number	1 September 2015 Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 7,468,390
ISSUED: December 23, 2008
INVENTORS: Gary Michael Ksander and Randy Lee Webb
FOR: Methods of Treatment and Pharmaceutical Composition

MS Hatch-Waxman PTE
Director for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C. § 156

Sir:

Pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*, Novartis Pharmaceuticals Corporation ("Applicant"), a Corporation organized under the laws of United States, hereby requests an extension, due to regulatory review, of the patent term of U.S. Patent No. 7,468,390, which was granted on December 23, 2008.

Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 7,468,390 by virtue of an assignment from the inventors, Gary Michael Ksander and Randy Lee, Webb to Novartis AG and subsequent assignment from Novartis AG to Novartis Pharmaceuticals Corporation. The assignment from the inventors to Novartis AG is recorded in the U.S. Patent and Trademark Office (USPTO) at Reel 21038 Frame 682 on June 4, 2008 and the assignment from Novartis AG to Novartis Pharmaceuticals Corporation is recorded in the U.S. Patent and Trademark Office (USPTO) at Reel 26002 Frame 790 on March 23, 2011. Copies of the assignments and recordation information are attached hereto as **Appendix A.**

In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are numbered analogously to 37 C.F.R . §1.740.

1. Identification of the Approved Product

The approved product is ENTRESTO™ (sacubitril and valsartan), which is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, in the form of a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. ENTRESTO™ is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

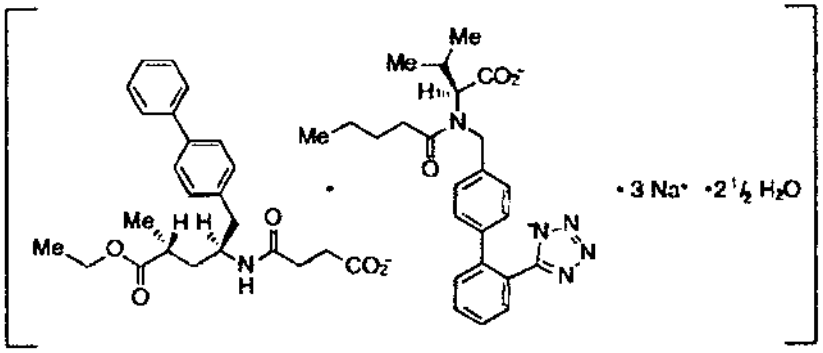
Chemical Name

The complex is chemically described as Octadecasodiumhexakis(4-{[(1S,3R)-1-([1,1′-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4oxobutanoate)hexakis(N-pentanoyl-N-{[2′-(1H-tetrazol-1-id-5-yl)[1,1′-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15).

Molecular Formula

Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3$ 2.5 H_2O. Its molecular mass is 957.99.

Structural Formula



Physical Form

ENTRESTO™ is provided as film-coated tablets for oral administration, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan.

2. Identification of the Federal Statute under which Regulatory Review Occurred

The approved product was subject to regulatory review under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355).

3. The Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing under section 505 of the Federal Food, Drug and Cosmetic Act on July 7, 2015. A copy of the Food and Drug Administration (FDA) approval letter is attached hereto as **Appendix B.**

4. Active Ingredient Statement

The active ingredients in ENTRESTO™ are sacubitril and valsartan. Sacubitril, either alone or in combination with another active ingredient, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act prior to the approval of NDA No. 207620 by the United States Food and Drug Administration on July 7, 2015.

Valsartan was approved for commercial marketing both alone and in combination with other active ingredients. Valsartan capsules were approved under the trade name DIOVAN® on December 23, 1996, and valsartan tablets were approved on July 8, 2001, under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for treatment of hypertension. On August 14, 2002, both valsartan capsules and tablets were approved for treatment of heart failure (NYHA class II-IV) in patients who are intolerant to an ACE (angiotensin converting enzyme) inhibitor. On August 3, 2005, the use of valsartan 40, 80, 160, and 320 mg tablets (DIOVAN®) was approved in the treatment of patients with post-myocardial infarction: In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, valsartan is indicated to reduce cardiovascular mortality.

Valsartan and hydrochlorothiazide was approved under the trade name DIOVAN HCT® on March 6, 1998 under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for treatment of hypertension.

Valsartan and amlodipine besylate tablets were approved under the trade name EXFORGE® on June 20, 2007, under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for the treatment of hypertension.

Valsartan, amlodipine besylate and hydrochlorothiazide tablets were approved under the trade name EXFORGE HCT® on April 30, 2009, under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for the treatment of hypertension.

5. Statement of Timely Filing

The last day on which this application could be submitted is September 4, 2015, which is 60 days beginning on the date of approval of NDA No. 207620 (July 7, 2015). This application is timely filed, because it is being submitted on or prior to September 4, 2015.

6. Identification of Patent for which Extension is Sought

This application seeks to extend the term of U.S. Patent No. 7,468,390, which issued December 23, 2008 to inventors Gary Michael Ksander and Randy Lee Webb. The term of U.S. Patent No. 7,468,390, as calculated under 35 U.S.C. § 154, would otherwise expire on November 27, 2023.[1]

7. Patent Copy

A complete copy of U.S. Patent No. 7,468,390, identified in **section 6** above, is attached as **Appendix C.**

8. Copy of Any Disclaimer, Certificate of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate Issued in the Patent

No Reexamination certificate, no certificate of correction, no disclaimer, and no Reissue has been issued, filed or requested with respect to U.S. Patent No. 7,468,390. A copy of a receipt of the only maintenance fee payment required to date is provided herewith in **Appendix D**.

[1] Applicant was awarded 317 days of patent term adjustment (PTA), resulting in an expiration date of November 27, 2023. This expiration date is used in all calculations in the instant application.

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

U.S. Patent No. 7,468,390 claims the approved product, ENTRESTO™. Claims 1 and 2 of U.S. Patent No. 7,468,390 read on the approved product (they recite compositions that include the approved product).

Claim 1 reads as follows:

> 1. A pharmaceutical composition comprising:
>
> (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and
>
> (ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof,
>
> wherein the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) the NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered in combination achieve a greater anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt administered alone and (ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone, and a pharmaceutically acceptable carrier.

Claim 1 reads on the approved product as follows:

As mentioned above, the approved product, ENTRESTO™, is a combination of sacubitril and valsartan. In claim 1, valsartan is explicitly recited in (i) and sacubitril is recited as N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in (ii).

10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(A) IND 77318 became effective on April 8, 2007 and IND 104628 became effective on October 31, 2009. IND 77318 was the first IND for the administration of sacubitril/valsartan for hypertension.

IND 104628 was for the administration of sacubitril/valsartan for heart failure and makes a cross reference to certain IND 77318 data such as pharmacology and toxicity information.

(B) A New Drug Application (NDA) for ENTRESTO™ was initially submitted to the FDA on December 17, 2014 with NDA No. 207620.

(C) NDA No. 207620 was approved on July 7, 2015.

11. Brief Description of Activities Undertaken During the Regulatory Review Period

As brief description of the significant activities undertaken during the applicable regulatory review period and the significant dates applicable to such activities is, attached hereto as chronologies for INDs 77318 and 104628 (**Appendix E**), and NDA 207620 (**Appendix F**).

12. Opinion of Eligibility for Extension and Statement of Length of Extension Claimed

Applicant is of the opinion that U.S. Patent No. 7,468,390 is eligible for extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a)

U.S. Patent No. 7,468,390 claims a product as defined in 37 C.F.R. § 1.710(b)(1).

(b) 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

The term of U.S. Patent No. 7,468,390 (expiring November 27, 2023) has not expired before the submission of this application.

(c) 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of U.S. Patent No. 7,468,390 has never been extended under 35 U.S.C. § 156.

(d) 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

The application for extension of the term of U.S. Patent No. 7,468,390 is submitted by the authorized attorney of the owner of record thereof in accordance with the requirements of 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

(e) 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

The approved product, ENTRESTO™, has been subjected to a regulatory review period under 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 37 C.F.R. § 1.720(h)

No other patent term has been extended for the same regulatory review period for the approved product, ENTRESTO™.

(g) 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(e)(1)

The permission for the commercial marketing or use of the approved product, ENTRESTO™, is the first received permission for commercial marketing or use of

ENTRESTO™ under section 505, the provision of law under which the applicable regulatory review occurred.

12.1 Calculation of length of extension claimed under 37 C.F.R. § 1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. 7,468,390 requested by Applicant is 1296 days, which length was calculated in accordance with 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began April 8, 2007 (the effective date of IND No. 77318) and ended on July 7, 2015 (the date NDA No. 207620 was issued), amounting to a total of 3014 days, which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period," began on April 8, 2007 and ended on December 17, 2014, which is 2811 days;

(ii) The period for review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Application Period," began on December 17, 2014 and ended on July 7, 2015, which is 203 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (12.1)(a) above (3014 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (December 23, 2008), i.e., 626 days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., zero days, and

(iii) One-half of the number of days remaining in the period in subparagraph (12.1)(a)(i) after subtracting the number of days in subparagraphs (12.1)(b)(i) and (12.1)(b)(ii), which is one-half of (2811 - [626 + 0]) = 1092 days;

which results in a period of 3014 - [626 + 0 + 1092 days] = 1296 days.

(c) The number of days as determined in subparagraph (12.1)(b) (1296 days), when added to the original term (November 27, 2023 (original expiry date + 317 days PTA)), would result in the date of June 15, 2027.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (July 7, 2015) would result in the date of July 7, 2029.

(e) The earlier date as determined by subparagraphs (12.1)(c) and (12.1)(d) is June 15, 2027.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 7,468,390 (November 27, 2023), results in the date November 27, 2028.

(g) The earlier date as determined in subparagraphs (12.1)(e) and (12.1)(f) is June 15, 2027.

13. Duty of Disclosure Acknowledgement Under 37 C.F.R. § 1.740(a)(13)

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought. Applicant hereby informs the Director that Patent Term Extension applications for United States Patent Numbers 8,101,659; 8,404,744; 8,796,331; and 8,877,938 are being concurrently filed for ENTRESTO™.

14. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

15. Correspondence Address Required by 37 C.F.R. § 1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080
(862) 778-5806

Certification Under 37 C.F.R. § 1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof (for a total of three copies) in accordance with 37 C.F.R. § 1.740(b).

Respectfully submitted,

David Kurlandsky
Attorney for Applicant
Reg. No. 41,505
(862) 778-5806

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080

Date: September 1, 2015

Attachments: Appendix A-F

APPENDIX A

Assignment / Recordation Information

Patent Assignment Abstract of Title

Total Assignments: 2

Application #: 10341868 **Filing Dt:** 01/14/2003 **Patent #:** 7468390 **Issue Dt:** 12/23/2008

PCT #: NONE **Intl Reg #:** **Publication #:** US20030144215 **Pub Dt:** 07/31/2003

Inventors: Gary Michael Ksander, Randy Lee Webb

Title: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Assignment: 1

Reel/Frame: 021038 / 0682 **Received:** 06/04/2008 **Recorded:** 06/04/2008 **Mailed:** 06/04/2008 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: KSANDER, GARY MICHAEL **Exec Dt:** 02/20/2003

WEBB, RANDY LEE **Exec Dt:** 02/26/2003

Assignee: NOVARTIS AG
LICHTSTRASSE 35
BASEL, SWITZERLAND 4056

Correspondent: MAUREEN MCGEE
ONE HEALTH PLAZA
101/2H06
EAST HANOVER, NJ 07936

Assignment: 2

Reel/Frame: 026002 / 0790 **Received:** 03/23/2011 **Recorded:** 03/23/2011 **Mailed:** 03/28/2011 **Pages:** 7

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: NOVARTIS AG **Exec Dt:** 03/17/2011

Assignee: NOVARTIS PHARMACEUTICALS CORPORATION
ONE HEALTH PLAZA
EAST HANOVER, NEW JERSEY 07936

Correspondent: LINDA ADAMS
NOVARTIS PHARMACEUTICALS CORP.
ONE HEALTH PLAZA
EAST HANOVER, NJ 07936

Search Results as of: 08/13/2015 14:20:00 PM

Disclaimer:
Assignment information on the assignment database reflects assignment documents that have been actually recorded.
If the assignment for a patent was not recorded, the name of the assignee on the patent application publication or patent may be different.
If you have any comments or questions concerning the data displayed, contact OPR / Assignments at 571-272-3350

Close Window

ASSIGNMENT

We,

Gary Michael Ksander	residing at	37 The Flume Amherst, New Hampshire 03031
Randy Lee Webb	residing at	17 Honeyman Drive Flemington, New Jersey 08822,

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Novartis AG**, a company organized under the laws of the Swiss Confederation, having a place of business at Lichtstrasse 35, Basel, Switzerland 4056, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for the United States and its territories and possessions in and to the invention entitled:

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

invented by us and described in the application for United States Letters Patent

Application No. 10/341,868, filed January 14, 2002,

including (1) said application for United States Letters Patent and all continuations and divisions thereof (including further continuations and divisions such as, but not limited to, continuations of continuations and divisions of continuations), (2) all United States Letters Patent which may be issued and/or granted on all such applications, (3) all applications for reissues and extensions of and reexamination certificates for all such United States Letters Patent and (4) all reissues and extensions and reexamination certificates issued for all such United States Letters Patent, the said interest being the entire ownership of said invention and all of said applications, United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates to be held and enjoyed by the said Novartis AG and its successors and assigns to the full end of the terms to which said United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of said applications for United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates in said assignee.

Signed this 24th day of February, 2003 by _____
Gary Michael Ksander

Signed this 26th day of February, 2003 by _____
Randy Lee Webb

ASSIGNMENT

WHEREAS, **Novartis AG**, a company organized under the laws of the Swiss Confederations, of Lichtstrasse 35, 4056 Basel, Switzerland, its successors, assigns and legal representatives (hereinafter "Assignor") is the owner of all the right, title and interest in and to the United States Patent applications listed on attached Schedule A;

WHEREAS, **Novartis Pharmaceuticals Corporation**, corporation organized under the laws of the State of Delaware, with corporate offices at One Health Plaza, East Hanover, New Jersey 07936 (hereinafter "ASSIGNEE") desires to acquire said interest of Assignor in said inventions and patent application and **Novartis AG** is willing to assign its interest therein to **Novartis Pharmaceuticals Corporation;**

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, Assignor, acting through its legal representatives, all right, title and interest in said inventions and patent application and any divisions, reissues, continuations, continuations-in-part, and extensions thereof, for the United States and its territorial possessions, the same to be held and enjoyed by the Assignee for its use and enjoyment, and for the use and enjoyment of its successors, assigns or other legal representatives, as fully and entirely as the same would have been held and enjoyed by the Assignor, if this assignment and sale nad not be made.

IN WITNESS WHEREOF, Assignor has caused this Assignment to be duly executed this 17 th day of March, 2011.

NOVARTIS AG

_____ L.S.
Name: Peter J. Waibel
Title: Head, U.S. Patent Litigation
Duly Authorized Signatory

_____ L.S.
Name: Joseph T. Majka
Title: Duly Authorized Signatory
Patent Attorney

Schedule A
DIOVAN / EXFORGE
Novartis AG

Patent No.	Date of Issuance	Docket No.
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6174910	02/18/1997	PAT020753-US-PCT
6485745	11/26/2002	PAT020921-US-CNT
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6294197	09/25/2001	PAT020921-US-PCT
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7,468,390	12/23/2008	PAT032219-US-NP
6869970	03/22/2005	PAT032345-US-NP
7700784	04/20/2010	PAT033615-US-PCT
7728024	06/01/2010	PAT034353-US-PCT

Application No.	Date of Filing	Docket No.
11/208131	08/19/2005	PAT020921-US-REI
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12/863213	01/16/2009	PAT052466-US-PCT

APPENDIX B

FDA Approval Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207620

NDA APPROVAL

Novartis Pharmaceuticals Corp,
Attention: Masha Berkhin, PharmD
Global Program Regulatory Director
One Health Plaza
Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated December 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ENTRESTO (sacubitril/valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

We acknowledge receipt of your amendments dated January 15, 16 (two), 20, 22, 28 (two), 30, February 2, 5, 11, 18, 20, 24, 26, March 3, 10, 12, 13, 17, April 2, 3, 8, 15 (two), 16, 20, 21, 24, 29, May 1, 4, 6, 7, 13, 15 (two), 22, 26, June 2, 3, 4, 11, 12, 15, 19, 25, 26, and July 1, 2, and 6, 2015.

This new drug application provides for the use of ENTRESTO (sacubitril/valsartan) Tablets, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an angiotensin converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

In addition, the revised comparability protocols for 1) drug product manufacturing site, control, batch size, and process and 2) (b)(4) intermediate manufacturing site, control, batch size, and process as included in Submission 0000 dated September 30, 2014 are approved. Regulatory notification of changes to the approved protocols must be made via a prior approval supplement.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 11, 2015, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for ENTRESTO was not referred to an FDA advisory committee because:

- The safety profile is acceptable for ENTRESTO to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

  ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.
- The application did not raise significant safety or efficacy issues that were unexpected for a drug of these classes
- The application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease
- Outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. The causes and mechanisms of heart failure are different in children compared to adults. Heart failure in children is most commonly caused by congenital heart malformations and cardiomyopathy whereas the primary etiology of adult heart failure is ischemic heart disease due to atherosclerotic coronary artery disease. The form of heart failure seen in adults is rare in children; hence conducting a trial is highly impractical.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of angioedema in Black patients or to identify an unexpected serious risk of cognitive dysfunction with the use of Entresto (sacubitril/valsartan).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess or identify these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2924-1 Conduct an epidemiologic study using claims or electronic health records data to evaluate the incidence of angioedema in Black patients treated with Entresto compared to a control drug. A target sample size, supported by sample size calculation, should be included in the protocol.

The timetable you submitted on June 19, 2015, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	December 2015
Final Protocol submission	July 2016
Interim Report #1	July 2017
Interim Report #2	July 2018
Final Report Submission:	July 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious risks of cognitive dysfunction with the use of Entresto (sacubitril/valsartan).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2924-2 A multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and PET imaging in patients with chronic heart failure with preserved ejection fraction.

The timetable you submitted on July 6, 2015, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission	November 2015
Final Protocol submission	April 2016
Trial Completion	October 2021
Final Report Submission:	March 2022

Submit the protocols to your IND 104628, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2924-3 Development of a new dissolution method for all the strengths with demonstrated discriminating ability, [redacted] (b) (4), and setting of the final dissolution acceptance criterion for Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg using the new dissolution method and data from the overall multipoint dissolution profile from a minimum of 12 commercial batches per strength, manufactured under the same conditions as those used for the manufacture of the batches used in pivotal clinical trials. The FDA will be open to providing feedback during the method's development process as needed.

The timetable you submitted on June 25, 2015, states that you will conduct this study according to the following schedule:

Dissolution Method Development Report Submission:	February 2016
Final Report Submission:	July 2016

Submit clinical protocols to your IND 104628 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call:

Alexis Childers, RAC
Senior Regulatory Project Manager
(301) 796-0442

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
07/07/2015

APPENDIX C

Copy of 7468390 Patent

US007468390B2

(12) **United States Patent**
Ksander et al.

(10) **Patent No.: US 7,468,390 B2**
(45) **Date of Patent: Dec. 23, 2008**

(54) **METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Gary Michael Ksander**, Amherst, NH (US); **Randy Lee Webb**, Flemington, NJ (US)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 317 days.

(21) Appl. No.: **10/341,868**

(22) Filed: **Jan. 14, 2003**

(65) **Prior Publication Data**

US 2003/0144215 A1 Jul. 31, 2003

Related U.S. Application Data

(60) Provisional application No. 60/386,792, filed on Jun. 7, 2002, provisional application No. 60/349,660, filed on Jan. 17, 2002.

(51) **Int. Cl.**
A61K 31/235 (2006.01)
A61K 31/41 (2006.01)
A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/533**; 514/381; 514/561; 514/563

(58) **Field of Classification Search** 514/533, 514/381, 561, 563

See application file for complete search history.

