(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 January 2005 (27.01.2005)

WIPO | PCT

(10) International Publication Number
WO 2005/007081 A9

(51) International Patent Classification:
A61K 31/19 (2006.01) *A61K 31/557* (2006.01)

(21) International Application Number:
PCT/US2004/016401

(22) International Filing Date:
24 May 2004 (24.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/472,407 22 May 2003 (22.05.2003) US

(71) Applicant *(for all designated States except US)*: **UNITED THERAPEUTICS CORPORATION** [US/US]; 1735 Connecticut Avenue, N.W., Third Floor, Washington, D.C. 20009 (US).

(72) Inventors; and

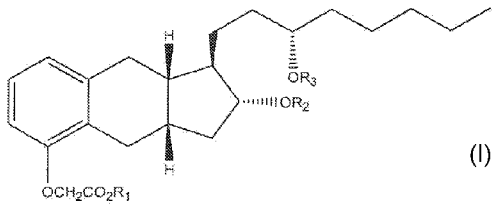
(75) Inventors/Applicants *(for US only)*: **PHARES, Ken** [US/US]; 194 Amber Wood Run, Chapel Hill, NC 27516 (US). **MOTTOLA, David** [US/US]; One Park Drive, Research Triangle Park, NC 27709 (US).

(74) Agents: **MAEBIUS, Stephen, B.** et al.; FOLEY & LARDNER LLP, Washington Harbour, 3000 K Street N.W., Suite 500, Washington, DC 20007-5143 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS



(I)

FIGURE 1A

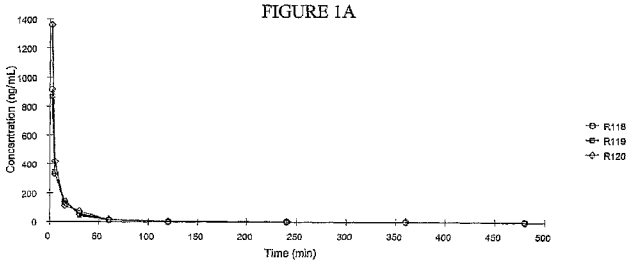
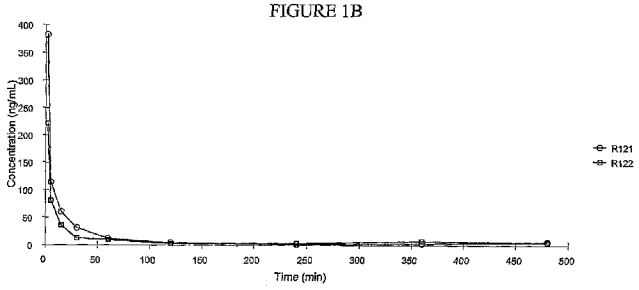


FIGURE 1B



(57) Abstract: This invention pertains generally to prostacyclin analogs and methods for their use in promoting vasodilation, inhibiting platelet aggregation and thrombus formation, stimulating thrombolysis, inhibiting cell proliferation (including vascular remodeling), providing cytoprotection, preventing atherogenesis and inducing angiogenesis. Generally, the compounds and methods of the present invention increase the oral bioavailability and circulating concentrations of treprostinil when administered orally. Compounds of the present invention have formula (I).

WO 2005/007081 A9

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(88) **Date of publication of the international search report**:
14 April 2005

(48) **Date of publication of this corrected version**:
26 January 2017

(15) **Information about Correction**:
see Notice of 26 January 2017

COMPOUNDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application claims benefit of U.S. Provisional Application Serial No. 60/472,407, filed on May 22, 2003, the entire contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

This invention pertains generally to prostacyclin analogs and methods for their use in promoting vasodilation, inhibiting platelet aggregation and thrombus formation, stimulating thrombolysis, inhibiting cell proliferation (including vascular remodeling), providing cytoprotection, preventing atherogenesis and inducing angiogenesis. Through these prostacyclin-mimetic mechanisms, the compounds of the present invention may be used in the treatment of/for: pulmonary hypertension, ischemic diseases (e.g., peripheral vascular disease, Raynaud's phenomenon, Scleroderma, myocardial ischemia, ischemic stroke, renal insufficiency), heart failure (including congestive heart failure), conditions requiring anticoagulation (e.g., post MI, post cardiac surgery), thrombotic microangiopathy, extracorporeal circulation, central retinal vein occlusion, atherosclerosis, inflammatory diseases (e.g., COPD, psoriasis), hypertension (e.g., preeclampsia), reproduction and parturition, cancer or other conditions of unregulated cell growth, cell/tissue preservation and other emerging therapeutic areas where prostacyclin treatment appears to have a beneficial role. These compounds may also demonstrate additive or synergistic benefit in

combination with other cardiovascular agents (e.g., calcium channel blockers, phosphodiesterase inhibitors, endothelial antagonists, antiplatelet agents).

