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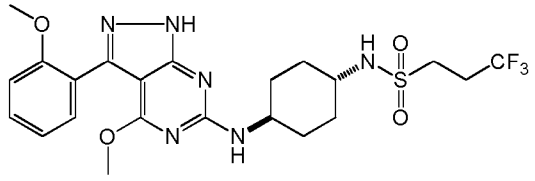
(54) Title: ANTILEISHMANIAL PYRAZOLOPYRIMIDINES



(I)

(57) Abstract: The 3,3,3-trifluoro-N-((1,4-trans)-4-((4-methoxy-3-(2-methoxyphenyl)-1H- pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide, having the Formula (I): (I) or a salt thereof, compositions comprising the compound, its use in the treatment or prevention of leishmaniasis, particularly visceral leishmaniasis.

ANTILEISHMANIAL PYRAZOLOPYRIMIDINES

COMPOUNDS

Technical Field of the invention

This invention provides a compound, 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide and salts thereof, pharmaceutical compositions comprising it, and its use in therapy, for example in the treatment of the leishmaniasis, particularly visceral leishmaniasis (also known as VL).

Background of the invention

Leishmaniasis is caused in humans and animals by protozoan parasites from several leishmania species that are transmitted to hosts by the bites of infected female phlebotomine sandflies.

There are three main human forms of leishmaniasis – visceral (often known as kala-azar and the most serious form of the disease), cutaneous (the most common), and mucocutaneous (the most disfiguring). Most leishmaniases are zoonoses (diseases that can be transmitted from animals to humans) and the reservoir hosts include many species of mammals. Dogs are important reservoirs of *L. infantum* responsible for visceral leishmaniasis.

Animals can also suffer from visceral, cutaneous and mucocutaneous forms of the disease.

It is estimated that 350 million people are at risk of the disease (most of them are children), with 1.3 million new cases and 20 000 to 30 000 deaths per year. (Leishmaniasis Worldwide and Global Estimates of Its Incidence. Alvar J. et al. (2012) PLoS ONE 7(5): e35671. doi:10.1371/journal.pone.0035671).

Current treatments have serious drawbacks in terms of efficacy, safety, drug resistance, stability, cost and the majority lack an oral dosing option (Structures, Targets and Recent Approaches in Anti-Leishmanial Drug Discovery and Development. Seifert K., Open Med Chem J. 2011; 5:31–39. doi: 10.2174/1874104501105010031). Geographical efficacy variation in the current treatments has started to be observed – for example, the efficacy of liposomal amphotericin B in East Africa is below what is seen in the Indian sub-continent for the same dosage ((a)Berman JD, Badaro R, Thakur CP, Wasunna KM, Behbehani K, et al. (1998) Efficacy and safety of liposomal amphotericin B (AmBisome) for visceral leishmaniasis in endemic developing countries. Bull World Health Organ 76: 25–32. (b) Eltahir A. G. Khalil, Teklu Weldegebreal, Brima M. Younis et al. Safety and Efficacy of Single Dose versus Multiple Doses of AmBisome® for Treatment of Visceral Leishmaniasis in Eastern Africa: A Randomised Trial. PLOS Neglected Tropical Diseases: published 16 Jan 2014

(info:doi/10.1371/journal.pntd.0002613). Efficacy rates are also found to vary within Africa (Hailu A, Musa A, Wasunna M, Balasegaram M, Yifru S, et al. (2010) Geographical Variation in the Response of Visceral Leishmaniasis to Paromomycin in East Africa: A Multicentre, Open-Label, Randomized Trial. PLoS Negl Trop Dis 4(10): e709. doi:10.1371/journal.pntd.0000709).

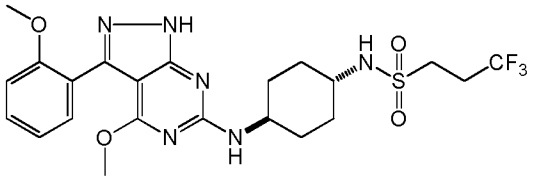
As such there is a real unmet medical need for new oral drugs and combination therapies for the treatment and potential elimination of this disease in certain geographical areas, requiring the development of multiple new oral agents.

WO 2005/121107 and US 2005/277655 disclose certain pyrazolo-pyrimidine compounds as cyclin-dependent kinase inhibitors useful for the treatment of cancer.