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(Continued)

Primary Examiner—Jennifer Kim
(74) *Attorney, Agent, or Firm*—Gregory D. Ferraro

(57) **ABSTRACT**

The invention relates a pharmaceutical composition comprising a combination of:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier and to a method for the treatment or prevention of a condition or disease

selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of the pharmaceutical composition to a mammal in need thereof.

3 Claims, No Drawings

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METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

BACKGROUND OF THE INVENTION

The renin angiotensin system is a complex hormonal system comprised of a large molecular weight precursor, angiotensinogen, two processing enzymes, renin and angiotensin converting enzyme (ACE), and the vasoactive mediator angiotensin II (Ang II). See *J. Cardiovasc. Pharmacol.*, Vol. 15, Suppl. B, pp. S1-S5 (1990). The enzyme renin catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I, which has minimal biological activity on its own and is converted into the active octapeptide Ang II by ACE. Ang II has multiple biological actions on the cardiovascular system, including vasoconstriction, activation of the sympathetic nervous system, stimulation of aldosterone production, antinatriuresis, stimulation of vascular growth and stimulation of cardiac growth. Ang II functions as a pressor hormone and is involved the pathophysiology of several forms of hypertension.

The vasoconstrictive effects of angiotensin II are produced by its action on the non-striated smooth muscle cells, the stimulation of the formation of the adrenergenic hormones epinephrine and norepinephrine, as well as the increase of the activity of the sympathetic nervous system as a result of the formation of norepinephrine. Ang II also has an influence on electrolyte balance, produces, e.g., anti-natriuretic and antidiuretic effects in the kidney and thereby promotes the release of, on the one hand, the vasopressin peptide from the pituitary gland and, on the other hand, of aldosterone from the adrenal glomerulosa. All these influences play an important part in the regulation of blood pressure, in increasing both circulating volume and peripheral resistance. Ang II is also involved in cell growth and migration and in extracellular matrix formation.

Ang II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes that are termed, e.g., AT 1- and AT 2-receptors. In recent times great efforts have been made to identify substances that bind to the AT 1-receptor. Such active ingredients are often termed Ang II antagonists. Because of the inhibition of the AT 1-receptor such antagonists can be used, e.g., as anti-hypertensives or for the treatment of congestive heart failure, among other indications. Ang II antagonists are therefore understood to be those active ingredients which bind to the AT 1-receptor subtype.

Inhibitors of the renin angiotensin system are well-known drugs that lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described. See, e.g, *N. Eng. J. Med.*, Vol. 316, No. 23, pp. 1429-1435 (1987). A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which includes the drugs captopril, enalapril, lisinopril, benazepril and spirapril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide Ang II, it has been reported in *Hypertension*, Vol. 16, No. 4, pp. 363-370 (1990), that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in *Circ. Res.*, Vol. 66, No. 1, pp. 242-248 (1990), to be mediated by elevation of bradykinin levels rather than inhibition of Ang II formation. Consequently, it cannot be presumed that the effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino terminal side of aromatic amino acids. See *Biochem. J.*, Vol. 241, pp. 237-247 (1987). Substrates for this enzyme include, but are not limited to, atrial natriuretic factors (ANFs), also known as ANPs, brain natriuretic peptide (BNP), met and leu enkephalin, bradykinin, neurokinin A and substance P.

ANPs are a family of vasodilator, diuretic and anti-hypertensive peptides which have been the subject of many recent reports in the literature. See, e.g., *Annu. Rev. Pharm. Tox.*, Vol. 29, pp. 23-54 (1989). One form, ANF 99-126, is a circulating peptide hormone which is released from the heart during conditions of cardiac distension. The function of ANF is to maintain salt and water homeostasis, as well as to regulate blood pressure. ANF is rapidly inactivated in the circulation by at least two processes: a receptor-mediated clearance reported in *Am. J. Physiol.*, Vol. 256, pp. R469-R475 (1989), and an enzymatic inactivation via NEP reported in *Biochem. J.*, Vol. 243, pp. 183-187 (1987). It has been previously demonstrated that inhibitors of NEP potentiate the hypotensive, diuretic, natriuretic and plasma ANF responses to pharmacological injection of ANF in experimental animals. The potentiation of ANF by two specific NEP inhibitors is reported by Sybertz et al., *J. Pharmacol. Exp. Ther.*, Vol. 250, No. 2, pp. 624-631 (1989), and in *Hypertension*, Vol. 15, No. 2, pp. 152-161 (1990), while the potentiation of ANF by NEP in general was disclosed in U.S. Pat. No. 4,749,688. In U.S. Pat. No. 4,740,499, Olins disclosed the use of thiorphan and kelatorphan to potentiate atrial peptides. Moreover, NEP inhibitors lower blood pressure and exert ANF-like effects, such as diuresis and increased cyclic guanosine 3',5'-monophosphate (cGMP) excretion in some forms of experimental hypertension. The anti-hypertensive action of NEP inhibitors is mediated through ANF because antibodies to ANF will neutralize the reduction in blood pressure.

Darrow et al. in European Patent Application No. 498361 disclose treating hypertension or congestive heart failure with a combination of certain Ang II antagonists or certain renin inhibitors with certain NEP inhibitors.

Powell et al. in European Patent Application No. 726072 disclose treating hypertension or congestive heart failure with a combination of the Ang II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4]nonan-4-one with a NEP inhibitor or a dual acting vasopeptidase inhibitor (single molecular entity with both ACE and NEP inhibitory activities). Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of antihypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for more efficacious combination therapy which has less deleterious side effects.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

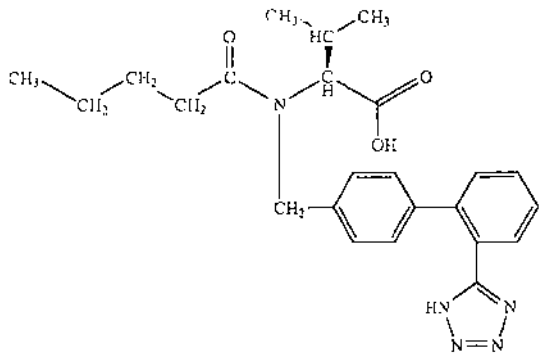
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one aspect, the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a NEP inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.

In another embodiment, the present invention relates to methods of treating cardiac and renal related conditions by administration of the pharmaceutical composition comprising valsartan plus a NEP inhibitor.

Valsartan is the AT 1-receptor antagonist (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2;(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine of formula (I)

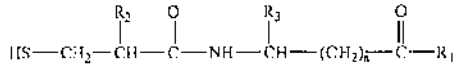
(I)



and is disclosed in EP 0443983 A and U.S. Pat. No. 5,399,578, the disclosures of which are incorporated herein in their entirety as if set forth herein.

A NEP inhibitor useful in said combination is a compound of the formula (II)

(II)



and pharmaceutically acceptable salts thereof,

wherein

R_2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, $-(CH_2)_{1\ to\ 4}$-phenyl, or $-(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, $-(CH_2)_{1\ to\ 4}$-phenyl, or $-(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_1 is hydroxy, alkoxy of 1 to 7 carbons, or NH_2;

n is an integer from 1 to 15; and

the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, Cl, Br or F.

Preferred selective NEP inhibitors of formula (II) include compounds, wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1 to 9; and

R_1 is hydroxy.

Even more preferred selective NEP inhibitors of formula (II) are reported in the literature as SQ 28,603 which is the compound of formula (II), wherein

R_2 is benzyl;

R_3 is hydrogen;

n is one; and

R_1 is hydroxy.

The preparation of the selective NEP inhibitors of formula (II), wherein R_2 is other than trifluoromethyl are disclosed by Delaney et al. in U.S. Pat. No. 4,722,810. The preparation of the selective NEP inhibitors of formula (II), wherein R_2 is trifluoromethyl are disclosed by Delaney et al. in U.S. Pat. No. 5,223,516.

NEP inhibitors within the scope of the present invention include compounds disclosed in U.S. Pat. No. 4,610,816, herein incorporated by reference, including in particular N-[N-[1(S)-carboxyl-3-phenylproplyl]-(S)-phenylalanyl]-(S)-isoserine and N-[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine; compounds disclosed in U.S. Pat. No. 4,929,641, in particular, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; SQ 28603 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine), disclosed in South African Patent Application No. 84/0670; UK 69578 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid) and its active enantiomer(s); thiorphan and its enantiomers; retro-thiorphan; phosphoramidon; and SQ 29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]-heptanoic acid). Also suitable for use are any prodrug forms of the above-listed NEP inhibitors, e.g., compounds in which one or more carboxylic acid groups are esterified

NEP inhibitors within the scope of the present invention also include the compounds disclosed in U.S. Pat. No. 5,217,996, particularly, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; the compounds disclosed in EP 00342850, particularly (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; the compounds disclosed in GB 02218983, particularly 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; the compounds disclosed in WO 92/14706, particularly N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; the compounds disclosed in EP 00343911; the compounds disclosed in JP 06234754; the compounds disclosed in EP 00361365, particularly 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; the compounds disclosed in WO 90/09374, particularly 3-[1-(Cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; the compounds disclosed

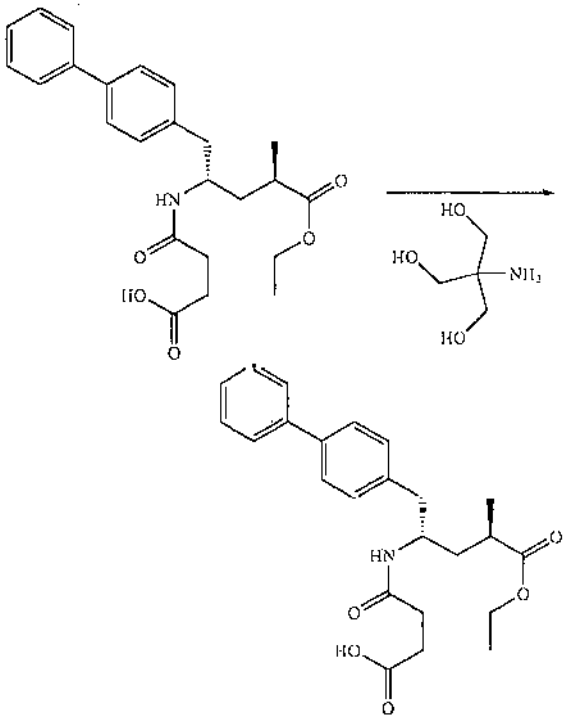
in JP 07157459, particularly N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; the compounds disclosed in WO 94/15908 particularly N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; the compounds disclosed in U.S. Pat. No. 5,273,990 particularly (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; the compounds disclosed in U.S. Pat. No. 5,294,632 particularly (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; the compounds disclosed in U.S. Pat. No. 5,250,522, particularly β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; the compounds disclosed in EP 00636621, particularly N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; the compounds disclosed in WO 93/09101, particularly 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; the compounds disclosed in EP 00590442 particularly ((L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N-[N-[(L)-[1-[(2,2-dimethyl-1 ,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N -[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl) propanoyl]-(S)-isoserine, N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbunyl]-(S)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane carbonyl]-(S)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; and the compounds disclosed in WO 93/10773 particularly N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group, for example, COOH, can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises, e.g., both a carboxy and an amino group.

With respect to N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, preferred salts include the sodium salt disclosed in U.S. Pat. No. 5,217,996, the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt. Preparation of the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt may be carried out as follows:

Triethanolamine

To N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (349 mg, 0.848 mmol) is added 5 ml of ethyl ether and 0.113 mL (0.848 mmol) of triethanolamine in 1 mL of ethyl acetate. The solid was collected and dried melting at 69-71° C.



Tris(hydroxymethyl)aminomethane

To N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (3.2 g, 7.78 mmol) is added 32 ml of ethyl acetate and 940 mg (7.78 mmol) tris(hydroxymethyl)aminomethane. The suspension is diluted with 45 ml of ethyl acetate and refluxed overnight (~20 hours). The reaction is cooled to 0° C., filtered, solid washed with ethyl acetate and dried melting at 114-115° C.

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated.

It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective anti-hypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic or other secondary type of hypertension) through improved efficacy, as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan and NEP inhibitor therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan plus NEP inhibitor combination is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, combination therapy using valsartan and a NEP inhibitor can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted, such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's; glaucoma and stroke.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications.

Representative studies are carried out with a combination of valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, e.g. applying the following methodology:

Drug efficacy is assessed in various animal models including the deoxycorticosterone acetate-salt (DOCA-salt) rat and the spontaneously hypertensive rat (SHR), either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water).

The DOCA-salt test model utilizes either an acute or chronic study protocol. An acute study procedure involves assessment of the effects of various test substances over a six-hour experimental period using rats with indwelling femoral arterial and venous catheters. The acute study procedure evaluates test substances for their ability to reduce blood pressure during the established phase of DOCA-salt hypertension. In contrast, the chronic study procedure assesses the ability of test substances to prevent or delay the rise in blood pressure during the development phase of DOCA-salt hypertension. Therefore, blood pressure will be monitored in the chronic study procedure by means of a radiotransmitter. The radiotransmitter is surgically implanted into the abdominal aorta of rats, prior to the initiation of DOCA-salt treatment and thus, prior to the induction of hypertension. Blood pressure is chronically monitored for periods of up to six weeks (approximately one week prior to DOCA-salt administration and for five weeks thereafter).

Rats are anesthetized with 2-3% isoflurane in oxygen inhalant followed by Amytal sodium (amobarbital) 100 mg/kg, i.p. The level of anesthesia is assessed by a steady rhythmic breathing pattern.

Acute Study Procedure:

Rats undergo a unilateral nephrectomy at the time of DOCA implantation. Hair is clipped on the left flank and the back of the neck and scrubbed with sterile alcohol swabs and povidone/iodine. During surgery rats are placed on a heating pad to maintain body temperature at 37° C.

A 20 mm incision is made through the skin and underlying muscle to expose the left kidney. The kidney is freed of surrounding tissue, exteriorized and two ligatures (3-0 silk) are tied securely around the renal artery and vein proximal to their juncture with the aorta. The renal artery and vein are then severed and the kidney removed. The muscle and skin wounds are closed with 4-0 silk suture and stainless steel wound clips, respectively. At the same time, a 15 mm incision is made on the back of the neck and a three-week-release pellet (Innovative Research of America, Sarasota, Fla.) containing DOCA (100 mg/kg) is implanted subcutaneously (s.c.). The wound is then closed with stainless-steel clips and both wounds are treated with povidone/iodine; the rats are given a post-surgical intramuscular (i.m.) injection of procaine penicillin G (100,000 U) and buprenorphine (0.05-0.1 mg/kg) s.c. The rats are immediately placed on 1% NaCl+0.2% KCl drinking water; this treatment continues for at least 3 weeks at which time the animals have become hypertensive and available for experimentation.

Forty-eight hours prior to experimentation, animals are anesthetized with isoflurane and catheters are implanted in the femoral artery and vein for measuring arterial pressure, collection of blood and administration of test compounds. Rats are allowed to recover for 48 hours while tethered in a Plexiglas home cage, which also serves as the experimental chamber.

Chronic Study Procedure:

This procedure is the same as above except that rats are implanted with a radiotransmitter, 7-10 days prior to the unilateral nephrectomy and initiation of DOCA and salt. In addition, rats do not undergo surgery for placement of femoral arterial and venous catheters. Radiotransmitters are implanted as described in Bazil et al., "Telemetric Monitoring of Cardiovascular Parameters in Conscious Spontaneously Hypertensive Rats", *J. Cardiovasc. Pharmacol.*, Vol. 22, pp. 897-905 (1993).

Protocols are then set-up on the computer for measurement of blood pressure, heart rate, etc., at pre-determined time points. Baseline data is collected at various time points and over various time intervals. For example, baseline or pre-dose values usually consist of data collection and averaging over three consecutive, 24-hour time periods prior to drug administration.

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during, and after drug administration. All measurements are performed in unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months. For studies of this duration, rats are dosed orally (1-3 mL/kg vehicle), no more than twice daily or drug is administered via the drinking water or mixed with food. For studies of a shorter duration, that is, up to 8 weeks, drugs are given via s.c. implanted osmotic minipumps. Osmotic minipumps are selected based on drug delivery rate and time. Valsartan dosages range from 1-10 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester range from 10-50 mg/kg/day.

Additionally, SHRs are utilized to study the effects of valsartan in combination with N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic

acid ethyl ester. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the renin angiotensin system (RAS) or chronic salt depletion to activate the RAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the various test substances. Experiments performed in SHRs are supplied by Taconic Farms, Germantown, N.Y. (Tac:N(SHR) IBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul, Minn.) is implanted into the lower abdominal aorta of all test animals between the ages of 14-16 weeks of age. All SHRs are allowed to recover from the surgical implantation procedure for at least two weeks prior to the initiation of the experiments. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24-hour period and are made up of the 144-10 minute samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24-hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12-hour light dark cycle.

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is measured five times per week. Valsartan and N-(3carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water, and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days. Typical dosages for valsartan in drinking water range from 3-30 mg/kg/day whereas the dosage of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is highly dependent upon the specific agent used. In most situations, a daily dose will not exceed 50 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1-30 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy.

When drugs are administered by oral gavage, the dose of valsartan ranges from 1-50 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester does not exceed 100 mg/kg/day.

Upon completion of the chronic studies, SHR or DOCA-salt rats are anesthetized and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported. All values reported for blood pressure and cardiac mass represent the group mean ± sem.

Vascular function and structure are evaluated after treatment to assess the beneficial effects of the combination. SHR are studied according to the methods described by Intengan et al., *Circulation*, Vol. 100, No. 22, pp. 2267-2275 (1999). Similarly, the methodology for assessing vascular function in DOCA-salt rats is described in Intengan et al., *Hypertension*, Vol. 34, No. 4, Part 2, pp. 907-913 (1999).

The available results indicate an unexpected therapeutic effect of a combination according to the invention.

In one aspect is the object of this invention to provide a pharmaceutical combination composition, e.g., for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke which composition comprises:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof, and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. The unit dose form may also be a fixed combination.

A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

A therapeutically effective amount of each of the component of the combination of the present invention may be administered simultaneously or sequentially and in any order.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

The typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; betacyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

The invention also relates to combining separate pharmaceutical compositions in kit form. That is a kit combining two separate units: a valsartan pharmaceutical composition and a NEP inhibitor pharmaceutical composition. The kit form is particularly advantageous when the separate components must be administered in different dosage forms, e.g., parenteral valsartan formulation and oral NEP formulation; or are administered at different dosage intervals.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1-90%, preferably of from about 1% to about 80%, of the active compounds. Pharmaceutical preparations for enteral or parenteral administration are, e.g., in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, e.g., using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated, e.g., for a patient of approximately 75 kg in weight.

Valsartan is supplied in the form of suitable dosage unit form, e.g., a capsule or tablet, and comprising a therapeutically effective amount, e.g., from about 20 mg to about 320 mg, of valsartan which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting, e.g., with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied once a day (q.d.) or twice a day (b.i.d.) in heart failure patients with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is q.d. or b.i.d. administration in heart failure.

In case of NEP inhibitors, preferred dosage unit forms are, e.g., tablets or capsules comprising, e.g., from about 20 mg to about 800 mg, preferably from about 50 mg to about 700 mg, even more preferably from about 100 mg to about 600 mg and even more preferably from about 100 mg to about 300 mg, administered q.d.

The above doses encompass a therapeutically effective amount of the active ingredients of the present invention.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

FORMULATION EXAMPLE 1

Film-Coated Tablets

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan (= active ingredient)	80.00	
Microcrystalline cellulose/Avicel PH 102	54.00	NF, Ph. Eur
Crospovidone	20.00	NF, Ph. Eur
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	0.75	Ph. Eur, NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	0.75	Ph. Eur, NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water*		
DIOLACK Pale Red 00F34899	7.00	
Total Tablet Mass	167.00	

*Removed during processing.