BACKGROUND OF THE INVENTION

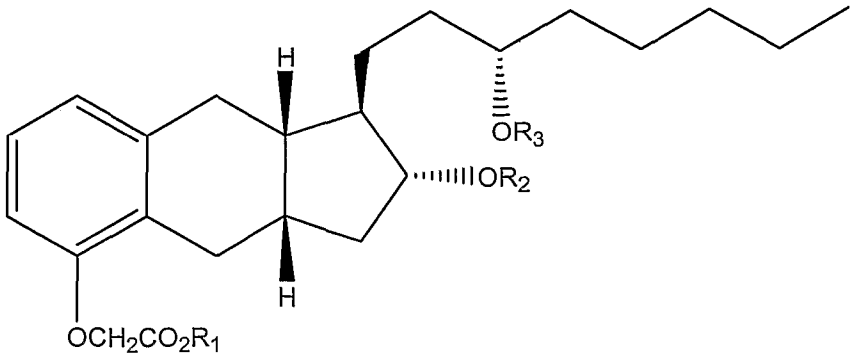
Many valuable pharmacologically active compounds cannot be effectively administered orally for various reasons and are generally administered via intravenous or intramuscular routes. These routes of administration generally require intervention by a physician or other health care professional, and can entail considerable discomfort as well as potential local trauma to the patient.

One example of such a compound is treprostinil, a chemically stable analog of prostacyclin. Although treprostinil sodium (Remodulin®) is approved by the Food and Drug Administration (FDA) for subcutaneous administration, treprostinil as the free acid has an absolute oral bioavailability of less than 10%. Accordingly, there is clinical interest in providing treprostinil orally.

Thus, there is a need for a safe and effective method for increasing the systemic availability of treprostinil via administration of treprostinil or treprostinil analogs.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a compound having structure I:



wherein,

R^1 is independently selected from the group consisting of H, substituted and unsubstituted benzyl groups, and groups wherein OR^1 are substituted or unsubstituted glycolamide esters;

R^2 and R^3 may be the same or different and are independently selected from the group consisting of H, phosphate and groups wherein OR^2 and OR^3 form esters of amino acids or proteins, with the proviso that all of R^1, R^2 and R^3 are not H;

an enantiomer of the compound;

and pharmaceutically acceptable salts of the compound and polymorphs.

In some of these embodiments, R^1 is a substituted or unsubstituted benzyl group, such as $CH_2C_6H_5$. In other embodiments, OR^1 is a substituted or unsubstituted glycolamide ester, R^1 is $-CH_2CONR^4R^5$, R^4 and R^5 may be the same or different and are independently selected from the group consisting of H, OH, substituted and unsubstituted alkyl groups, $-(CH_2)_mCH_3$, $-CH_2OH$, and $-CH_2(CH_2)_nOH$, with the proviso that m is 0, 1, 2, 3 or 4, and n is 0, 1, 2, 3 or 4. In certain of these embodiments one or both of R^4 and R^5 are independently selected from the group consisting of H, -OH, $-CH_3$, or $-CH_2CH_2OH$. In any of the previously discussed embodiments, one or both of R^2 and R^3 can be H. In some enantiomers of the compound R^1=R^2=R^3=H, or R^2=R^3=H and R^1=valinyl amide.

In still further embodiments of the present compounds R^2 and R^3 are independently selected from phosphate and groups wherein OR^2 and OR^3 are esters of amino acids, dipeptides, esters of tripeptides and esters of tetrapeptides. In some compounds only one of R^2 or R^3 is a phosphate group. In other compounds R^2 and R^3 are independently selected from groups wherein OR^2 and OR^3 are esters of amino acids, such as esters of glycine or alanine. In any of the above embodiments, one of R^2 and R^3 are H. In certain of the present compounds, the oral bioavailability of the compound is greater than the oral bioavailability of treprostinil, such as at least 50% or 100% greater than the oral bioavailability of treprostinil. The above compounds can further comprise an inhibitor of p-glycoprotein transport. Any of these compounds can also further comprise a pharmaceutically acceptable excipient.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.