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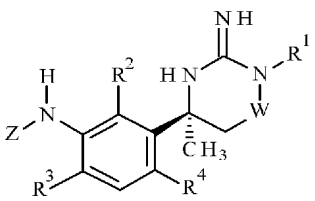

(I)

(57) Abstract: The application relates to a series of 2-imino-6-methylhexahydropyrimidin-4-one derivatives and 3-imino-5-methyl-l,2,4-thiadiazinane 1,1-dioxide derivatives of formula (I), substituted by an arylaminophenyl or heteroarylaminophenyl moiety. The compounds are potent inhibitors of the growth and propagation of the Plasmodium falciparum parasite in human blood and thus useful as pharmaceutical agents for the treatment of malaria.

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ANTIMALARIAL HEXAHYDROPYRIMIDINE ANALOGUES

The present invention relates to a class of heterocyclic compounds, and to their use in therapy. More particularly, this invention is concerned with pharmacologically active substituted hexahydropyrimidine derivatives, and analogues thereof. These compounds are potent inhibitors of the growth and propagation of the *Plasmodium falciparum* parasite in human blood, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of malaria.

Malaria is a mosquito-borne infectious disease, caused by a parasite of the genus *Plasmodium*, which has devastating consequences. In 2010, an estimated 225 million cases were reported, with 610,000 to 971,000 deaths, approximately 80% of which occurred in sub-Saharan Africa, mostly in young children (aged 5 years or less).

The compounds in accordance with the present invention, being potent inhibitors of the growth and propagation of the *P. falciparum* parasite in human blood, are therefore beneficial in the treatment of malaria.

In addition, the compounds in accordance with the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of this invention may be useful as radioligands in assays for detecting pharmacologically active compounds.

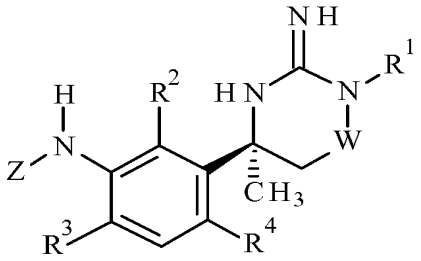
WO 2017/142825 describes a family of heterocyclic compounds which are stated to be potent inhibitors of *P. falciparum* growth *in vitro* that may be useful for the treatment of malaria.

WO 2017/089453 and WO 2017/144517 describe heterocyclic compounds which are stated to be potent and selective inhibitors of plasmepsin V activity that are beneficial in the treatment of malaria.

WO 2016/172255, WO 2016/118404 and WO 2011/044181 describe certain classes of heterocyclic compounds which are stated to be BACE inhibitors that may be useful for treating Aβ-related pathologies including Alzheimer's disease.

WO 2008/103351, WO 2006/065277 and WO 2005/058311 describe a family of heterocyclic compounds that are stated to be aspartyl protease inhibitors. The compounds described in those publications are also stated to be effective in a method of inhibiting *inter alia* plasmepsins (specifically plasmepsins I and II) for treatment of malaria.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

W represents C(O) or $S(O)_2$;

Z represents aryl or heteroaryl, either of which groups may be optionally substituted by one or more substituents;

R^1 represents C_{2-6} alkyl, optionally substituted by hydroxy; or R^1 represents C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{4-9} heterobicycloalkyl, C_{4-9} spiroheterocycloalkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^2, R^3 and R^4 independently represent hydrogen, halogen or trifluoromethyl.

The compounds in accordance with the present invention are encompassed within the broadest generic scope of WO 2016/172255, WO 2016/118404, WO 2011/044181, WO 2008/103351, WO 2006/065277 and WO 2005/058311. There is, however, no specific disclosure in any of those publications of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for use in therapy.

The present invention also provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of malaria.

The present invention also provides a method for the treatment and/or prevention of malaria which comprises administering to a patient in need of such treatment an

effective amount of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof.

The present invention also provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prevention of malaria.