The film-coated tablet is manufactured, e.g., as follows:

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again premixed in a diffusion mixer, compacted in a roller compactor and then sieve through a screening mill. To the resulting mixture, the rest of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200 are added and the final blend is made in a diffusion mixer. The whole mixture is compressed in a rotary tabletting machine and the tablets are coated with a film by using Diolack pale red in a perforated pan

FORMULATION EXAMPLE 2

Film-coated tablets

Components	Composition Per Unit (mg)	Standards
Granulation:		
Valsartan [= active ingredient]	160.00	
Microcrystalline cellulose/Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	1.50	Ph. Eur, NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	1.50	Ph. Eur, NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry ® Light Brown 00F13172	10.00	
Total Tablet Mass	330.00	

The film-coated tablet is manufactured, e.g., as described in Formulation Example 1.

FORMULATION EXAMPLE 3

Film-coated tablets

Components	Composition Per Unit (mg)	Standards
Core Internal Phase		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (colloidal silicon dioxide) [= glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= lubricant]	2.00	USP/NF
Crospovidone [= disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= binding agent]	124.00	USP/NF
External Phase		
Silica, colloidal anhydrous (colloidal silicon dioxide) [= glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= lubricant]	2.00	USP/NF
Film Coating		
Opadry Brown 00F16711*	9.40	
Purified water**	—	
Total Tablet Mass	199.44	

*The composition of the Opadry brown 00F16711 coloring agent is tabulated below.
**Removed during processing

Opadry ® Composition:

Ingredient	Approximate % Composition
Iron oxide, black (C.I. No. 77499, E 172)	0.50
Iron oxide, brown (C.I. No. 77499, E 172	0.50
Iron oxide, red (C.I. No. 77491, E 172)	0.50
Iron oxide, yellow (C.I. No. 77492, E 172)	0.50
Macrogolum (Ph. Eur)	4.00
Titanium dioxide (C.I. No. 77891, E 171)	14.00
Hypromellose (Ph. Eur)	80.00

-continued

The film-coated tablet is manufactured, e.g., as described in Formulation Example 1.

FORMULATION EXAMPLE 4

Capsules

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total Tablet Mass	209.50

The tablet is manufactured, e.g., as follows:

Granulation/Drying

Valsartan and microcrystallin cellulose are spray-granulated in a fluidized bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidized bed dryer.

Milling/Blending

The dried granulate is milled together with crospovidone and magnesium stearate. The mass is then blended in a conical screw type mixer for approximately 10 minutes.

Encapsulation

The empty hard gelatin capsules are filled with the blended bulk granules under controlled temperature and humidity conditions. The filed capsules are de-dusted, visually inspected, weight-checked and quarantined until by Quality Assurance department.

FORMULATION EXAMPLE 5

Capsules

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00
Magnesium stearate	2.60
Sodium lauryl sulphate	1.20

-continued

Capsules

Components	Composition Per Unit (mg)
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total Tablet Mass	342.00

The formulation is manufactured, e.g., as described in Formulation Example 4.

FORMULATION EXAMPLE 6

Hard Gelatine Capsule

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium lauryl sulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcystalline cellulose	21.10
Total Tablet Mass	130.00

FORMULATION EXAMPLE 7

A hard gelatin capsule, comprising as active ingredient, e.g., (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine, can be formulated, e.g., as follows:

Components	Composition Per Unit (mg)
(1) Valsartan	80.00
(2) Microcystalline cellulose	110.0
(3) Polyvidone K30	45.2
(4) Sodium lauryl sulfate	1.2
(5) Crospovidone	26.0
(6) Magnesium stearate	2.6

Components (1) and (2) are granulated with a solution of components (3) and (4) in water. The components (5) and (6) are added to the dry granulate and the mixture is filled into size 1 hard gelatin capsules.

All publications and patents mentioned herein are incorporate by reference in their entirety as if set forth in full herein.

What is claimed is:

1. A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof,

wherein the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) the NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered in combination achieve a greater anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt administered alone and (ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone, and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof.

3. A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof and in a second container a pharmaceutical composition comprising valsartan or a pharmaceutically acceptable salt thereof wherein the amounts of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts and valsartan or a pharmaceutical acceptable salt thereof administered in combination achieve a greater anti-hypertensive effect than the sum of the therapeutic effects achievable with the amounts of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-Biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salts thereof administered alone and valsartan or a pharmaceutically acceptable salt thereof administered alone.

* * * * *

APPENDIX D

Maintenance Fee Receipt

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INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER NJ 07936-1080

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	ENTITY STATUS	ATTY DKT NUMBER
7468390	**$1,130.00**	**$0.00**	**05/23/12**	**10341868**	**12/23/08**	**01/14/03**	**04**	**LARGE**	**4-32219A**

PTOL-439 (Rev. 09/2006)

APPENDIX E

IND Chronology

FDA Interaction Date	Content Summary
3/8/2007	Original IND for LCZ696 in the treatment of hypertension. The purpose of this IND is to support a phase 1 clinical study in healthy volunteers to generate pharmacokinetic information on LCZ696. Please note that this IND was originally submitted under IND 75,612, but FDA issued a new IND number after receiving the submission. (PS)
3/16/2007	FDA LETTER Acknowledging receipt of the original IND submitted on March 8, 2007.
3/27/2007	Email from FDA asking for clarification on the original IND.
4/3/2007	Email response to FDA CMC questions (ES)
4/13/2007	At this time, Novartis is submitting a CMC information amendment in response to the FDA request on April 2, 2007. The FDA requested the following: A detailed description of the container closure system for the LCZ696 drug substance, and a certificate of analysis (C of A) for the clinical batch of the LCZ696 300 mg drug product (PS)
4/25/2007	FDA LETTER Comments and requests for information on the clinical and chemistry sections of the IND.
4/27/2007	HA meeting minutes of the March 29, 2007, FDA/Novartis Pre-IND meeting to discuss Novartis' proposed Phase 2 development plan under IND 77,318.
4/30/2007	Request for Type B meeting to seek the Division's input and comments on Novartis' proposed development program for LCZ696 which would establish it as a safe and effective first-line antihypertensive (PS)
5/3/2007	Response to FDA comments and request for information made in the FDA letter dated April 25, 2007 (PS)
5/24/2007	Novartis is hereby notifying the FDA that they plan to submit on June 26, 2007 for the Agency's review and assessment the following carcinogenicity study protocols 104 week oral (gavage) carcinogenicity study in rats; and 104 week oral (gavage) carcinogenicity study in mice (PS)
6/5/2007	15 day IND safety report, reporting a new unexpected finding of hydrocephaly in an embryo fetal development study in rabbits (PS)
6/28/2007	This Amendment provides updated information 'concerning the LCZ696 drug substance synthesis and controls as well as CMC information for new LCZ696 film-coated tablets: 100 mg (KN 6002384.002), 200 mg (KN 6002385.002) and 400 mg (KN 6002386.002). In addition, CMC information for a 100 mg AHU377 comparator product (KN 6002372.001), and VAL489 80 mg (KN 3748175,010) and 160 mg (KN 3748183.010) comparator products is provided. Placebo documentation to .match the three LCZ696 film-coated tablets (KNs 6002387.001, 6002387,002 and 60023S7.003), AHU377 comparator product (KN 6002373.001) and the two VAL489 comparator products (KN 3755667.030) is also included. (PS)
6/28/2007	Request for special protocol assessment for Protocol 104 week oral (gavage) carcinogenicity study in mice (Appendix 1); and 104 week oral (gavage) carcinogenicity study in rats (Appendix 2) (PS)

FDA Interaction Date	Content Summary
7/6/2007	FDA LETTER Acknowledging receipt of serial number 005 submitted on June 29, 2007, for a special carcinogenicity protocol assessment.
7/9/2007	New protocol CLCZ696A2103 new protocol entitled: An open-label
7/9/2007	FDA FAX Responding the Carcinogenicity Special Protocol Assessment Request.
7/11/2007	Briefing book for Pre-IND meeting scheduled for August 15, 2007 to discuss the intended development of this product (PS)
8/13/2007	Email from FDA containing the 2nd Pre-IND meeting FDA preliminary responses.
8/15/2007	Novartis meeting minutes (not submitted) of the August 15, 2007 Pre-IND meeting to discuss issues associated with the development of LCZ-696, a molecule containing the active moieties of valsartan and AHU, a neutral endopeptidase inhibitor (NEPI) in a 1:1 ratio. The product is being developed for the treatment of hypertension.
8/16/2007	FDA LETTER Pre-IND meeting confirmation for the August 15, 2007 Type B meeting.
9/5/2007	New protocol Study CLCZ696A2201 entitled: A multi-center
9/18/2007	New investigators to Study CLCZ696A2201 (PS)
9/18/2007	FDA meeting minutes of the Type B meeting between Novartis and the FDA held on August 15, 2007 to discuss issues associated with the development of LCZ-696, a molecule containing the active moieties of valsartan and AHU, a neutral endopeptidase inhibitor (NEPI) in a 1:1 ratio. The product is being developed for the treatment of hypertension.
9/18/2007	TELECON with FDA to discuss Novartis' inquiry regarding confirming LCZ eligible for 3 years of marketing exclusivity, not 5 years as it contains valsartan.
9/19/2007	Email regarding the FDA meeting minutes of the August 15, 2007 Type B meeting.
10/3/2007	New investigators to study CLCZ696A2201. (PS)
10/16/2007	New investigators to Study CLCZ696A2201. (PS)
11/28/2007	New investigators to Study CLCZ696A2201. (PS)
1/9/2008	New investigator to study CLCZ696A2201. (PS)
2/21/2008	New investigator to study CLCZ696A2201. (PS)
8/11/2008	Annual report covering the period April 8, 2007 to April 7, 2008 (eCTD-seq0017)
2/5/2009	Request for Type B meeting on April 6, 2009 to seek the Agency's feedback on Novartis' proposed clinical development program for LCZ696 in the treatment of chronic heart failure (PS)
2/11/2009	Record of Contact of telecon between Ed Lee of Novartis and Quynh Nguyen at the Cardio-Renal Division of FDA regarding the Type B meeting request submitted to IND 77,318 on February 5, 2009 (ES)
2/11/2009	Email correspondence providing the Agency with the re-submission of the Type B meeting request that was previously submitted to IND 77,318 on February 5, 2009 as Ser. No. 018 (PS)

FDA Interaction Date	Content Summary
2/23/2009	General Correspondence requesting withdrawal of Type B Meeting request, submitted to the FDA on February 5, 2009 in Sequence No. 0018 (eCTD-seq-0019)
3/20/2009	Submission of an Information Amendment to provide updated Chemistry, Manufacturing and Controls information regarding LCZ696 drug substance, drug product, and placebo (eCTD-seq0020)
5/6/2009	Submission of New Protocol for study CLCZ696B2214, entitled 'A twelve-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the efficacy, safety and tolerability of LCZ696 compared to valsartan in patients with chronic heart failure and preserved left-ventricular ejection fraction' (eCTD-seq0021)
6/5/2009	Annual Report covering the period from April 07, 2008 to April 07, 2009 (eCTD-seq0022)
10/22/2009	Submission of New Protocol, CLCZ696B2105, entitled 'An open-label, single dose study to investigate the absorption, distribution, metabolism, and elimination of 200 mg [14C]LCZ696 and its metabolites in healthy male subjects.' (eCTD-seq0023)
11/18/2009	Submission of New Investigators to studies LCZ696B2105, LCZ696B2214 (eCTD-seq0024)
12/10/2009	Submission of New Investigators to study CLCZ696B2214 (eCTD-seq0025)
12/17/2009	Submission of New Investigators to study LCZ696B2214 (eCTD-seq0026)
1/8/2010	Submission of Information Amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance, drug product, and placebo (eCTD-seq0027)
1/13/2010	Submission of New Investigators for study LCZ696B2214 (eCTD-seq0028)
2/24/2010	Submission of Change in Protocol: Amendment 1 to study CLCZ696B2214 (eCTD-seq0029)
4/21/2010	Submission of New Investigators to study CLCZ696A2201 (eCTD-seq0030)
4/29/2010	Submission of Change in Protocol; Amendment # 2 to study CLCZ696B2214 (eCTD-seq0032)
4/30/2010	Submission of New Investigator to study LCZ696B2214 (eCTD-seq0031)
6/3/2010	Submission of Annual Report covering the period from April 7, 2009 to April 7, 2010 (eCTD-seq0033)
6/9/2010	Submission of Changes in Protocol to studies CLCZ696A2102, CLCZ696A2103, CLCZ696A2201 and Transfer of Obligations to studies CLCZ696A2102 CLCZ696A2103, CLCZ696A2201, CLCZ696B2105, CLCZ696B2214 (eCTD-seq0034)
6/15/2010	Submission of Amendment # 1 to study CLCZ696A2201 and New Investigator to study CLCZ696B2214 (eCTD-seq0035)
8/9/2010	Submission of Amendment 3 to protocol CLCZ69662214
8/30/2010	Safety Report PHHO2010TW11790 (eCTD-seq0038)
9/1/2010	Submission of New Investigators to study LCZ696B2214 (eCTD-seq0037)

FDA Interaction Date	Content Summary
9/23/2010	New Investigator for protocol CLCZ696B2214 (eCTD-seq0039).
9/27/2010	Transfer of obligation for study CLCZ976B2214 (eCTD-seq0040)
10/20/2010	Safety Report PHHO2010GB13984 (eCTD-seq0041)
10/26/2010	CMC amendment to provide for changes to the analytical methods, drug product specifications, and packaging information (eCTD-seq0042).
11/17/2010	CMC Amendment to provide updated information for the drug substance and drug product (eCTD-seq0043).
12/3/2010	This Correspondence provides information about immediate change in contact at Novartis for this application.
12/6/2010	Correspondence sent to the FDA to notify them of the intent to export LCZ696 tablets for investigational use (PS).
12/9/2010	Telecon held on December 9, 2010 to confirm the receipt of the export notice for LCZ696.
12/17/2010	New Protocol CLCZ696A2223, a multi-center, randomized, double-blind, placebo and active controlled, parallel group study to evaluate the dose response of AHU377 in combination with valsartan 320 mg after 8 week treatment in patients with mild-to-moderate systolic hypertension (eCTD-seq0045).
12/17/2010	Transfer of Obligation for protocol CLCZ696B2214 (eCTD-seq0046)
12/22/2010	New Investigators for protocol LCZ696A2223 (eCTD-seq-0047)
1/7/2011	Safety Report PHHO2010TW19816 7-day Safety Report (PS).
1/10/2011	Safety Report PHHO2010TW19816 (eCTD-seq0049)
1/13/2011	New Investigator(s) for protocol(s) CLCZ696A2223 and CLCZ696B2214 (eCTD-seq0048).
1/18/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0050)
2/4/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0051)
2/11/2011	Submission of an Information Amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance (eCTD-seq0052)
2/22/2011	Safety Report PHHO2010TW19816;follow-up(eCTD-seq0053)
2/28/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0055)
3/4/2011	Transfer of Obligations for protocol CLCZ696A2223 (eCTD-seq0054).
4/6/2011	New investigator for protocol CLCZ696A2223(eCTD-seq0056)
4/8/2011	Submission of Change in Protocol; Amendment # 1 to study CLCZ696B2223 (eCTD-seq0057)
4/21/2011	New Investigator for CLCZ696A2223 (eCTD-seq0058).
5/23/2011	Annual Report covering the period from 07-April-2010 to 07-April-2011 (eCTD-seq0059).
6/8/2011	Novartis is submitting an Information Amendment to provide updated CMC Information regarding the clinical trial material. (eCTD-seq0060)

FDA Interaction Date	Content Summary
6/23/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0061)
6/30/2011	Amendment 2 to Protocol CLCZ696A2223 (eCTD-seq0062)
7/12/2011	Safety Report PHHO2010TW19998 7-Day safety report (PS).
7/18/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0063)
7/18/2011	Safety Report PHHO2010TW19998 (eCTD-seq0064)
9/9/2011	New investigators for protocols LCZ696B2214 & LCZ696A2223 (eCTD-seq0065)
9/14/2011	Safety Report PHHO2010TW19998; follow-up (eCTD-seq0067)
9/14/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0066)
10/21/2011	CMC information amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance and clinical trial material. (eCTD-seq0068)
10/25/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0070)
10/25/2011	Safety Report PHHO2010TW19998; follow-up (eCTD-seq0069)
11/18/2011	New Investigator for protocol LCZ696A2223 (eCTD-seq0071).
1/12/2012	New Investigator(s) for protocol(s) LCZ696A2223 (eCTD-seq0072).
3/22/2012	Change in regulatory contact from Simon Ducher to Leigh Strachan (eCTD-seq0073)
5/18/2012	Transfer of obligations for study LCZ696B2214 (eCTD-seq0075)
6/4/2012	Annual Report covering the period from 07April2011 to 07April2012 (eCTD-seq0074)
7/24/2012	Information Amendment to provide updated Chemistry, Manufacturing and Controls Information for a new formulation of LCZ696 50 mg Film-coated tablets (FMI, Final Marketing Image). Reference is made to 6002752_AMEN_CP_840_2 for a complete summary of the changes (eCTD-seq0076).
8/8/2012	New Protocol CLCZ696A2222, entitled 'A randomized, double-blind, crossover study to assess the effects of LCZ696 and valsartan in Asian patients with salt-sensitive hypertension (eCTD-seq0077)"
9/12/2012	New Investigator for protocol LCZ696A2222 (eCTD-seq0078)
9/21/2012	New Protocol CLCZ696A2216 entitled A randomized
10/25/2012	Novartis is submitting an Information Amendment to provide updated Chemistry, Manufacturing and Controls information for a new comparator and placebo to match the comparator. In addition, minor updates to control of LCZ696 drug product as well as an updated packaging sites list are included. Reference is made to 6002752_AMEN_CP_840_3 for a complete summary of the changes. (eCTD-seq0079)
11/2/2012	Safety Report PHHO2012JP015393 (eCTD-seq0081)
11/19/2012	FDA advice-information request regarding protocol CLCZ696A2216.
11/19/2012	Safety Report PHHO2012JP015393; follow-up (eCTD-seq0082)
12/10/2012	New Investigators for protocol lcz696a2216 (eCTD-seq0083).

FDA Interaction Date	Content Summary
12/12/2012	Response to FDA request dated November 19, 2012 regarding new protocol CLCZ696A2216. (eCTD-seq0084)
12/17/2012	Safety Report PHHO2012JP015393; follow-up (eCTD-seq 0085)
12/24/2012	Submission of Transfer of Obligations for Study No. CLCZ696A2222. (eCTD-seq0086)
12/27/2012	Safety Report PHHO2012JP018459 7-Day safety report (PS)
1/4/2013	Safety Report PHHO2012JP018459 (eCTD-seq 0087)
1/7/2013	Safety Report PHHO2012JP018459 follow-up (eCTD-seq0088)
1/18/2013	Amendment 1 to Protocol CLCZ696A2222 (eCTD-Seq0090)
1/18/2013	New Investigators for Study CLCZ696A2216. (eCTD-seq0089)
1/21/2013	Safety Report PHHO2012JP018459; follow-up (eCTD-seq0091)
1/24/2013	Safety Report PHHO2013JP000956 (eCTD-seq0092)
1/25/2013	Safety Report PHHO2013JP000998 (eCTD-seq0093)
1/31/2013	Safety Report PHHO2012JP018459; follow-up (eCTD-seq0094)
2/1/2013	Safety Report PHHO2013ZA001555 (eCTD-seq0096)
2/1/2013	Safety Report PHHO2013JP001480 (eCTD-seq0095)
2/5/2013	Safety Report PHHO2013JP000956; follow-up (eCTD-Seq0097)
2/6/2013	P Safety Report HHO2013JP000998; follow-up (eCTD-seq0098)
2/7/2013	Safety Report PHHO2013JP000956; follow-up (eCTD-seq0099)
2/12/2013	Safety Report PHHO2011BR17514 7-Day safety report (PS).
2/14/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0100)
2/19/2013	Safety Report PHHO2013JP000998; follow-up (eCTD-seq0101)
2/20/2013	Safety Report PHHO2012DE013453; follow-up (eCTD-seq0102)
2/20/2013	Safety Report PHHO2011BR17514 Follow-up (eCTD-seq0103)
2/23/2013	Safety Report PHHO2013JP000956; follow-up (eCTD-seq0105)
2/25/2013	New Investigators for protocols CLCZ696A2222, CLCZ696A2216 (eCTD-seq0104)
2/27/2013	Safety Report PHHO2013JP001480; follow-up (eCTD-seq0106)
2/27/2013	Safety Report PHHO2013DE002628 (eCTD-seq0107)
3/11/2013	Novartis is submitting an information Amendment to provide updated Chemistry, Manufacturing and Control information for a comparator (Olmesartan Medoxomil). (eCTD-seq0108)
3/14/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0109) The receipts are not available for this submission.
3/15/2013	Safety Report PHHO2013DE002628 Follow-up (eCTD-seq0110) The receipts are not available for this submission.
3/22/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0111)
3/22/2013	Safety Report PHHO2010IL18897 Follow-up (eCTD-seq0112)
3/26/2013	Safety Report PHHO2013JP004048 (eCTD-seq0114)
3/28/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0115)

FDA Interaction Date	Content Summary
4/5/2013	Novartis is submitting an Information Amendment to provide updated CMC information for a placebo matching a valsartan comparator. This amendment supports a batch specific extension for this placebo in the on-going trial CLCZ696A2222 (new shelf life: 63 months). (eCTD-seq0117)
4/5/2013	Clinical Information Amendment is submitted to provide final Clinical Study Report for LCZ696B2214 (eCTD-Seq0113)
4/5/2013	Safety Report PHHO2012JP018459; follow-up (eCTD-seq0116)
4/11/2013	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0118)
4/16/2013	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0119)
4/16/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0120)
4/16/2013	Safety Report PHHO2012BR018051 7-day report (PS)
4/17/2013	Safety Report PHHO2013JP004048; follow-up (eCTD-seq0121)
4/18/2013	Safety Report PHHO2012BR018051 (eCTD-seq0123)
4/24/2013	This submission is to provide the recently updated Investigator's Brochure (edition 12) for LCZ696 which can be found in Section 1.14.4.1 (eCTD-seq0122)
4/30/2013	Amendment 2 for Protocol CLCZ696A2222 (eCTD-Seq0124)
5/1/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0126)
5/1/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0125)
5/6/2013	Safety Report PHHO2013BR005937 7-day report (PS)
5/8/2013	Safety Report PHHO2013JP005683 (eCTD-seq0128)
5/13/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0129)
5/14/2013	Safety Report PHHO2013BR005937 (eCTD-seq0130)
5/15/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0131)
5/21/2013	Safety Report PHH02011TW09929; follow-up (eCTD-seq0132)
5/21/2013	Safety Report PHHO2011SI18084 Follow-up (eCTD-seq0133)
5/29/2013	Safety Report PHHO2013JP005683 Follow-up (eCTD-seq0134)
5/30/2013	Safety Report PHHO2013US006665 (eCTD-seq0135)
6/4/2013	Annual Report covering the period from April 08, 2012 through April 07, 2013 (eCTD-seq0127)
6/4/2013	PHHO2011BR17560 Follow-up (eCTD-seq0136)
6/6/2013	PHHO2011BR09808 Follow-up (eCTD-seq0140) The Receipts are not available for this submission.
6/6/2013	Safety Report PHHO2012FR018676 Follow-up (eCTD-seq0139)
6/7/2013	Safety Report PHHO2013JP000956 Follow-Up (eCTD-seq0141)
6/12/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0143)
6/13/2013	Safety Report PHH02013JP000956 Follow-up (eCTD-seq0144)
6/14/2013	Safety Report PHHO2013JP005683; follow-up (eCTD-seq0142).
6/18/2013	In accordance with 21 CFR §312.31, Novartis is providing the Clinical Study Reports for CLCZ696A2201 entitled A multi-center

FDA Interaction Date	Content Summary
6/19/2013	The purpose of this submission is to complete the record by submitting the actual reports to the application (eCTD-seq0138)
6/21/2013	Safety Report PHH02013JP000956 Follow-up (eCTD-seq0146)
6/26/2013	Information Amendment-CMC - Novartis is submitting an information Amendment to provide updated Chemistry, Manufacturing and Control information for a comparator (amlodipine besylate tablets) and placebo matching this comparator in addition to other minor CMC updates.
6/27/2013	Safety Report PHHO2013JP000956 follow-up (eCTD-seq0149)
7/1/2013	Safety Report PHH02011TW09929 Follow-up (eCTD-seq0150)
7/3/2013	New Protocol CLCZ696A2320
7/3/2013	Email response to FDA as to whether or not the new Phase 3 protocols are to be considered pivotal studies.
7/4/2013	New Protocol for CLCZ696A2318 entitled 'A randomized, 8-week, double-blind, parallel-group, active controlled, multicenter study to evaluate the efficacy and safety of LCZ696 200 mg in comparison with olmesartan 20 mg in patients with essential hypertension not adequately responsive to olmesartan 20 mg treatment' and TOO (eCTD-Seq0148)
7/5/2013	Safety Report PHHO2013US006665 follow-up (eCTD-seq0151)
7/12/2013	Safety Report PHHO2013US006665 Follow-up (eCTD-seq0153)
7/13/2013	Safety Report PHHO2012GB017225 follow-up (eCTD-seq0152)
7/18/2013	Safety Report PHHO2013JP000956 Follow-Up (eCTD-seq0154)
7/31/2013	Safety Report PHHO2013PH009418 7-Day (PS)
8/1/2013	Information Amendment to provide updated Chemistry, Manufacturing and Control information for LCZ696 film-coated tablets 50 mg, 100 mg, 200 mg and 400 mg and to introduce a new placebo (matching 50 mg FMI formulation. Reference is made to 6002572 AMEN_CP_840_6 for detailed information (eCTD-seq0155)
8/1/2013	Cross reference to the Clinical Study Report for CLCZ696A2124 (eCTD-seq0156).
8/2/2013	Safety Report PHHO2012ZA008690 7-Day safety report (PS).
8/2/2013	Safety Report PHH02013ZA008690 (eCTD-seq0158)
8/2/2013	Safety Report PHHO2013JP000956 Follow-Up (eCTD-seq0159)
8/6/2013	Safety Report PHHO2012FR018676 Follow-Up (eCTD-seq0160)
8/8/2013	Safety Report PHHO2013JP000956 follow-up (eCTD-seq0163)
8/8/2013	Safety Report PHHO2012BR018051follow-up (eCTD-seq0161)
8/8/2013	Safety Report PHHO2013DE002628 follow-up (eCTD-seq0162)
8/8/2013	Safety Report PHHO2013PH009418 (eCTD-seq0164)
8/9/2013	Safety Report PHHO2012NL008767 Follow-Up (eCTD-seq0165)
8/12/2013	New Protocol for clcz696a2126 entitled A randomized
8/14/2013	Submission of updated Transfer of Sponsor Obligations for study CLCZ696A2320. (eCTD-seq0166)

FDA Interaction Date	Content Summary
8/15/2013	Email exchange with FDA will let us conduct study CLCZ696A2126 under the existing HTN IND. However, any further studies regarding the effect of LCZ696 on amyloid-' concentrations in cerebrospinal fluid would need to be to a new IND to the Division of Neurology Products (DNP).
8/19/2013	CMC Information Amendment (Pubs 74563) (eCTD-seq0167)
8/22/2013	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0170)
8/22/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0169)
8/22/2013	Safety Report PHHO2010TW19998 Follow-up (eCTD-seq0168)
8/30/2013	FDA LETTER providing statistical comments and recommendations for LCZ696A2318 and LCZ696A2320.
9/9/2013	Safety Report PHHO2013TW011210 7-Day safety report (PS)
9/10/2013	Safety Report PHHO2013TW011210 (eCTD-seq0172)
9/12/2013	New Investigator for protocol LCZ696A2216 (eCTD-seq0171)
9/13/2013	New Investigators for protocols CLCZ696A2318, A2320 (eCTD-seq0173)
9/24/2013	Amendment 1 to Study CLCZ696A2126. (eCTD-seq0176)
9/30/2013	New Investigator Batch for protocols CLCZ696A2318, A2320, A2126 (eCTD-seq0175)
10/1/2013	Safety Report PHHO2012JP017363 (eCTD-seq0178).
10/4/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0179)
10/9/2013	Clinical Information Amendment eCTD-seq0180)
10/10/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0182)
10/11/2013	New Investigator A2318,A2320 (eCTD-seq0181)
10/21/2013	Submission provides updated Transfer of Sponsor Obligations for study LCZ696A2126. (eCTD-seq0183)
10/21/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0184)
10/24/2013	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0177)
11/1/2013	Safety Report PHHO2013JP005683, followup (eCTD-seq0186)
11/6/2013	New Investigator(s) for protocol(s) LCZ696A2318, LCZ696A2320 (eCTD-seq0185)
11/12/2013	Novartis is providing 15 day IND safety report to report a new, unexpected, and potentially adverse finding of increased levels of amyloid beta (A') in the cerebrospinal fluid (CSF), in the absence of changes of levels in the brain, which was observed during a 2-week oral investigative study in cynomolgus monkeys treated with LCZ696. (eCTD-seq0187)
11/26/2013	NEW INVESTIGATORS/Change in Form FDA 1572;(eCTD-seq0188)
11/27/2013	Safety Report PHHO2012AR010257 Follow-up (eCTD-seq0190)
11/29/2013	Information Amendment (Clinical)
12/5/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0191)
12/12/2013	Information Amendment-Clinical: Submitting an Erratum to the recently updated Investigator Brochure (Edition 13) (eCTD-Seq0192)
12/19/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0193)

FDA Interaction Date	Content Summary
1/15/2014	Amendment 01 to Protocol CLCZ696A2320, CLCZ696A2320E1 (eCTD-seq0194)
1/16/2014	Safety Report PHHO2013TW011210; follow up (eCTD-seq0196)
1/21/2014	Safety Report Protocol Amendment (New investigator) LCZ696A2318; eCTDseq0195
2/5/2014	PHHO2013TW011210; follow-up (eCTD-seq0197)
2/27/2014	CMC Information amendment is submitted to provide information on Comparator, Olmesartan medoxomil 10mg, 20mg and 40mg Hard non-gelatin capsule tablet content regarding the extension of Shelf-life from 18 months to 24 months and extension of In-use period from 1 month to 1.5 months based on available additional stability data. (eCTD-Seq0198)
2/27/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0199)
3/4/2014	Safety Report PHHO2011IS18084; follow-up (eCTD-seq0200)
3/18/2014	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0201)
3/27/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0205)
3/28/2014	Information Amendment-Clinical: Update IB Edition-14 is being submitted (eCTD-Seq0203)
3/28/2014	Request to submit the DSUR in lieu of the annual report using the existing reporting period July 31, 2013 - July 30, 2014. (eCTD-seq0202)
3/29/2014	Safety Report PHHO2013TW011210; Follow-up (eCTD-seq0204)
4/7/2014	Safety Report PHHO2012FR018676; follow-up (eCTD-seq0206)
4/17/2014	Email to FDA to inform project manager that data from A2126, which was run under this IND, has been submitted to IND 104,628 and a cross reference statement is pending.
4/18/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0209)
4/22/2014	The purpose of this submission is to provide a cross reference in [Module 1.4.4] to preliminary information submitted to IND 104,628 about LCZ696A2126, which is being run under this IND. (eCTD-seq0208)
4/25/2014	FDA Letter requesting follow up information regarding the statistical considerations for Protocol LCZ696A2318.
4/25/2014	FDA Letter providing agreement to Novartis' proposal (submitted March 28, 2014) for switching to the DSUR after the IND Annual Report due June 5th is submitted.
4/25/2014	FDA Letter requesting changes to Section 6 of the Investigator's Brochure.
5/7/2014	Submission provides response to FDA request dated April 25, 2014 regarding study CLCZ696A2318 along with an update on recruitment for CLCZ696A2318 and change in contact from Leigh Strachan to Masha Berkhin. (eCTD-seq0211)
5/9/2014	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0212)
5/12/2014	Safety Report PHHO2012GB001045, follow-up (eCTDseq 0213)
5/20/2014	New Investigator for Protocol CLCL696A2216 and 1572 Changes (eCTD-seq0214)
5/28/2014	Safety Report PHHO2014IT007104 (eCTD-seq0215)

FDA Interaction Date	Content Summary
5/28/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0216)
5/29/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0217)
5/30/2014	Annual Report covering the period from 08 April 2013 through 07 April 2014 (eCTD-seq0210)
6/10/2014	Safety Report PHHO2014IT007104; follow-up (eCTD-seq0218)
6/16/2014	Novartis is submitting updated version of the Investigator's Brochure Edition 15 (eCTD-seq0219)
6/18/2014	Amendment 1 to protocol CLCZ696A2216 (eCTD-seq0220)
6/27/2014	CMC Information Amendment Pubs 85228 (eCTD-seq0221)
7/6/2014	Safety Report PHHO2014US008920 (eCTD-seq0223)
7/10/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0224)
7/14/2014	Novartis is providing the Clinical Study Report for CLCZ696A2222. (eCTD-seq0222)
7/14/2014	Safety Report PHHO2010GB15448; follow-up (eCTD-seq0225)
7/15/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0228)
7/15/2014	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0226)
7/16/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0229)
7/19/2014	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0230)
7/21/2014	Safety Report PHHO2011FI06062 Follow-up (eCTD-seq0231)
7/31/2014	Novartis is submitting an information Amendment to include the current information on LCZ696 drug substance and LCZ696 50mg, 100mg, 200mg and 400mg and placebo Film-coated tablet. (eCTD-seq0233)
8/5/2014	Safety Report PHHO2013SK004806 7-day (eCTD-seq0234)
8/6/2014	Novartis is submitting clinical study report for study CLCZ696A2126 (eCTD-seq0232)
8/11/2014	Safety Report PHHO2012RU017982 7-day safety report (eCTD-seq0237)
8/12/2014	Safety Report PHHO2010HU17146 Follow-up (eCTD-seq0238)
8/14/2014	Safety Report PHHO2013SK004806 (eCTD-seq0239)
8/15/2014	Safety Report PHHO2011IN11799; follow-up (eCTD-seq0247)
8/15/2014	Safety Report PHHO2012AR010257; follow-up (eCTD-seq0246)
8/15/2014	Safety Report PHHO2012GB017225; follow-up (eCTD-seq0245)
8/15/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0244)
8/18/2014	FDA advice information request letter regarding Investigator's Brochure Edition 15, dated June 4, 2014.
8/18/2014	Safety Report PHHO2014RU006393; 7-Day safety report (eCTD-seq0248)
8/20/2014	Safety Report PHHO2012RU017982 (eCTD-seq0249)
8/21/2014	Safety Report PHHO2012PH006218 (eCTD-seq0251)
8/25/2014	Safety Report PHHO2013IN010949 (eCTD-seq0252)
8/25/2014	Safety Report PHHO2014RU006393 (eCTD-seq0253)

FDA Interaction Date	Content Summary
8/25/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0254)
9/1/2014	Safety Report PHHO2012US009119 7-Day safety report (eCTD-seq0255)
9/5/2014	Safety Report PHHO2014US008920; follow-up (eCTD-seq0256)
9/8/2014	Safety Report PHHO2012US009119 (eCTD-seq0257)
9/26/2014	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0258)
9/30/2014	DSUR Annual report covering the period from 31July 2013 through 30June 2014 (eCTD-seq0250)
10/7/2014	Novartis is amending the base DSUR 104,628 by providing Regional Appendix 2 (List of subjects who died during the reporting period) and Appendix 3 (List of subjects who dropped out of studies during the reporting period). (eCTD-seq0259)
10/14/2014	Safety Report PHHO2011FI06062; Follow-up (eCTD-seq0261)
10/15/2014	Safety Report PHHO2013CN003844 7-Day safety report (eCTD-seq0262)
10/17/2014	New Investigator CLCZ696A2216 (eCTD-seq0260)
10/24/2014	Safety Report PHHO2012GB006694; follow-up (eCTD-seq0264)
1/23/2015	Novartis is submitting an information Amendment to inform the agency regarding the changes to specifications (eCTD-seq0268).
1/26/2015	Amendment 2 to CSR CLCZ696B2214. (eCTD-seq0267)
2/10/2015	Safety Report PHHO2013CN003844 (eCTD-seq0263)
2/26/2015	CMC Information Amendment to inform the agency regarding a typographical error in the description of Valsartan 80mg film-coated tablet that were used as a comparator in LCZ696 clinical study D2301 (eCTD-Seq0273).
2/27/2015	Clinical Information amendment to provide the Clinical Study Report for CLCZ696A2201 and CLCZ696A2223 (eCTD-Seq0269)
3/23/2015	Novartis is submitting Amendment 1 for CSRs CLCZ696A2201 and CLCZ696A2223. (eCTD-seq0270)
4/9/2015	Submission provides CSR's CLCZ696A2315 and CLCZ696A2318. (eCTD-seq0272)
4/16/2015	Clinical Information Amendment Updated IB Ed 16 (eCTD-seq0274)
4/17/2015	Amendment 1 to protocol CLCZ696A2216 (eCTD-seq0275).
6/10/2015	Submission provides CSRs CLCZ696A2219, CLCZ696A2219E1, LCZ696A1306, LCZ696A2316, LCZ696A2319, LCZ696A1304 and LCZ696A1305. (eCTD-seq0271)
6/26/2015	Information Amendment - CMC: To inform the agency regarding the addition of Singapore Pharmaceutical Manufacturing Pte .Ltd. as additional manufacturing and quality control site for LCZ696 50mg, 100mg, 200mg (eCTD-Seq0277)

FDA Interaction Date	Content Summary
2/20/2009	Request for Type B meeting to obtain feedback on proposed clinical development program for treatment of chronic heart failure. Meeting is requested to be held on April 13, 2009 (PS)
3/5/2009	FDA letter providing meeting confirmation for Pre-IND meeting, scheduled for April 22, 2009
3/20/2009	Submission of Briefing Book in support of Type B meeting to discuss the proposed clinical development program for the use of LCZ696 in the treatment of chronic heart failure has been scheduled for Wednesday, April 22, 2009 (PS)
6/2/2009	FDA meeting minutes for Pre-IND Meeting of April 22, 2009
6/9/2009	Briefing Book for Special Protocol Assessment for Study CLCZ696B2314
6/30/2009	Email providing the Agency with the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is referenced in Novartis' SPA
7/1/2009	Email correspondence providing the Agency with reference for Green, Porter, et al. 2000
7/16/2009	FDA LETTER stating that FDA does not agree with the special protocol assessment request dated June 9, 2009.
7/23/2009	Email regarding April 22, 2009 meeting and FDA comments regarding special protocol assessment received on July 16, 2009.
7/24/2009	Request for FDA Type A Pre-IND meeting to discuss the Agency's response to Special Protocol Assessment for Study CLCZ696B2314 dated July 16, 2009 (PS).
7/30/2009	FDA Letter granting Type A meeting as per Novartis' request on July 24, 2009, to discuss the Agency's response the Special Protocol Assessment for Study CLCZ696B2314
8/5/2009	Briefing book for the Type A meeting scheduled for August 20, 2009 to discuss the Agency's response to your Special Protocol Assessment for Study CLCZ696B2314. (ES) Note: This BB was submitted to Archives without cover letter of form.
8/18/2009	FDA Fax Providing SPA Follow-up Meeting Preliminary Responses
8/19/2009	Email correspondence regarding preliminary response to Type A meeting
8/20/2009	Novartis recap of meeting with the FDA to reach agreement on key elements of the proposed outcomes trial protocol CLCZ696B2314, which was previously submitted to the Agency under a Special Protocol Assessment (SPA)
8/27/2009	FDA minutes of the August 20, 2009 Type A SPA Follow-up teleconference with Novartis.
10/1/2009	Submission of Original IND for the indication of chronic heart failure (eCTD-seq0005)
10/15/2009	FDA Letter acknowledging receipt of Original IND
11/3/2009	Amendment providing updated drug substance stability data (up to 24 months) which support an extension in the re-test period from 24 months to 36 months (eCTD-seq0007)
11/6/2009	FDA Letter providing comments and requesting information regarding the development of LCZ696 for chronic heart failure and reduced ejection fraction.