Where any of the groups in the compounds of formula (I) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, such groups will be unsubstituted, or substituted by one, two or three substituents, generally by one or two substituents.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their pharmaceutically acceptable salts. Standard principles underlying the selection and preparation of pharmaceutically acceptable salts are described, for example, in *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, ed. P.H. Stahl & C.G. Wermuth, Wiley-VCH, 2002.

Suitable alkyl groups which may be present on the compounds of use in the invention include straight-chained and branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, 2,2-dimethylpropyl and 3-methylbutyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio", "C_{1-6} alkylsulfonyl" and "C_{1-6} alkylamino" are to be construed accordingly.

The term "C_{3-7} cycloalkyl" as used herein refers to monovalent groups of 3 to 7 carbon atoms derived from a saturated monocyclic hydrocarbon, and may comprise benzo-fused analogues thereof. Suitable C_{3-7} cycloalkyl groups include cyclopropyl, cyclobutyl, benzocyclobutenyl, cyclopentyl, indanyl, cyclohexyl and cycloheptyl.

The term "aryl" as used herein refers to monovalent carbocyclic aromatic groups derived from a single aromatic ring or multiple condensed aromatic rings. Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

The term "C_{3-7} heterocycloalkyl" as used herein refers to saturated monocyclic rings containing 3 to 7 carbon atoms and at least one heteroatom selected from oxygen,

sulphur and nitrogen, and may comprise benzo-fused analogues thereof. Suitable heterocycloalkyl groups include oxetanyl, azetidinyl, tetrahydrofuranyl, dihydrobenzofuranyl, dihydrobenzothienyl, pyrrolidinyl, indolinyl, isoindolinyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, imidazolidinyl, tetrahydropyranyl, chromanyl, dioxanyl, tetrahydrothiopyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, 1,2,3,4-tetrahydroquinoxalinyl, hexahydro-[1,2,5]thiadiazolo-[2,3-*a*]pyrazinyl, homopiperazinyl, morpholinyl, benzoxazinyl, thiomorpholinyl, azepanyl, oxazepanyl, diazepanyl, thiadiazepanyl and azocanyl.

The term "C_{4-9} heterobicycloalkyl" as used herein refers to monovalent groups of 4 to 9 carbon atoms derived from a saturated bicyclic hydrocarbon, comprising one or more heteroatoms selected from oxygen, sulphur and nitrogen. Typical heterobicycloalkyl groups include 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 7-oxabicyclo[2.2.1]hexanyl, 6-azabicyclo[3.2.0]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, quinuclidinyl, 2-oxa-5-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 8-oxabicyclo-[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]nonanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl, 3,7-dioxa-9-azabicyclo[3.3.1]nonanyl and 3,9-diazabicyclo[4.2.1]nonanyl.

The term "C_{4-9} spiroheterocycloalkyl" as used herein refers to saturated bicyclic ring systems containing 4 to 9 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, in which the two rings are linked by a common atom. Suitable spiroheterocycloalkyl groups include 5-azaspiro[2.3]hexanyl, 5-azaspiro[2.4]-heptanyl, 2-oxaspiro[3.3]heptanyl, 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]-heptanyl, 3-oxa-6-azaspiro[3.3]heptanyl, 6-thia-2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro-[3.4]octanyl, 2-oxa-6-azaspiro[3.5]nonanyl, 7-oxa-2-azaspiro[3.5]nonanyl, 2-oxa-7-azaspiro[3.5]nonanyl and 2,4,8-triazaspiro[4.5]decanyl.

The term "heteroaryl" as used herein refers to monovalent aromatic groups containing at least five atoms derived from a single ring or multiple condensed rings, wherein one or more carbon atoms have been replaced by one or more heteroatoms selected from oxygen, sulfur and nitrogen. Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, thieno[2,3-*c*]pyrazolyl, thieno[3,2-*c*]-pyridinyl, dibenzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*c*]-pyridinyl, pyrrolo[3,4-*b*]pyridinyl, pyrazolyl, pyrazolo[1,5-*a*]pyridinyl, pyrazolo[3,4-*d*]-

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