FDA Interaction Date	Content Summary
11/10/2009	General Correspondence providing the Agency with notification of intent to submit Carcinogenicity study for protocol assessment within 30 days (eCTD-seq0008)
11/11/2009	Request for Type C meeting to discuss the proposed strategy for utilizing a Patient Reported Outcomes (PRO) instrument in the Phase 3 outcomes study (CLCZ696B2314) in chronic heart failure being conducted under this IND (eCTD-seq0009)
11/16/2009	FDA letter granting Type C meeting on January 21, 2010, to discuss proposed strategy for utilizing a Patient Reported Outcomes (PRO) instrument in your Phase 3 outcomes study (CLCZ696B2314) in chronic heart failure.
12/1/2009	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0010)
12/15/2009	Request for Special Protocol Assessment of the proposed Carcinogenicity Study Protocols in the mouse and rat, which will be included as part of the toxicology package to support the chronic heart failure indication under this IND. Included in the SPA package are the (eCTD-seq0012)
12/16/2009	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0011)
12/17/2009	Briefing Book for the Type C meeting to be held on January 21, 2010 to discuss the Patient Reported Outcomes instrument for Study CLCZ696B2314 (eCTD-seq0013).
1/6/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0014)
1/7/2010	Request for Carcinogenicity Study Protocol Assessment for rat study 0870373 (eCTD-seq0015)
1/19/2010	FDA fax providing Novartis with the Agency's preliminary responses in preparation for the Type C meeting scheduled for January 21, 2010 (PS)
1/22/2010	Submission of New Investigator to study CLCZ696B2314 (eCTD-seq0016)
2/8/2010	Submission of New Investigator to study CLCZ696B2314 (eCTD-seq0017)
2/10/2010	Submission of Information Amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance, drug product, and (eCTD-seq0018)
2/12/2010	Type C meeting minutes from January 21, 2010 meeting
3/5/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0019)
3/24/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0020)
4/22/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0021)
5/6/2010	Submission of New Investigators to studies CLCZ696B2314 (eCTD-seq0022)
5/27/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0023)
6/8/2010	Submission of Transfer of Obligations to study CLCZ696B2314 (eCTD-seq0024)
6/18/2010	Submission of New Investigators to study LCZ696B2314 (eCTD-seq0025)
7/7/2010	Study CLCZ696B2314 new investigator (eCTD-seq0026)
7/28/2010	Safety Report PHHO2010DE10636 (eCTD-seq0028)
7/30/2010	Submission of New Investigator to study CLCZ696B2314 (eCTD-seq0027)
8/3/2010	Safety Report PHHO2010DE10636; follow-up (eCTD-seq0029)
8/9/2010	Safety Report PHHO2010DE10636; follow-up (eCTD-seq0030)
8/24/2010	Safety Report PHHO2010DE10636; follow-up (eCTD-seq0032)

FDA Interaction Date	Content Summary
8/25/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0031)
9/17/2010	New Investigators for protocol CLCZ696B2314 (eCTD-seq0033)
10/22/2010	Safety Report PHHO2010GB15448 7-day safety report. (PS)
10/22/2010	New Investigators for Protocol CLCZ696B2314 (eCTD-seq0034)
10/22/2010	Safety Report PHHO2010GB15448; (eCTD-seq0035)
10/27/2010	Safety Report PHHO2010GB13984; (eCTD-seq0037)
11/3/2010	7 Day Safety Report PHHO2010HU16306 (PS).
11/4/2010	New Investigator(s) for protocol(s) LCZ696B2314 (eCTD-seq0036)
11/11/2010	Safety Report PHHO2010HU16306; (eCTD-seq0038)
11/19/2010	New Investigators for protocols CLCZ696B2314 (eCTD-seq0039)"
11/22/2010	Safety Report PHHO2010GB16454 (eCTD-seq0040)
11/24/2010	Safety Report PHHO2010HU17146 (eCTD-seq0043)
11/24/2010	Safety Report PHHO2010HU16306; follow-up (eCTD-seq0044)
11/29/2010	Safety Report PHHO2010TW17370 (eCTD-seq0046)
11/29/2010	7 Day safety report PHHO2010GB16454 (PS).
11/30/2010	Safety Report PHHO2010HU17146; follow-up (eCTD-seq0047)
12/1/2010	Amendment to provide for an extension of shelf life for a comparator for use in clinical studies (eCTD-seq0045).
12/6/2010	Change in responsibility to Simon Ducher (eCTD-seq0042).
12/7/2010	Safety Report PHHO2010GB13984;follow-up (eCTD-seq0050)
12/7/2010	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0049)
12/7/2010	Safety Report PHHO2010TW17370 (eCTD-seq0051)
12/8/2010	7 Day Safety report PHHO2010DE18191 (PS).
12/8/2010	Safety Report PHHO2010HU17146; follow-up (eCTD-seq0052)
12/9/2010	New Investigator for protocol CLCZ696B2314 (eCTD-seq0048)
12/13/2010	Safety Report PHHO2010DE18191 (eCTD-seq0054)
12/17/2010	Amendment 1 to protocol CLCZ696B2314 (eCTD-seq0053).
12/20/2010	Annual Report covering the period from 01-Nov-2009 to 31-Oct-2010 (eCTD-seq0041)
12/20/2010	7 Day safety report PHHO2010US18903 (PS).
12/21/2010	Request for Type C meeting to discuss the proposed strategy for utilizing a Patient Reported Outcomes instrument in patients with preserved chronic heart failure (eCTD-seq0055).
12/22/2010	Safety Report PHHO2010TW11790 (eCTD-seq0057)
12/22/2010	Safety Report PHHO2010IL18897 (eCTD-seq0056)
12/28/2010	Safety Report PHHO2010TW11790; follow-up (eCTD-seq0060)
1/3/2011	FDA LETTER confirming the Type C meeting to be held on March 1, 2011 to discuss the proposed strategy for using a Patient Reported Outcomes instrument.
1/3/2011	Safety Report PHHO2010US18903; follow-up (eCTD-seq0061)
1/5/2011	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0062)
1/13/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0063)

FDA Interaction Date	Content Summary
1/21/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0065)
1/22/2011	Safety Report PHHO2010US18903 (eCTD-seq0058)
1/25/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0064).
1/28/2011	Safety Report PHHO2010DE18191; follow-up (eCTD-seq0059)
1/31/2011	Briefing Book for the Type C meeting to be held on March 1, 2011 to discuss the strategy for utilizing a Patient Reported Outcomes instrument (eCTD-seq0066).
2/2/2011	Email from the FDA cancelling the meeting to be held on March 1, 2011 because the review of the briefing document will be completed in mid-April.
2/18/2011	New Investigators for protocol CLCZ696B2314 (eCTD-seq0067)
2/18/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0068)
2/18/2011	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0069)
3/15/2011	Safety Report PHHO2011IL04325 7-Day safety report (PS).
3/22/2011	Safety Report PHHO2011IL04325 (eCTD-seq0071)
3/31/2011	Safety Report PHHO2010GB13984; follow-up (eCTD-seq0072)
4/6/2011	New Investigators for protocol CLCZ696B2314 (eCTD-seq0070)
4/7/2011	Safety Report PHHO2010HU18329 (eCTD-seq0073)
4/12/2011	Safety Report PHHO2011FI06062 7-Day safety report (PS).
4/13/2011	Safety Report PHHO2011FI06062 (eCTD-seq0074)
4/18/2011	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0075)
4/20/2011	FDA comments on submission dated January 31, 2011 regarding PRO SYMPL-HF.
4/26/2011	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0077)
5/3/2011	New Investigators for protocol CLCZ696B2314 (eCTD-seq0076).
5/3/2011	Safety Report PHHO2011PL07181 (eCTD-seq0078)
5/14/2011	Safety Report PHHO2011HU06255 (eCTD-seq0080)
5/16/2011	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0081)
5/20/2011	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0082)
5/24/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0079)
5/25/2011	Safety Report PHHO2011PL07181; follow-up (eCTD-seq0083)
6/10/2011	Safety Report PHHO2011BR09808 7-Day safety report (PS).
6/15/2011	Response to FDA advice letter dated April 20, 2011 regarding PRO SYMPL-HF. (eCTD-seq0084)
6/17/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0085)
6/17/2011	Safety Report PHHO2011BR09808 (eCTD-seq0087)
6/21/2011	Safety Report PHHO2011TW09929 (eCTD-seq0088)
6/22/2011	Amendment # 2 to protocol CLCZ696B2314 (eCTD-seq0086).
6/22/2011	Telecon regarding request for teleconference with FDA to discuss a new PRO instrument (SYMPL-HF).
6/23/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0089)
6/27/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0091)
7/1/2011	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0092)
7/6/2011	New Investigator for protocol CLCZ696B2314 (eCTDseq0090)
7/6/2011	Safety Report PHHO2011HU06255; follow-up (eCTD-seq0093)

FDA Interaction Date	Content Summary
7/12/2011	FDA response to Novartis request for clarification regarding FDA advice letter dated April 20, 2011.
7/12/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0094)
7/15/2011	Safety Report PHHO2011HU06255; follow-up (eCTD-seq0095)
7/18/2011	Safety Report PHHO2011IN11799 7-Day safety report (PS).
7/22/2011	Safety Report PHHO2011IN11799 (eCTD-seq0096)
7/26/2011	FDA minutes of the July 19, 2011 teleconference with Novartis to discuss advice letter dated July 12, 2011.
8/1/2011	Safety Report PHHO2011GB12663 7-Day safety report (PS).
8/1/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0097)
8/5/2011	Email notification to FDA regarding enalapril comparator used in CLCZ696B2314 trial.
8/8/2011	Safety Report PHHO2011GB12663 (eCTD-seq0098)
8/12/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0099)
8/18/2011	Safety Report PHHO2011PH11140 7-Day safety report (PS)
8/22/2011	Change in Transfer of Obligations for Protocol CLCZ696B2314 (new CRO). (eCTD-seq0100)
8/24/2011	Safety Report PHHO2011GB12663; follow-up (eCTD-seq0101)
8/25/2011	Safety Report PHHO2011PH11140 (eCTD-seq0103)
8/26/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0104)
8/30/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0102)
9/2/2011	Submission of notifications to the FDA about supply issue of enalapril in CLCZ696B2314. (eCTD-seq0105)
9/9/2011	Transfer of Obligations for Protocol CLCZ696B2314. (eCTD-seq0106)
9/14/2011	Safety Report PHHO2011FR14817 (eCTD-seq0107)
9/22/2011	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0108)
9/23/2011	Safety Report PHHO2011PH15876 7-Day Safety Report (PS)
9/26/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0109)
9/29/2011	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0112)
9/29/2011	Safety Report PHHO2011PH15876 (eCTD-seq0111)
10/3/2011	Safety Report PHHO2010HU17146; follow-up (eCTD-seq0113)
10/7/2011	New Investigators for Protocol CLCZ696B2314 (eCTD-seq0110)
10/7/2011	Safety Report PHHO2011TW16144 (eCTD-seq0114)
10/20/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0116)
10/20/2011	Safety Report PHHO2011BR17560 (eCTD-seq0115)
11/1/2011	New Investigator's for Protocol CLCZ696B2314 (eCTD-seq0117)
11/2/2011	Safety Report PHHO2011IS18084 7-Day safety report (PS)
11/3/2011	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0119)
11/8/2011	Safety Report PHHO2011IS18084 (eCTD-seq0120)
11/29/2011	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0121)
12/9/2011	Annual Report covering the period from 31-Oct-2010 to 31-Oct-2011 (eCTD-seq0118)
12/21/2011	New Investigator for protocol CLCZ696B2314 (eCTD-Seq0122).

FDA Interaction Date	Content Summary
12/22/2011	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0123)
1/4/2012	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0124)
1/11/2012	Email from FDA agreeing to request an EOP2 meeting for HF-PEF indication under IND 104,628.
1/18/2012	Safety Report PHHO2012BE001036 7-Day safety report (PS)
1/18/2012	Safety Report PHHO2012GB001045 7-Day safety report (PS)
1/24/2012	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0125)
1/24/2012	Safety Report PHHO2012BE001036; (eCTD-seq0126)
1/25/2012	Safety Report PHHO2012GB001045 (eCTD-seq0127)
2/1/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0128)
2/3/2012	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0130)
2/3/2012	Safety Report PHHO2012ZA001868 7-Day safety report (PS)
2/9/2012	New Investigators for protocol CLCZ696B2314 (eCTD-seq0131).
2/9/2012	Safety Report PHHO2012ZA001868; (eCTD-seq0132)
2/15/2012	Safety Report PHHO2012BR002454 (eCTD-seq0133).
2/28/2012	Safety Report PHHO2012BR002454; follow-up (eCTD-seq0135)
3/2/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0129)
3/2/2012	New Protocol for Study CLCZ696B2107 (eCTD-seq0134)
3/7/2012	Safety Report PHHO2012PL003313 (eCTD-seq0136)
3/13/2012	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0137).
3/20/2012	Safety Report PHHO2012BR003913 (eCTD-seq0138)
3/26/2012	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0140).
3/27/2012	New Investigator for Protocol CLCZ696B2107 and CLCZ696B2314 (eCTD-seq0139)
3/29/2012	Submission contains Investigator Brochure Edition 11, dated March 13, 2012 replacing Edition 10, dated February 21, 2011. (eCTD-seq0141)
4/5/2012	Safety Report PHHO2012BR003913; follow-up(eCTD-seq0142)
4/9/2012	Safety Report PHHO2012TW003618 (eCTD-seq0144)
4/9/2012	Safety Report PHHO2012PL003313 (eCTD-seq0145)
4/13/2012	Novartis is requesting a Type B EOP2 meeting to seek feedback from the Agency on the proposed clinical development program for LCZ696 for the treatment of heart failure in patients with preserved ejection fraction. (eCTD-seq0143)
4/16/2012	Safety Report PHHO2012TW003618; follow-up (eCTD-seq0148)
4/17/2012	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0146)
4/20/2012	Change in transfer of obligations for protocol CLCZ696B2314 (new CRO). (eCTD-seq0147)
4/20/2012	New Protocol for Study LCZ696A2120 (eCTD-seq0149)
5/1/2012	FDA letter advising Type B EOP2 meeting granted for June 18, 2012.
5/8/2012	New investigator for protocol LCZ696A2120,CLCZ696B2314 (eCTD-seq0150)
5/9/2012	Safety Report PHHO2012GB006694 (eCTD-seq0152)
5/14/2012	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0153).
5/14/2012	Briefing Book for the June 18, 2012 Type B EOP2 meeting (eCTD-seq0151). (BLINDED)

FDA Interaction Date	Content Summary
5/29/2012	Safety Report PHHO2012BR005720 (eCTD-seq0154)
6/1/2012	Safety Report PHHO2012HK007713 (eCTD-seq0155)
6/8/2012	Safety Report PHHO2011IN12674 7-Day Safety report (PS).
6/12/2012	New Protocol CLCZ696A2119, entitled 'An open label, three-period, single sequence study to evaluate the pharmacokinetic drug-drug interaction between LCZ696 and amlodipine in healthy volunteers' (eCTD-seq0156)
6/13/2012	FDA preliminary response to meeting questions for meeting scheduled for June 18, 2012.
6/18/2012	Safety Report PHHO2011IN12674 (eCTD-seq0157)
6/20/2012	Safety Report PHHO2010HU18329 (eCTD-seq0158)
6/20/2012	Safety Report PHHO2012BR008797 (eCTD-seq0159)
6/21/2012	Safety Report PHHO2012NL008767 (eCTD-seq0160)
6/25/2012	Email to FDA containing Novartis meeting minutes from the EOP2 meeting held on June 18, 2012 for the HF-PEF indication.
6/26/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0163)
6/26/2012	Safety Report PHHO2011BR17560; follow-up (eCTD-seq0162)
7/3/2012	New Investigators for protocol CLCZ696A2119, B2314 (eCTD-seq0161)
7/5/2012	Safety Report PHHO2012BR008797; follow-up (eCTD-seq0165)
7/9/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0166)
7/9/2012	Safety Report PHHO2011BR17560; follow-up (eCTD-seq0167)
7/10/2012	New Protocol CLCZ696B2122, entitled 'An open-label, three-period, single-sequence study to evaluate the pharmacokinetic drug-drug interaction between LCZ696 and metformin in healthy volunteers of Japanese descent' (eCTD-seq0164)
7/12/2012	Safety Report PHHO2012AR010257 7-Day safety report (PS)
7/17/2012	FDA meeting minutes from EOP2 meeting held on June 18, 2012.
7/18/2012	Safety Report PHHO2012BR008797; follow-up (eCTD-seq0172)
7/20/2012	Request for Type C CMC meeting to gain agreement on the proposed drug substance staring materials. Submission includes briefing book. (eCTD-seq0170)
7/23/2012	New Investigators for protocols LCZ696B2122,B2314 (eCTD-seq0171)
7/24/2012	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0174)
7/24/2012	Safety Report PHHO2012AR010257 (eCTD-seq0173)
7/25/2012	Safety Report PHHO2011BR17514 (eCTD-seq0175)
7/25/2012	Email regarding objection to proposed EOP2 meeting minutes changes.
8/2/2012	Change in regulatory contact from Simon Ducher to Alison Mickle (eCTD-seq0177)
8/9/2012	Study CLCZ696B2114 new protocol, includes transfer of obligations. (eCTD-seq0168)
8/9/2012	Study CLCZ696B2125 new protocol, includes transfer of obligations (eCTD-seq0169)
8/10/2012	Safety Report PHHO2012EC005568 (eCTD-seq0178)
8/17/2012	Safety Report PHHO2012US011818 7-Day safety report (PS)

FDA Interaction Date	Content Summary
8/22/2012	New Investigators for protocols CLCZ696B2114, CLCZ696B2125 and CLCZ696B2314 (eCTD-seq0179)
8/22/2012	Safety Report PHHO2012NL008767; follow-up (eCTD-seq0180)
8/23/2012	Safety Report PHHO2012GB011913 (eCTD-seq0181)
8/23/2012	Safety Report PHHO2012US011818 (eCTD-seq0182)
8/31/2012	Safety Report PHHO2012US011818; follow-up (eCTD-seq0184)
8/31/2012	Safety Report PHHO2012IS012355 (eCTD-seq0185)
9/11/2012	New Investigator for protocol CLCZ696B2314 (eCTD-seq0183)
9/11/2012	Safety Report PHHO2012GB011913; follow-up (eCTD-seq0187)
9/13/2012	New Investigator(s) for protocol(s) CLCZ696B2314 (eCTD-seq0186).
9/18/2012	Novartis' request on July 23, 2012 to propose two changes to the meeting minutes related to the reflection of the role of AHU in the indication statement and role of valsartan in the treatment of HF-PEF. On July 25, 2012 Novartis was informed by the FDA Project Manager that the minutes were deemed to accurately reflect the discussion and therefore the minutes will not be modified as per Novartis proposed changes. (eCTD-seq0188)
9/20/2012	Safety Report PHHO2012PE012764 7-Day safety report (PS)
9/21/2012	New Protocol CLCZ696B2113, entitled An open-label
9/21/2012	Safety Report PHHO2010HU18329; follow-up(eCTD-seq0191)
9/21/2012	Safety Report PHHO2012PE012764 7-Day safety report (PS)
9/25/2012	Safety Report PHHO2012DE013453 7-Day safety report (PS)
9/26/2012	Submission provides a drug supply issue notification for study CLCZ696B2314 whereby the allocated study medication for two patients was switched. (eCTD-seq0192)
9/27/2012	New Investigator(s) for Protocol CLCZ696B2314 (eCTD-seq0190)
9/27/2012	Safety Report PHHO2012TR013235 (eCTD-seq0193)
9/28/2012	Safety Report PHHO2012IN013259 (eCTD-seq0195)
9/29/2012	Safety Report PHHO2012PE012764 (eCTD-seq0194)
10/3/2012	Safety Report PHHO2012ES007783 (eCTD-seq0199)
10/3/2012	Safety Report PHHO2012DE013453 (eCTD-seq0198)
10/3/2012	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0197)
10/5/2012	Novartis telephone report regarding the objection to the HF-PEF end of phase 2 meeting minutes (S-0188).
10/9/2012	Safety Report PHHO2012PE012764; follow-up (eCTD-seq0201)
10/9/2012	Safety Report PHHO2012BR013598 (eCTD-seq0202)
10/11/2012	Novartis is requesting for FDA feedback for LCZ696B2314 (PARADIGM) ' Statistical Analysis Plan. (eCTD-seq0196)
10/12/2012	Safety Report PHHO2012TR013235; follow-up (eCTD-seq0204)
10/18/2012	Safety Report PHHO2012IS012355; follow-up (eCTD-seq0206)
10/19/2012	New Investigator for protocol CLCZ696B2314 (eCTD-seq0200)
10/22/2012	Safety Report PHHO2012DE014709 (eCTD-seq0207)
10/23/2012	New Investigator for Protocol CLCZ696B2113 (eCTD-Seq0203)

FDA Interaction Date	Content Summary
10/24/2012	Information amendment - Pharmacology/toxicology for Reports DMPK R0900652, 0970613, 0870734 (eCTD-seq0205)
10/31/2012	Safety Report PHHO2012ZA015482 7-Day safety report (PS)
10/31/2012	Safety Report PHHO2012IL015128 (eCTD-seq0208)
11/1/2012	Safety Report PHHO2012EC015122 (eCTD-seq0209)
11/6/2012	Safety Report PHHO2012ZA015482 (eCTD-seq0210)
11/9/2012	FDA advice/information request regarding question in briefing package.
11/15/2012	Safety Report PHHO2012IL015128; follow up (eCTD-seq0212)
11/19/2012	New investigator for protocol CLCZ696B2122 (eCTD-seq0211)
11/21/2012	Safety Report PHHO2012ZA015482; follow-up (eCTD-seq0213)
11/21/2012	Safety Report PHHO2012BR016272 (eCTD-seq0214)
12/3/2012	Safety Report PHHO2012IL015128; follow-up (eCTD-seq0216)
12/3/2012	Safety Report PHHO2012IT005964 (eCTD-Seq0217)
12/11/2012	Safety Report PHHO2012ES004570 (eCTD-Seq0218)
12/12/2012	Annual Report covering the period from 01-November-2011 to 31-October-2012 (eCTD-seq0215)
12/13/2012	Safety Report PHHO2012ZA017679 7-Day Safety Report (PS)
12/17/2012	Pharm/Tox reports for Study 1170562, DMPK R1200239. (eCTD-seq0219)
12/18/2012	New protocol CLCZ696A2124 entitled, An open-label
12/19/2012	Safety Report PHHO2012DE014709; follow-up (eCTD-seq0222)
12/19/2012	Safety Report PHHO2012BR013598; follow-up (eCTD-seq0221)
12/20/2012	Safety Report PHHO2012ZA017679 (eCTD-seq0223)
12/24/2012	Safety Report PHHO2012ZA017679; follow-up (eCTD-seq0224)
1/3/2013	Safety Report PHHO2012FR018676 7-Day safety report (PS)
1/3/2013	Safety Report PHHO2012DE018401 (eCTD-seq 0226)
1/3/2013	Safety Report PHHO2012BR016272; follow-up (eCTD-seq 0225)
1/8/2013	Request to submit the DSUR in lieu of the annual report using the existing reporting period July 31, 2012 to July 30 2013.(eCTD-seq0227)
1/9/2013	Submission provides for a revised Transfer of Sponsor Obligation for Study CLCZ696B2314 to capture the addition of Cognizant Technology Solutions India Pvt. Ltd., as noted on the Transfer of Obligation in Module 1.3.1.4. (eCTD-seq0228)
1/9/2013	Safety Report PHHO2012FR018676 (eCTD-Seq0229)
1/10/2013	Safety Report PHHO2012DE018401; follow-up (eCTD-seq0230)
1/15/2013	Safety Report PHHO2012FR018676; follow-up (eCTD-seq0231)
1/18/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0232)
1/25/2013	Safety Report PHHO2013IN000955 (eCTD-seq0235)
1/25/2013	Safety Report PHHO2013IN000955 7-Day safety report (PS)
1/30/2013	Email correspondence from FDA regarding the SAP and Patient Narrative Proposal.
2/1/2013	Safety Report PHHO2013ZA001555 (eCTD-seq0238)
2/1/2013	Safety Report PHHO2012ES007783; follow-up (eCTD-seq0237)
2/4/2013	Safety Report PHHO2012ES007783; follow-up (eCTD-seq0239).

FDA Interaction Date	Content Summary
2/4/2013	Safety Report PHHO2012ES007783 Follow-Up (eCTD-seq0239)
2/5/2013	New Investigator for Study No. CLCZ696B2122. (eCTD-seq0236)
2/6/2013	Email from FDA regarding the pediatric plan timeline.
2/6/2013	Safety Report PHHO2013JP000998; follow-up (eCTD-seq0240)
2/7/2013	Safety Report PHHO2012IL015128; follow-up (eCTD-seq0242)
2/8/2013	Response to FDA email request dated January 30, 2013 regarding Statistical Analysis Plan. (eCTD-seq0241)
2/12/2013	PHHO2011BR17514 7-Day safety report (PS).
2/13/2013	New Investigator for protocol CLCZ696A2124 and TOO for CLCZ696B2122 (eCTD-seq0234).
2/14/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0243)
2/19/2013	Safety Report PHHO2013JP000998; follow-up (eCTD-seq0244)
2/20/2013	Safety Report PHHO2012DE013453; follow-up (eCTD-seq0245)
2/20/2013	Safety Report PHHO2011BR17514 Follow-up (eCTD-seq0246)
2/27/2013	FDA letter granting harmonized DSUR for IND 104,628.
2/27/2013	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0248)
3/6/2013	FDA letter is an agreement for the PARADIGM-HF statistical analysis plan (SAP).
3/12/2013	Amendment 3 to protocol CLCZ696B2314 (eCTD-Seq0247)
3/14/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0249) The receipts are not available for this submission.
3/15/2013	Safety Report PHHO2013DE002628 Follow-up (eCTD-seq0250) The receipts are not available for this submission.
3/22/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0251)
3/22/2013	Safety Report PHHO2010IL18897 Follow-up (eCTD-seq0252)
3/28/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0253)
4/1/2013	Novartis is providing a final summary of the case regarding a drug supply issue for study CLCZ696B2314. (eCTD-seq0254)
4/5/2013	Information Amendment: Clinical Study Report for CLCZ696B2214, PARAMOUNT - providing notification that the study report for CLCZ696B2214 (PARAMOUNT) has been submitted to IND 77318 (eCTD-Seq0255)
4/10/2013	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0256)
4/16/2013	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0257)
4/16/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0258)
4/16/2013	Safety Report PHHO2012BR018051 7-day report (PS)
4/18/2013	Safety Report PHHO2012BR018051 Follow-Up (eCTD-seq0260)
4/19/2013	Clinical Information Amendment submitted to provide an updated version of the Investigator's Brochure Edition 12 (eCTD-Seq0259)
5/1/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0263)
5/1/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0262)
5/1/2013	Safety Report PHHO2012EC015122 Follow-up (eCTD-seq0264)
5/3/2013	Submission of Transfer of Sponsor Obligation for Study CLCZ696A2124. (eCTD-seq0261)
5/3/2013	Safety Report PHHO2013BR001096 (eCTD-seq0265)

FDA Interaction Date	Content Summary
5/6/2013	Safety Report PHHO2013BR005937 7-day report (PS).
5/8/2013	Safety Report PHHO2013JP005683 (eCTD-seq0266)
5/9/2013	Safety Report PHHO2013BR001096 (eCTD-seq0267)
5/13/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0268)
5/14/2013	Safety Report PHHO2013BR005937 (eCTD-seq0270)
5/15/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0271)
5/17/2013	Clinical Study Report for CLCZ696B2107. (eCTD-seq0269)
5/17/2013	Safety Report PHHO2013CO006094 (eCTD-seq0272)
5/21/2013	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0273)
5/21/2013	Safety Report PHHO2011IS18084 Follow-up (eCTD-seq0274)
5/24/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0275)
5/29/2013	Safety Report PHHO2013JP005683 Follow-up (eCTD-seq0276)
5/30/2013	Safety Report PHHO2013US006665 (eCTD-seq0277)
5/31/2013	Safety Report PHH02010HU18329 Follow-up (eCTD-seq0278)
6/4/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0279)
6/6/2013	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0282)
6/6/2013	Safety Report PHHO2012FR018676 Follow-up (eCTD-seq0281)
6/12/2013	Clinical Information Amendment is submitted to provide the CSR for CLCZ696A2120. (eCTD-seq0280)
6/12/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0285)
6/12/2013	Safety Report PHH02013BR001096 Follow-up (eCTD-seq0284)
6/13/2013	Safety Report PHH02012EC015122 Follow-up (eCTD-seq0286)
6/14/2013	Safety Report PHHO2013JP005683; follow-up (eCTD-seq0283)
6/24/2013	Safety Report PHHO2013IL007648 Follow-Up (eCTD-seq0287)
6/27/2013	Safety Report PHHO2012EC015122 Follow-Up (eCTD-seq0288)
7/1/2013	Submission provides change in regulatory contact from Alison Mickle to Kanan Solanki. (eCTD-seq0290)
7/3/2013	Submission of revised Transfers of Sponsor Obligation for Studies CLCZ696A2119, CLCZ696A2120, CLCZ696B2107, CLCZ696B2114, CLCZ696B2122 and CLCZ696B2125. (eCTD-seq0289)
7/5/2013	Safety Report PHHO2013US006665 follow-up (eCTD-seq0293)
7/9/2013	Safety Report PHHO2013BR001096 Follow-Up (eCTD-seq0291)
7/11/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0295)
7/12/2013	Safety Report PHHO2013US006665 Follow-up (eCTD-seq0298)
7/13/2013	Safety Report PHHO2012GB017225 follow-up (eCTD-seq0296)
7/16/2013	New Protocol CLCZ696B2228, entitled A multicenter
7/17/2013	Safety Report PHHO2013IL007648 follow-up (eCTD-seq0299)
7/26/2013	Information amendment to protocol CLCZ696A2124 (eCTD-seq0300)
7/31/2013	Safety Report PHHO2013PH009418 7-Day (PS)
8/2/2013	Safety Report PHHO2012ZA008690 7-Day safety report (PS).
8/2/2013	Safety Report PHH02013ZA008690 (eCTD-seq0301)
8/6/2013	Safety Report PHHO2012FR018676 Follow-Up (eCTD-seq0303)

FDA Interaction Date	Content Summary
8/8/2013	Safety Report PHHO2012BR018051 follow-up (eCTD-seq0304)
8/8/2013	Safety Report PHHO2013DE002628 follow-up (eCTD-seq0305)
8/8/2013	Safety Report PHHO2013PH009418 (eCTD-seq0306)
8/9/2013	Safety Report PHHO2012NL008767 Follow-Up (eCTD-seq0308)
8/12/2013	Safety Report PHHO2012TL015128 Follow-Up (eCTD-req0310)
8/12/2013	Safety Report PHHO2012IT005094 Follow-Up (eCTD-seq0309)
8/14/2013	Email regarding Study D2301 Submission Timeline agreement from FDA.
8/14/2013	Clinical Information Amendment providing CSRs to studies CLCZ696B2122, CLCZ696B2114, CLCZ696B2125 and CLCZ696B2113. In addition Amendment 1 to Clinical Study Report CLCZ696B2107 is provided (eCTD-Seq0307).
8/16/2013	Submission of New Protocol CLCZ696D2301. (eCTD-seq0302)
8/19/2013	Safety Report PHHO2013CO006094 Follow-Up (eCTD-seq0311)
8/20/2013	Safety Report PHHO2012ES004570 follow-up (eCTD-seq0312)
8/20/2013	Safety Report PHHO2012IL015128 follow-up (eCTD-seq0313)
8/22/2013	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0316)
8/22/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0315)
8/22/2013	Safety Report PHHO2010TW19998 Follow-up (eCTD-seq0314)
8/23/2013	Safety Report PHHO2012BR005720 Follow-up (eCTD-seq0317)
9/5/2013	Safety Report PHHO2012IL015128 follow-up (eCTD-seq0319)
9/6/2013	Safety Report PHHO2012BR005720 follow-up (eCTD-seq0321)
9/9/2013	Safety Report PHHO2013TW011210 7-Day safety report PS.
9/10/2013	Response to FDA request dated June 18, 2012 regarding study CLCZ696D2301. (eCTD-seq0320)
9/10/2013	Safety Report PHHO2013TW011210 (eCTD-seq0322)
9/17/2013	Safety Report PHHO2013TW011210 follow up (eCTD-seq0323)
9/18/2013	Safety Report PHHO2012ES004570; follow-up (eCTD-seq0325)
9/19/2013	New Investigator for Study CLCZ696B2314 (eCTD-seq0324).
9/24/2013	Safety Report PHHO2012BR008797 follow-up (eCTD-seq0326)
9/25/2013	DSUR Annual report covering Period from 31 July 2012 through 30 July 2013 (eCTD-seq0318)
9/26/2013	New Protocol for CLCZ696B2116 entitled 'An open-label, two-period, single-sequence study to evaluate the pharmacokinetic and pharmacodynamic drug-drug interaction between orally administered LCZ696 and furosemide in healthy subjects' and TOO (eCTD-Seq0328)
10/4/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0329)
10/7/2013	Safety Report PHHO2013ES004570 follow-up (eCTD-seq0331)
10/9/2013	Clinical Information Amendment is submitted to provide notification that Amendment 1 of the Clinical Study Report for CLCZ696B2214 (PARAMOUNT) has been submitted to IND 77,318 (eCTD-seq0330).
10/10/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0332)
10/17/2013	New Investigator for Study CLCZ696D2301. (eCTD-seq0333)
10/21/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0336)

FDA Interaction Date	Content Summary
10/22/2013	Submission of change in regulatory contact from Dr. Kanan Solanki to Dr. Masha Berkhin. (eCTD-seq0335)
10/23/2013	New Investigators for Study LCZ696B2216 and Study LCZ696B2228. (eCTD-seq0334)
10/24/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0337)
10/24/2013	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0327)
10/25/2013	The purpose of this submission is to notify the Agency that following portfolio review Novartis has decided to postpone recruitment of study CLCZ696D2301; PARAGONHF (HFpEF). (eCTD-seq0339)
10/28/2013	New Investigators for Protocol LCZ696D2301 (eCTD-Seq0338)
10/30/2013	Safety Report PHHO2012HK007713 Follow-up (eCTD-seq0340)
10/31/2013	Safety Report PHHO2013BR001096 follow-up (eCTD-seq0341)
11/1/2013	Safety Report PHHO2013JP005683,followup (eCTD-seq0342)
11/8/2013	New Investigator for Study CLCZ696B2228. (eCTD-seq0344)
11/12/2013	New Investigator for Study CLCZ696D2301. (eCTD-seq0345)
11/12/2013	Novartis is providing a preclinical 15 day IND safety report to notify the Agency of a new, unexpected, and potentially adverse finding of increased levels of amyloid beta (A') in the cerebrospinal fluid (CSF), in the absence of changes of levels in the brain, which was observed during a 2-week oral investigative study in cynomolgus monkeys treated with LCZ696; the human translatability and potential consequences of these changes are currently unknown. (eCTD-seq0343)
11/20/2013	Submission is to provide the agency with the Statistical Analysis Plan (SAP) for study CLCZ696D2301 (PARAGON). (eCTD-seq0346)
11/25/2013	New Investigators for protocol LCZ696D2301 (eCTD-seq0060)
11/27/2013	Safety Report PHHO2012AR010257 Follow-up (eCTD-seq0348)
12/2/2013	Submission provides IB Edition 13 and updated ICFs. (eCTD-seq0349)
12/4/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0350)
12/10/2013	New Investigator(s) for protocol(s) CLCZ696B2228 and CLCZ696D2301 (eCTD-seq0351).
12/11/2013	Novartis is providing to the FDA the initial Pediatric Study Plan (iPSP). (eCTD-seq0352)
12/16/2013	Safety Report PHHO2012HK007713; follow-up (eCTD-seq0353)
12/19/2013	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0356)
12/19/2013	Safety Report PHHO2013TW011210 Follow-up (eCTD-seq0354)
12/31/2013	Safety Report PHHO2013ES016372; (eCTD-seq0357)
1/8/2014	New Investigators for Protocols CLCZ696B2228, CLCZ696D2301 and CLCZ696B2314 (eCTD-Seq0355)
1/16/2014	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0358)
2/5/2014	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0359)
2/12/2014	New Investigator for Studies CLCZ696B2228 and CLCZ696B2314. (eCTD-seq0360)
2/27/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0361)

FDA Interaction Date	Content Summary
2/27/2014	Safety Report PHHO2012ES004570; follow-up (eCTD-seq0362)
3/4/2014	Safety Report PHHO2011IS18084; follow-up (eCTD-seq0365)
3/7/2014	New Investigators for Protocol CLCZ696B2228 (eCTD-Seq0363)
3/7/2014	CMC Information Amendment (Seq 0364)
3/18/2014	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0367)
3/26/2014	Safety Report PHHO2014IN003017;(eCTD-seq0368)
3/27/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0371)
3/29/2014	Safety Report PHHO2013TW011210; Follow-up (eCTD-seq0370)
4/1/2014	Clinical Information Amendment which provides an updated version of the Investigator's Brochure Edition 14, dated 20-Mar-2014 (eCTD-Seq0369).
4/1/2014	Novartis is notifying FDA that on the March 28, 2014, the DMC of the CLCZ696B2314 (PARADIGM-HF) study unanimously recommended early closure of the trial for reasons of compelling efficacy following a preplanned interim analysis. (eCTD-seq0372)
4/7/2014	Safety Report PHHO2013BR001096; Follow-up (eCTD-seq0366)
4/7/2014	Safety Report PHHO2012FR018676; follow-up (eCTD-seq0374)
4/7/2014	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0373)
4/9/2014	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0375)
4/11/2014	New Investigator for protocol LCZ696B2228 (eCTD-seq0376)
4/14/2014	Submission is to provide the Agency with a proposed PARADIGM-HF Unblinding Plan for FDA review and comment. (eCTD-seq0377)
4/14/2014	FDA advice letter regarding agreement on iSPS.
4/14/2014	FDA advice information request for Novartis to submit an Agreed iPSP.
4/15/2014	Submission provides Amendment 4 to Protocol CLCZ696B2314, New Clinical Data from study CLCZ696A2126 and Pharmacology/Toxicology information. (eCTD-seq0379)
4/15/2014	The purpose of this submission is to provide the Agency with Amendment 1 to the PARADIGM-HF SAP. (eCTD-seq0378)
4/18/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0380)
4/30/2014	Telecon with the FDA to discuss our proposed PARADIGM-HF unblinding plan to facilitate early discussions with FDA and other Health Authorities (HAs).
5/8/2014	Submission provides a request for a Pre-NDA meeting with FDA. (eCTD-seq0381)
5/8/2014	FDA advice information request regarding Novartis submission containing a Statistical Analysis Plan (SAP) for Protocol CLCZ696D2301.
5/8/2014	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0386)
5/9/2014	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0387)
5/12/2014	Safety Report PHHO2012GB001045, follow-up (eCTDseq 0388)
5/13/2014	FDA granting Novartis request for a Type B meeting scheduled for June 25, 2014 to obtain concurrence from the Division on the proposed presentation and format for an electronic NDA submission.
5/13/2014	Submission is to provide the Agreed iPSP in both WORD and PDF formats. (eCTD-seq0391)

FDA Interaction Date	Content Summary
5/15/2014	CMC information Amendment is submited to introduce information on a new formulation (LCZ696 3.125mg Film Coated Tablets) (eCTD-Seq0392)
5/15/2014	Submission to provide the Agency with a new protocol, CLCZ696B2126. (eCTD-seq0385)
5/20/2014	New Investigator(s) for protocol(s) CLCZ696B2228 and Revised 1572 for protocol(s) CLCZ696B2314 (eCTD-seq0390).
5/22/2014	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0396)
5/22/2014	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0394)
5/23/2014	The purpose of this submission is to provide the FDA with a Rolling Submission Request as well as a Fast Track Designation request. (eCTD-seq0397)
5/23/2014	Novartis is submitting the Briefing Book for the Pre-NDA Type B meeting scheduled for June 25,2014. (eCTD-seq0395)
5/28/2014	Safety Report PHHO2014IT007104 (eCTD-seq0398)
5/28/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0399)
5/28/2014	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0400)
5/29/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0401)
6/3/2014	Safety Report PHHO2014IN003017; follow-up (eCTD-seq0402)
6/9/2014	Email to FDA regarding information pertaining to question 2C of the Briefing Book sent in May for the pre-NDA meeting on June 25th.
6/10/2014	Safety Report PHHO2014IT007104; follow-up (eCTD-seq0404)
6/12/2014	Amendment 1 to protocol CLCZ696B2228 (eCTD-seq0403).
6/13/2014	FDA letter notifying Novartis of agreement to their Agreed iPSP.
6/16/2014	Novartis is submitting updated version of the Investigator's Brochure Edition 15 (eCTD-seq0405)
6/16/2014	Submission is to provide the Agency with the PARADIGM-HF (CLCZ696B2314) baseline characteristics publication in the European Journal of Heart Failure (2014). (eCTD-seq0407)
6/17/2014	Safety Report PHHO2013IN007292;follow-up(eCTD-seq0408)
6/18/2014	New Investigator for Study CLCZ696B2126, CLCZ696B2228 and CLCZ696B2314. (eCTD-seq0406)
6/19/2014	Submission is to provide the Agency with a request for a proprietary name review for Entresto. (eCTD-seq0410)
6/19/2014	FDA preliminary comments for the Type B meeting scheduled June 25, 2014 to obtain concurrence from the Division on the proposed presentation and format for an electronic NDA submission.
6/19/2014	Email correspondence from FDA regarding eDISH data set.
6/23/2014	FDA has reviewed Novartis request and conclude that the required criteria have been met and are designating as a Fast Track development program the investigation of LCZ696 for the treatment of patients with heart failure with reduced Ejection Fraction (HFrEF). We have also reviewed your request for submission of portions for review of your planned marketing.
6/26/2014	Amendment 1 to Protocol CLCZ696D2301. Submission also provides a response to the SAP comments received on 5/8/2014. (eCTD-seq0409)

FDA Interaction Date	Content Summary
6/30/2014	Response to FDA's Preliminary Comments dated June 19, 2014. (eCTD-seq0411)
6/30/2014	Safety Report PHHO2014US008920 (eCTD-seq0413)
7/7/2014	Novartis is requesting a CMC Type B meeting with FDA. (eCTD-seq0412)
7/9/2014	Safety Report PHHO2013IN007292; follow-up (eCTD-seq0414)
7/10/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0416)
7/11/2014	The purpose of this submission is to provide the Agency with Amendment 2 to the PARADIGM-HF SAP. (eCTD-seq0414)
7/14/2014	Email correspondence with FDA in regards to PARADIGM-HF SAP.
7/14/2014	FDA minutes from the Type C meeting dated June 25, 2014 to obtain concurrence on the proposed presentation and format for an electronic NDA submission.
7/14/2014	In preparation for the Type B CMC meeting, enclosed are the briefing book and 2 appendices. (eCTD-0417)
7/14/2014	Safety Report PHHO2010GB15448; follow-up (eCTD-seq0418)
7/15/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0421)
7/15/2014	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0422)
7/15/2014	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0419)
7/16/2014	Email to FDA with Novartis pre-NDA meeting minutes dated June 25, 2014.
7/16/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0425)
7/16/2014	Safety Report PHHO2012IL015128 Follow-up (eCTD-seq0423)
7/16/2014	Safety Report PHHO2012PL003313 follow-up (eCTD-seq0424)
7/19/2014	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0427)
7/21/2014	Novartis is requesting a Type C meeting with FDA to share the top line data from PARADIGM-HF and continue discussions related to data driven topics. (eCTD-seq0429)
7/21/2014	Safety Report PHHO2011FI06062 Follow-up (eCTD-seq0428)
7/22/2014	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0431)
7/25/2014	FDA granting Novartis a Type C meeting scheduled September 22, 2014 to discuss the top line results of your pivotal phase III study, PARADIGM-HF.
7/25/2014	Submission is to provide the Agency with a new clinical study protocol, CLCZ696B2317. (eCTD-seq0426)
7/28/2014	New Investigator for protocol CLCZ696D2301 (eCTD-seq0430)
7/31/2014	Safety Report PHHO2012HK007713 Follow-up (eCTD-seq0433)
8/1/2014	Safety Report PHHO2013RU001322 7-Day Safety report (eCTD-seq0434)
8/4/2014	FDA granting Novartis request for a Type B meeting scheduled for Auguast 14, 2014 to discuss the Novartis approach for the supply of intermediates in the synthesis of LCZ696.
8/4/2014	Safety Report PHHO2010SK18613 7-Day Safety report (eCTD-seq0437)
8/4/2014	Safety Report PHHO2013IN010818 7-Day Safety report (eCTD-seq0438)
8/4/2014	Safety Report PHHO2013PH013229 7-day (eCTD-seq0436)
8/4/2014	Safety Report PHHO2013ZA015856 7-day (eCTD-seq0439)
8/5/2014	The purpose of this submission is to provide two clarifications in regards to the FDA meeting minutes dated June 25, 2014. (eCTD-seq0435)

FDA Interaction Date	Content Summary
8/5/2014	Safety Report PHHO2013PH013229 7-Day. (eCTD-seq0436)
c	Safety Report PHHO2012HK008472 7-Day Safety report (eCTD-seq0440)
8/5/2014	Safety Report PHHO2013SK004806 7-day (eCTD-seq0441)
8/6/2014	Novartis is submitting clinical study report for study CLCZ696A2126 (eCTD-seq0432)
8/7/2014	FDA preliminary comments to questions for the Type B meeting scheduled for August 14, 2014 to discuss the Novartis approach for the supply of intermediates in the synthesis of LCZ696.
8/7/2014	15-day IND Safety Reports for multiple Case Numbers. (eCTD-seq0447)
8/7/2014	Safety Report: PHHO2011US09057, PHHO2011DK15547, PHHO2011BR17438, PHHO2013US003391, PHHO2012US010292, PHHO2012US011722, PHHO2013ES002749, PHHO2013IN005416, PHHO2013PH000734, PHHO2013RU000937, PHHO2013EC015808, PHHO2013ES015219, PHHO2013DK004754, PHHO2013DE006467, PHHO2013CZ012058, PHHO2013CO012535, PHHO2013BR008240, PHHO2013BE006968, PHHO2012ZA017859, PHHO2012ZA009538, PHHO2012ZA001868, PHHO2012US015945, PHHO2012US008541, PHHO2012US005669, PHHO2012TW017726, PHHO2012BR007861 (eCTD-seq0445)
8/7/2014	Safety Report: PHHO2012RU012030, PHHO2012PL012082, PHHO2013IN015895, PHHO2013NL016945, PHHO2013NL007092, PHHO2012PL009369, PHHO2012PE008660, PHHO2012PE002268, PHHO2012PA012287, PHHO2012PA012287, PHHO2012MX012696, PHHO2012MX005808, PHHO2012KR013885, PHHO2012GB007230, PHHO2012GB002757, PHHO2012FR006226, PHHO2012FI005049, PHHO2012EE018381, PHHO2012DK013888, PHHO2012DE013416, PHHO2012DE011372, PHHO2012DE004433, PHHO2012CZ015409, PHHO2012CA010107, PHHO2012BR017241, PHHO2012BR016850, PHHO2012BR016818, PHHO2012BR008516, PHHO2012BR005262, PHHO2012BR002423, PHHO2012BE010457 (eCTD-seq0446)
8/7/2014	Safety Report PHHO2012BR007861 7-Day safty report (eCTD-seq0444)
8/11/2014	P Safety Report HHO2012RU017982; 7-Day report (eCTD-seq0448)
8/11/2014	Safety Report PHHO2013PH013229. (eCTD-seq0449)
8/11/2014	Safety Report PHHO2013CO005157 7-Day safety report (eCTD-seq0451)
8/12/2014	Safety Report PHHO2013IN010818 (eCTD-seq0455)
8/12/2014	Safety Report PHHO2010SK18613 (eCTD-seq0454)
8/12/2014	Safety Report PHHO2013TR009017 (eCTD-seq0452)
8/12/2014	Safety Report PHHO2013SK008706 (eCTD-seq0453)
8/12/2014	Safety Report PHHO2010HU17146 Follow-up (eCTD-seq0458)
8/12/2014	Safety Report PHHO2013ZA015856. (eCTD-seq0450)
8/13/2014	Novartis is informing the Agency that CMC information in referenced IND 77,318 has been updated. (eCTD-seq0457)

FDA Interaction Date	Content Summary
8/13/2014	Safety Report: PHHO2011TW05094,PHHO2013BR009267,PHHO2013IN001817,PHHO2013IN001851,PHHO2013IN013024,PHHO2013IN015054,PHHO2014PH000579 Follow-up (eCTD-seq0459)
8/14/2014	Safety Report PHHO2013SK004806 (eCTD-seq0460)
8/15/2014	Safety Report PHHO2010IN16648 (eCTD-seq0472)
8/15/2014	Safety Report PHHO2010IT15164 (eCTD-seq0471)
8/15/2014	Safety Report PHHO2011IN11799; follow-up (eCTD-seq0470)
8/15/2014	Safety Report PHHO2012AR010257; follow-up (eCTD-seq0469)
8/15/2014	Safety Report PHHO2012GB017225; follow-up (eCTD-seq0468)
8/15/2014	Safety Report PHHO2012IN017070 (eCTD-seq0466)
8/15/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0467)
8/17/2014	Safety Report PHHO2013CO005157 (eCTD-seq0474)
8/18/2014	Safety Report PHHO2014RU006393; 7-Day safety report (eCTD-seq0473)
8/20/2014	New Investigator LCZ696D2301 (Seq 0456)
8/20/2014	Safety Report: PHHO2011TW05094, PHHO2013BR009267, PHHO2013IN001817, PHHO2013IN001851, PHHO2013IN013024, PHHO2013IN015054, PHHO2014PH000579 (eCTD-seq0476)
8/20/2014	Safety Report PHHO2012RU017982 (eCTD-seq0475)
8/21/2014	This submission provides responses to FDA's preliminary comments to the pre-NDA Type B CMC briefing document. (eCTD-seq0464)
8/21/2014	Safety Report PHHO2012PH006218 (eCTD-seq0478)
8/21/2014	Safety Report PHHO2013DE015885 (eCTD-seq0479)
8/25/2014	Safety Report PHHO2013IN010949 (eCTD-seq0480)
8/25/2014	Safety Report PHHO2014RU006393 (eCTD-seq0481)
8/25/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0482)
9/1/2014	Safety Report PHHO2012US009119 7-Day safety report (eCTD-seq0486)
9/3/2014	Safety Report PHHO2011PL08780 (eCTD-seq0489)
9/3/2014	Safety Report PHHO2011PL08780; 7-Day safety report (eCTD-seq0483)
9/4/2014	The purpose of this submission is to provide the FDA with a proposal for the 120 day safety update. (eCTD-seq0484)
9/4/2014	The purpose of this submission is to provide the Agency with the New England Journal of Medicine article titled 'Angiotensin'Neprilysin Inhibition versus Enalapril in Heart Failure'. (eCTD-seq0488)
9/4/2014	Novartis has some clarifications regarding the additional requests # 8, 18, and 30 contained in the Preliminary comments. (eCTD-seq0487)
9/5/2014	Safety Report PHHO2014US008920; follow-up (eCTD-seq0490)
9/8/2014	New Investigator(s) for protocol(s) CLCZ696D2301 (eCTD-seq0485)
9/8/2014	New protocol for CLCZ696B2318M (eCTD-seq0491)

FDA Interaction Date	Content Summary
9/8/2014	Submission provides an follow-up to the August 14th, Type B CMC meeting with FDA to discuss Novartis's approach for the supply of intermediates in the synthesis of LCZ696-ABA. (eCTD-seq0492)
9/8/2014	Safety Report PHHO2012US009119 (eCTD-seq0493)
9/12/2014	Novartis telecon report regarding the Extended Access Program.
9/15/2014	The purpose of this submission is to provide the Agency with slides for the PARADIGM-HF Top Line Data Review Meeting on September 22, 2014. (eCTD-seq0494)
9/15/2014	Safety Report PHHO2014ZA009494 (eCTD-seq0495)
9/17/2014	Email to and from FDA regarding follow-up on the CMC meeting.
9/18/2014	FDA acknowledgement letter of Novartis Treatment Protocol.
9/18/2014	FDA minutes from the Type B meeting dated August 14, 2014 with Novartis to seek an agreement with the Agency on Novartis' approach for the supply of intermediates in the synthesis of LCZ696-ABA.
9/24/2014	New Investigators for protocol CLCZ696D2301 (eCTD-seq0496)
9/24/2014	Safety Report PHHO2012EC015122; follow-up (eCTD-seq0497)
9/26/2014	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0498)
9/29/2014	DSUR Annual report submission covering the period July 31, 2013 through July 30, 2014 (eCTD-Seq0477).
10/2/2014	FDA advice information request regarding amendment dated September 4, 2014, containing clarifications in response to FDA's pre-NDA preliminary comments dated June 19, 2014.
10/2/2014	Email from FDA with Advice-Information Request letter.
10/3/2014	New Investigator for Protocol CLCZ696D2301. (eCTD-seq0500)
10/7/2014	Novartis is submitting an amendment to the DSUR by providing Regional Appendix 2 (List of subjects who died during the reporting period) and Appendix 3 (List of subjects who dropped out of studies during the reporting period). (eCTD-seq0499)
10/8/2014	Novartis telecon report regarding the LCZ696 Extended Access Program (B2318M) is safe to proceed in the US.
10/9/2014	Safety Report PHHO2014GB004572 (eCTD-seq0501)
10/14/2014	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0503)
10/15/2014	Safety Report PHHO2013CN003844 7-Day safety report (eCTD-seq0504)
10/15/2014	Safety Report PHHO2013CN003844 (eCTD-seq0505)
10/16/2014	Safety Report PHHO2013CO005157;follow-up (eCTD-seq0506)
10/21/2014	New Investigators for protocols CLCZ696D2301, CLCZ696D2314 (eCTD-seq0502)
10/22/2014	FDA minutes from the Type C Top-Line Results meeting dated September 22, 2014 to discuss top-line results of your pivotal phase III study, PARADIGMHF.
10/24/2014	Safety Report PHHO2012GB006694; follow-up (eCTD-seq0508)
10/27/2014	Slides for Friday's TC regarding Pediatric.
10/28/2014	20141028 0507 New Investigator D2301,B2314 (Seq 507)
10/31/2014	Novartis telecon report regarding the PPSR strategy for LCZ696.
11/10/2014	amended Treatment Protocol to protocol CLCZ696B2318M (eCTD-seq0509).

FDA Interaction Date	Content Summary
11/13/2014	The purpose of this submission is to provide the draft PARAGON-HF protocol amendment for FDA review. (eCTD-seq0512)
11/13/2014	Follow up to the August 14, 2014 Type B CMC Meeting.
11/18/2014	New Investigators for protocols CLCZ696D2301, CLCZ696B2317 (eCTD-seq0513)
11/21/2014	FDA letter for proprietary name Entresto accepted.
12/18/2014	New Investigator(s) for protocol(s) CLCZ696D2301, CLCZ696B2317 (eCTD-seq0515)
12/22/2014	Clinical information amendment to submit the Clinical Study Report for CLCZ696B2228 (eCTD-seq0516)
12/22/2014	Clinical Information Amendment to submit the Clinical Study Report for CLCZ696B2314 (Paradigm-HF) (eCTD-seq0517)
1/14/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0518).
1/23/2015	The purpose of this submission is to submit the Clinical Study Report for CLCZ696B2126 (eCTD-Seq0519)
1/26/2015	Amendment 2 for Protocol CLCZ696B2214. (eCTD-seq0520)
1/28/2015	FDA information request regarding study D2301.
1/29/2015	Submission of updated Transfer of Sponsor Obligations version 02, for Study LCZ696B2317. (eCTD-seq0521)
2/2/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0522).
2/6/2015	The purpose of this submission is to provide the Agency with a Proposed Pediatric Study Request (PPSR). (eCTD-seq0523)
2/24/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0524).
2/26/2015	Information Amendment to the IND 77,318 Seq No: 0273 (Cross-reference to IND 104,628) submitted on February 26, 2015 to inform the Agency regarding a typographical error in the description of Valsartan 80mg film-coated tablet that were used as a comparator in LCZ696 clinical study D2301 (eCTD-Seq0525)
3/4/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0526).
3/25/2015	Reference is also made to original protocol submission for study CLCZ696B2317, submitted to FDA on July 25, 2014 (S-0426).
3/26/2015	Clinical information amendment to submit the Clinical Study Report and Amendment 1 for CLCZ696A2201 and CLCZ696A2223 (eCTD-seq0527)
3/27/2015	Response to FDA request dated January 28, 2015 regarding PARAGON-HF cognitive function assessment. (eCTD-seq0530)
4/1/2015	Protocol Amendment- New Investigator (eCTD-seq 0529)
4/10/2015	Protocol amendment - New Protocol for the study CLCZ696B2132 (eCTD-seq0532)
4/13/2015	FDA has reviewed Novartis' proposed pediatric study request and are unable to issue a Written Request based on the submission.
4/17/2015	Clinical Information Amendment Updated IB Ed 16 (Seq 0531)

FDA Interaction Date	Content Summary
4/24/2015	New Investigator CLCZ696D2301 (Seq 0533)
5/14/2015	Submission provides Amendment 2 for Protocol CLCZ696D2301 along with revised TOO. (eCTD-seq0534)
5/14/2015	PROTOCOL AMENDMENT: Change in Protocol CLCZ696B2317 Amendment 2 (eCTD-seq0535)
5/18/2015	New Investigator(s) for protocol(s) CLCZ696D2301, CLCZ696B2317 and CLCZ696B2132 (eCTD-seq0536)
5/28/2015	PHHO2015GB008891. (eCTD-seq0538)
6/3/2015	Submission provides the response to the 'inadequate study request' letter and an updated PPSR that incorporates all of the changes from the response. (eCTD-seq0537)
6/8/2015	Submission is to provide a letter from Dr. Robert Shaddy, a pediatric cardiologist, sharing his perspective and support on the proposed Novartis pediatric study. (eCTD-seq0540)
6/8/2015	Amendment 1 to protocol CLCZ696B2132 (eCTD-seq0539).
6/12/2015	Amendment to Protocol CLCZ696D2301 (eCTD-seq0541)
6/18/2015	Clinical Information Amendment (eCTDseq-0542)
7/6/2015	New Protocol CLCZ696B2130 (eCTD-seq0545)
7/13/2015	New Investigators for Protocol LCZ696D2301 and 1572 Changes (eCTD-Seq0546)

APPENDIX F

NDA Chronology

FDA Interaction Date	Content Summary
9/30/2014	Submission of part 1 Original NDA for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. (eCTD-seq0000)
10/29/2014	Novartis is submitting part 2 of the rolling NDA for LCZ696 for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. (eCTD-seq0001)
11/20/2014	FDA email request regarding an updated 356h form that list all manufacturing and testing sites with their current responsibilities.
11/25/2014	Response to FDA request dated November 20, 2014 regarding updated 356h form. (eCTD-seq0003)
12/15/2014	Amendment to pending application for NDA 207620 (eCTD-seq0004)
12/17/2014	Novartis is submitting part 3 of the rolling NDA for LCZ696 for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. LCZ696 was granted Fast Track designation on June 23, 2014. (eCTD-seq0002)
12/17/2014	FDA email request for CMC information.
1/5/2015	FDA acknowledgement letter for Original NDA Part 3 dated December 17, 2014.
1/6/2015	FDA request for Novartis to provide a description for categorical variables in your analysis datasets (e.g. BLFLG_1C, PSTB_1C, Period, Phase_1c, TRTC, TRT_1C in the AAEV dataset).
1/13/2015	Email correspondence with FDA in regards to Novartis' request for review of the proprietary name, Entresto.
1/15/2015	Reference is made to an email request received from the Agency on January 12, 2015 requesting a submission of the cover letter to include the statement 'REQUEST FOR PROPRIETARY NAME REVIEW' in bold, capital letters on the first page of each submission as outlined in the 'Guidance for Industry. (eCTD-seq0006)
1/16/2015	Response to FDA request dated December 16, 2014 regarding CMC information. (eCTD-seq0005)
1/16/2015	Submission is to provide updated stability data on LCZ696 film coated tablets. (eCTD-seq0007)
1/16/2015	Email request from FDA for Novartis to complete the ClinPharm and Cardiac Safety Table.
1/20/2015	Response to FDA request dated January 13, 2015 regarding dataset. (eCTD-seq0008)
1/22/2015	Response to FDA request dated January 16, 2015 regarding PK Datasets. (eCTD-seq0009)
1/28/2015	Response to FDA email request dated January 6, 2015 regarding Clinical/Stats. (eCTD0seq0010)
1/28/2015	Response to FDA email request dated January 16, 2015 requesting completion of the Clinical Pharmacology and Cardiac Safety Table. (eCTD-seq0011)
1/30/2015	Response to FDA request dated January 26, 2015 regarding Clinical Pharmacology information. (eCTD-seq0012)
2/2/2015	Response to FDA request dated January 27, 2015. (eCTD-seq0013)

FDA Interaction Date	Content Summary
2/5/2015	Response to FDA request dated February 29, 2015 regarding SAS Codes. (eCTD-seq0014)
2/9/2015	FDA is notifying Novartis that proprietary name Entresto is acceptable.
2/11/2015	Response to FDA request dated February 3, 2015 for clinical information. (eCTD-seq0016)
2/12/2015	FDA has completed their filing review and have determined that the application is sufficiently complete to permit a substantive review.
2/18/2015	Response to FDA request dated February 10, 2015 regarding Clinical information. (eCTD-seq0015)
2/20/2015	Response to FDA request dated February 13, 2015 regarding Clinical information. (eCTD-seq0017)
2/24/2015	Response to FDA request dated February 13, 2015 in regards to Biopharmaceutics. (eCTD-seq0018)
2/26/2015	Response to FDA request dated February 19, 2015 for Clinical information. (eCTD-seq0019)
3/3/2015	Response to FDA request dated February 19, 2015 for Clinical information. (eCTD-seq0020)
3/10/2015	Response to FDA request dated February 12, 2015 for Clinical information. (eCTD-seq0021)
3/12/2015	Response to FDA request dated February 27, 2015 regarding Clinical Information. (eCTD-seq0022)
3/13/2015	Response to FDA request dated February 19, 2015 for CMC information. (eCTD-seq0023)
3/17/2015	Response to FDA request dated March 9, 2015 for Clinical Information. (eCTD-seq0024)
4/2/2015	Response to FDA request dated March 26, 2015 for 10 patient narratives. (eCTD-seq0027)
4/3/2015	Response to FDA requests dated March 20th and March 30th 2015 regarding Clinical information. (eCTD-seq0026)
4/7/2015	FDA Mid-Cycle Communication letter regarding telecon dated March 19, 2015 to provide Novartis with an update on the status of the review of your application.
4/8/2015	Response to FDA request dated March 31, 2015 for CMC information. (eCTD-seq0028)
4/9/2015	Novartis telecon report regarding drug substance and labeling LCZ696 as a fixed dose combination.
4/15/2015	Response to FDA request dated March 27, 2015 for CMC information. (eCTD-seq0029)
4/15/2015	Submission is to provide the 120-Day Safety Update. (eCTD-seq0025)
4/16/2015	Novartis is submitting an request for a Type C CMC only meeting. (eCTD-seq0030)

FDA Interaction Date	Content Summary
4/20/2015	Response to FDA request dated April 14, 2015 to provide narratives for selected patients from PARADIGM-HF trial (CLCZ696B2314) with events of pregnancy and/or with spontaneous abortion. (eCTD-seq0031)
4/21/2015	Novartis is submitting the Briefing Book for the Type A CMC meeting. (eCTD-seq0032)
4/24/2015	Novartis is submitting a Request for Proprietary Name Review of Entresto. (eCTD-seq0033)
4/28/2015	Novartis telecon report regarding labeling LCZ696 as a fixed dose combination follow-up meeting.
4/29/2015	Response to FDA email request dated April 22, 2015 for Clinical information. (eCTD-seq0035)
5/1/2015	Response to FDA request dated April 21, 2015 regarding Clinical information. (eCTD-seq0034)
5/4/2015	Response to FDA request dated April 3, 2015 regarding updated labeling that removes reference to a MedGuide and replaces it with PPI. (eCTD-seq0036)
5/6/2015	Response to FDA request for Clinical information during the March 19, 2015 MCC meeting where FDA noted that a post marketing study may be needed to better characterize the risk of serious angioedema events in black patients treated with LCZ696 in the United States. (eCTD-seq0038)
5/7/2015	Response to FDA request dated April 24, 2015 for Clinical information. (eCTD-seq0037)
5/13/2015	Response to FDA request dated March 27, 2015 for updated CTD modules. (eCTD-seq0039)
5/15/2015	Response to FDA request dated March 27, 2015 requesting revised carton and container labeling. (eCTD-seq0040)
5/15/2015	Response to FDA request dated March 27, 2015 regarding labeling. (eCTD-seq0041)
5/20/2015	Email from FDA with attached labeling comments and PDF of labeling.
5/20/2015	FDA comments regarding labeling.
5/22/2015	Response to FDA request dated May 12, 2015 regarding labeling. (eCTD-seq0042)
5/26/2015	Response to FDA request dated May 15, 2015 for CMC information. (eCTD-seq0043)
5/26/2015	FDA Background Package for the LCM scheduled for June 8, 2015.
6/2/2015	Response to FDA request dated May 15, 2015 for updated CMC modules. (eCTD-seq0045)
6/3/2015	Response to FDA request dated May 21, 2015 to provide data needed to populate the ?Drug Trials Snapshots? website. (eCTD-seq0044)
6/4/2015	Submission provides Updated Proposed Labeling. (eCTD-seq0046)
6/8/2015	Email from FDA with comments regarding Novartis proposed post marketing study plan.

FDA Interaction Date	Content Summary
6/11/2015	Response to FDA request dated June 9, 2015 providing comments on Entresto carton, blister and container labeling. (eCTD-seq0048)
6/12/2015	Response to FDA request dated June 5, 2015 for Clinical information. (eCTD-seq0047)
6/15/2015	Submission is to follow-up to the clarification teleconference held on 11-June-2015 between FDA and Novartis representatives on the topic of LCZ696 50mg Film-coated tablets dissolution specifications. (eCTD-seq0049)
6/19/2015	The purpose of this submission is to send the final agreed timelines + rationale (already agreed via email with Alexis Childers on June 18th). (eCTD-seq0051)
6/19/2015	FDA has completed their review of the proposed proprietary name, Entresto and have concluded that it is conditionally acceptable.
6/23/2015	FDA request in regards to the PMC.
6/25/2015	Response to FDA request dated June 23, 2015 regarding CMC information. (eCTD-seq0052)
6/26/2015	Submission provides updated proposed labeling in response to FDA comments. (eCTD-seq0050)
7/1/2015	The purpose of this submission is to provide an official updated label in response to the comments. (eCTD-seq0053)
7/2/2015	The purpose of this submission is to provide updated labeling in response to FDA comments (eCTD-seq0054)
7/6/2015	Response to FDA request date July 6, 2015 requiring a post-marketing requirement (PMR) to assess cognitive function. (eCTD-seq0056)
7/7/2017	Approval of Entresto
7/9/2015	FDA approval of the shelf life for Entresto film-coated tablets packaged in HDPE bottles is 24 months and packaged in PVC blisters is 30 months.
7/16/2015	Submission of final printed labeling in SPL format. (eCTD-seq0055)
7/24/2015	FDA minutes from the LCM dated June 3, 2015.

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United States Patent and Trademark Office
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www.uspto.gov

Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

April 28, 2016

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 7,468,390 was filed on September 1, 2015, under 35 U.S.C. § 156. Please note that patent term extension applications for U.S. Patent No. 8,101,659, U.S. Patent No. 8,404,744, U.S. Patent No. 8,796,331 and U.S. Patent No. 8,877,938 for NDA 207620 for the human drug product ENTRESTO® (sacubitril and valsartan) were filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The assistance of your Office is requested in confirming that the product identified in the application, ENTRESTO® (sacubitril and valsartan), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

Department of Health and Human Services | Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002

AUG 25 2016

Re: ENTRESTO
Patent Nos.; 7468,390; 8,101,659; 8,404,744;
8,796,331; and 8,877,938
Docket Nos.: FDA-2016-E-1851;
FDA-2016-E-1878; FDA-2016-E-1879;
FDA-2016-E-1880; and FDA-2016-E-1882

The Honorable Michelle K. Lee
UnderSecretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Lee:

This is concerning the applications for patent term extension for U.S. Patent Nos. 7468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938, filed by Novartis Pharmaceuticals Corporation, under 35 U.S.C. 156. The human drug product claimed by the patent is ENTRESTO (sacubitril and valsartan), which was assigned new drug application (NDA) No. 207620.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that ENTRESTO (sacubitril and valsartan) is a combination product. One of the active ingredients, valsartan, has been previously approved for commercial marketing or use as a single ingredient, Novartis Pharmaceuticals, Diovan, NDA 20-665, or as a combination with other active ingredients in several products (e.g., Novartis Pharmaceuticals, Diovan HCT, NDA 20-818, ExForge, NDA 21-990, and others). The second active ingredient, sacubitil represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1).

The NDA was approved on July 7, 2015, which makes the submission of the patent term extension application on September 1, 2015, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

UNITED STATES PATENT AND TRADEMARK OFFICE

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Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

FEB 14 2017

Attention: Beverly Friedman

Dear Sir:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 7,468,390. The application was filed on September 1, 2015, under 35 U.S.C. § 156. Please note that patent term extension applications for U.S. Patent No. 8,877,938; U.S. Patent No. 8,796,331; U.S. Patent No. 8,404,744 and U.S. Patent No. 8,101,659 based on the regulatory review of NDA 207620 for the human drug product ENTRESTO® (sacubitril & valsartan) were filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The patent claims a product which has been subject to review under the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

RE: ENTRESTO® (sacubitril & valsartan)
Docket No. FDA-2016-E-1851

U.S. FOOD & DRUG ADMINISTRATION

AUG 14 2017

Re: ENTRESTO
Patent Nos.: 7,468,390;
8,101,659; 8,404,744; 8,796,331;
and 8,877,938
Docket Nos.: FDA-2016-E-1851;
FDA-2016-E-1878; FDA-2016-E-
1879; FDA-2016-E-1880; AND
FDA-2016-E-1882

Acting Director
United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 7,468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938, filed by Novartis Pharmaceuticals Corporation, under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the applications and have determined the regulatory review period for ENTRESTO (sacubitril and valsartan), the human drug product claimed by the patents.

The total length of the regulatory review period for ENTRESTO is 3,148 days. Of this time, 2,945 days occurred during the testing phase and 203 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: November 25, 2006.

   Novartis Pharmaceuticals Corporation claims that April 8, 2007, is the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was November 25, 2006, which was 30 days after FDA receipt of an earlier IND.

2. The date the application was initially submitted with respect to the new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act: December 17, 2014.

   FDA has verified the applicant's claim that the new drug application (NDA) for ENTRESTO (NDA 207620) was submitted on December 17, 2014.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002
www.fda.gov

3. The date the application was approved: July 7, 2015.

FDA has verified the applicant's claim that NDA 207620 was approved on July 7, 2015.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents PharmaOne Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of USPTO may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA has approved for marketing the human drug product ODOMZO (sonidegib phosphate). ODOMZO is indicated for the treatment of adult patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. Subsequent to this approval, the USPTO received a patent term restoration application for ODOMZO (U.S. Patent No. 8,178,563) from Novartis AG, and the USPTO requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated July 28, 2016, FDA advised the USPTO that this human drug product had undergone a regulatory review period and that the approval of ODOMZO represented the first permitted commercial marketing or use of the product. Thereafter, the USPTO requested that FDA determine the product's regulatory review period.

II. Determination of Regulatory Review Period

FDA has determined that the applicable regulatory review period for ODOMZO is 2,414 days. Of this time, 2,112 days occurred during the testing phase of the regulatory review period, while 302 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)) became effective:* December 15, 2008. FDA has verified the applicant's claim that December 15, 2008, is the date the investigational new drug application (IND) became effective.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* September 26, 2014. FDA has verified the applicant's claim that the new drug application (NDA) for ODOMZO (NDA 205266) was initially submitted on September 26, 2014.

3. *The date the application was approved:* July 24, 2015. FDA has verified the applicant's claim that NDA 205266 was approved on July 24, 2015.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the USPTO applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 169 days of patent term extension.

III. Petitions

Anyone with knowledge that any of the dates as published are incorrect may submit either electronic or written comments and, under 21 CFR 60.24, ask for a redetermination (see **DATES**). Furthermore, as specified in § 60.30 (21 CFR 60.30), any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition comply with all the requirements of § 60.30, including but not limited to: Must be timely (see **DATES**), must be filed in accordance with § 10.20, must contain sufficient facts to merit an FDA investigation, and must certify that a true and complete copy of the petition has been served upon the patent applicant. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Submit petitions electronically to *https://www.regulations.gov* at Docket No. FDA–2013–S–0610. Submit written petitions (two copies are required) to the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Dated: February 6, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–02658 Filed 2–8–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2016–E–1851; FDA–2016–E–1878; FDA–2016–E–1879; FDA–2016–E–1880; and FDA–2016–E–1882]

Determination of Regulatory Review Period for Purposes of Patent Extension; ENTRESTO

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency) has determined the regulatory review period for ENTRESTO and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of the U.S. Patent and Trademark Office (USPTO), Department of Commerce, for the extension of a patent which claims that human drug product.

DATES: Anyone with knowledge that any of the dates as published (in the **SUPPLEMENTARY INFORMATION** section) are incorrect may submit either electronic or written comments and ask for a redetermination by April 10, 2018. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by August 8, 2018. See "Petitions" in the **SUPPLEMENTARY INFORMATION** section for more information.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before April 10, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of April 10, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

• *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*

• If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

• *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

• For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket Nos. FDA–2016–E–1851; FDA–2016–E–1878; FDA–2016–E–1879; FDA–2016–E–1880; and FDA–2016–E–1882 for "Determination of Regulatory Review Period for Purposes of Patent Extension; ENTRESTO." Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with § 10.20 (21 CFR 10.20) and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6250, Silver Spring, MD 20993, 301–796–3600.

SUPPLEMENTARY INFORMATION:

I. Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of USPTO may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA has approved for marketing the human drug product ENTRESTO (sacubitril and valsartan). ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association Class II–IV) and reduced ejection fraction. Subsequent to this approval, the USPTO received patent term restoration applications for ENTRESTO (U.S. Patent Nos. 7,468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938) from Novartis Pharmaceuticals Corporation, and the USPTO requested FDA's assistance in determining the patents' eligibility for patent term restoration. In a letter dated August 25, 2016, FDA advised the USPTO that this human drug product had undergone a regulatory review period and that the approval of ENTRESTO represented the first permitted commercial marketing or use of the product. Thereafter, the USPTO requested that FDA determine the product's regulatory review period.

II. Determination of Regulatory Review Period

FDA has determined that the applicable regulatory review period for ENTRESTO is 3,148 days. Of this time, 2,945 days occurred during the testing phase of the regulatory review period, while 203 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(i)) became effective:* November 25, 2006. Novartis Pharmaceuticals Corporation claims that April 8, 2007, is the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was November 25,

2006, which was 30 days after FDA receipt of an earlier IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* December 17, 2014. FDA has verified the applicant's claim that the new drug application (NDA) for ENTRESTO (NDA 207620) was initially submitted on December 17, 2014.

3. *The date the application was approved:* July 7, 2015. FDA has verified the applicant's claim that NDA 207620 was approved on July 7, 2015.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the USPTO applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks 1,296 days, 732 days, 519 days, 270 days or 225 days of patent term extension.

III. Petitions

Anyone with knowledge that any of the dates as published are incorrect may submit either electronic or written comments and, under 21 CFR 60.24, ask for a redetermination (see **DATES**). Furthermore, as specified in § 60.30 (21 CFR 60.30), any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition must comply with all the requirements of § 60.30, including but not limited to: Must be timely (see **DATES**), must be filed in accordance with § 10.20, must contain sufficient facts to merit an FDA investigation, and must certify that a true and complete copy of the petition has been served upon the patent applicant. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Submit petitions electronically to *https://www.regulations.gov* at Docket No. FDA–2013–S–0610. Submit written petitions (two copies are required) to the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Dated: February 5, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–02592 Filed 2–8–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2017–N–6145]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by March 12, 2018.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202–395–7285, or emailed to *oira_submission@omb.eop.gov*. All comments should be identified with the OMB control number 0910–0566. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Ila S. Mizrachi, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–7726, *PRAStaff@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine—21 CFR 10.75

OMB Control Number 0910–0566—Extension

The Center for Veterinary Medicine's (CVM's) Guidance for Industry (GIF) #79, "Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine" (*https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052393.pdf*), describes the process by which CVM formally resolves disputes relating to scientific controversies. A scientific controversy involves issues concerning a specific product regulated by CVM related to matters of technical expertise and requires specialized education, training, or experience to be understood and resolved. The guidance details information on how CVM intends to apply provisions of existing regulations regarding internal review of Agency decisions. In addition, the guidance outlines the established procedures for persons who are sponsors, applicants, or manufacturers of animal drugs or other products regulated by CVM that wish to submit a request for review of a scientific dispute. When a sponsor, applicant, or manufacturer has a scientific disagreement with a written decision by CVM, they may submit a request for a review of that decision by following the established procedures discussed in the guidance.

CVM encourages applicants to begin the resolution of science-based disputes with discussions with the review team/group, including the Team Leader or Division Director. The Center prefers that differences of opinion regarding science or science-based policy be resolved between the review team/group and the applicant. If the matter is not resolved by this preferred method then CVM recommends that the applicant follow the procedures in GFI #79.

In the **Federal Register** of October 27, 2017 (82 FR 49836), FDA published a 60-day notice requesting public comment on the proposed collection of information. We received no comments.

FDA estimates the burden of this collection of information as follows:

U.S. FOOD & DRUG ADMINISTRATION

Re: ENTRESTO
Patent Nos. 7,468,390; 8,101,659;
8,404,744; 8,796,331;
and 8,877,938
Docket Nos. FDA-2016-E-1851
FDA-2016-E-1878
FDA-2016-E-1879
FDA-2016-E-1880
FDA-2016-E-1882

The Honorable Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

JUL 03 2019

Dear Director Iancu:

This is in regard to the patent term extension applications for U.S. Patent Nos. 7,468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938 filed by Novartis Pharmaceuticals Corporation under 35 U.S.C. § 156. The patents claim ENTRESTO (sacubitril and valsartan), a human drug product reviewed in new drug application (NDA) 207620.

In the February 9, 2018, issue of the Federal Register (83 Fed. Reg. 5781), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before August 8, 2018, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Building 51, Room 6250
Silver Spring, MD 20993
www.fda.gov

Please let me know if we can provide further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: David Kurlandsky
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