WO 2008/09457, WO 2008/094602 and Bioorganic & Medicinal Chemistry Letters (2011), 21(18), 5633-5637 disclose certain pyrazolo-pyrimidine compounds as protein kinase inhibitors useful for the treatment of cancer.

Summary of the Invention

The present invention provides the pyrazolo-pyrimidine compound 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide, having the Formula (I):



(I)

or a salt thereof.

The present invention also provides pharmaceutical compositions comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention also provides a method of treatment or prevention of leishmaniasis, particularly visceral leishmaniasis, which method comprises administering to a mammal in need thereof, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one aspect, the mammal is a human.

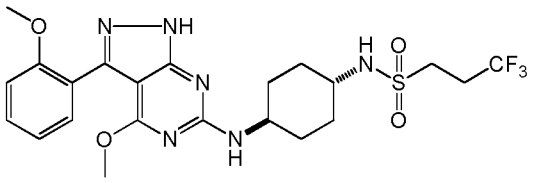
According to another aspect, the invention provides the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy, which therapy is human or veterinary.

In another aspect, the invention provides the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of leishmaniasis, particularly visceral leishmaniasis.

In another aspect, the invention provides the use of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of leishmaniasis, particularly visceral leishmaniasis.

Detailed description of the invention

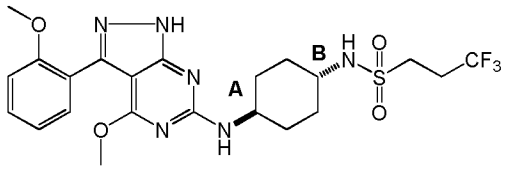
In a first aspect, the present invention is directed to 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide, the compound of Formula (I):



(I)

and salts thereof.

It is to be understood that for the compound of Formula (I), the stereochemistry shown at the positions denoted A and B below is *relative* stereochemistry, that is to say, the substituents on the cyclohexyl ring at positions A and B have a *trans* relationship to each other.



It is to be understood that reference herein to "compound(s) of the invention" means a compound of Formula (I), or a salt thereof

Since a compound of the invention is intended for use in pharmaceutical compositions it will readily be understood that it is provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compound of the invention may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention or pharmaceutically acceptable derivative thereof.

In one aspect of the invention, a compound of Formula (I) is provided in substantially pure form, preferably at least 60% pure, more suitably at least 75% pure and more preferably at least 85%, and especially at least 98% pure (% are on a weight for weight basis).

In one aspect of the invention, a compound of Formula (I) is in the form of a free base. In a further aspect of the invention, a compound of Formula (I) is in the form of a pharmaceutically acceptable salt.

Salts of the compounds of Formula (I) include pharmaceutically acceptable salts and salts which may not be pharmaceutically acceptable but may be useful in the preparation of compounds of Formula (I) and pharmaceutically acceptable salts thereof. In one aspect of the invention, a compound of Formula (I) is in the form of a pharmaceutically acceptable salt. Salts may be derived from certain inorganic or organic acids or bases.

Examples of salts are pharmaceutically acceptable salts. Pharmaceutically acceptable salts include acid addition salts. For a review on suitable salts see *Berge et al., J. Pharm. Sci., 66:1-19 (1977).*

Examples of pharmaceutically acceptable acid addition salts of a compound of Formula (I) include inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, orthophosphoric acid, nitric acid, phosphoric acid, or sulfuric acid, or with organic acids such as, for example, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, lactic acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid, maleic acid, glycerophosphoric acid, tartaric, benzoic, glutamic, aspartic, benzenesulfonic, naphthalenesulfonic such as 2-naphthalenesufonic, hexanoic acid or acetylsalicylic acid.

In one aspect of the invention, a compound of Formula (I) is in the form of a salt independently selected from a hydrochloric acid, hydrobromic acid, orthophosphoric acid, nitric acid, phosphoric acid, maleic acid or a p-toluenesulfonic acid or sulfuric acid salt. In another aspect, a compound of Formula (I) is in the form of a salt independently selected from a hydrochloric acid, maleic acid, sulfuric acid or a p-toluenesulfonic acid salt.

Examples of pharmaceutically acceptable inorganic base addition salts of a compound of Formula (I) include salts of ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like.

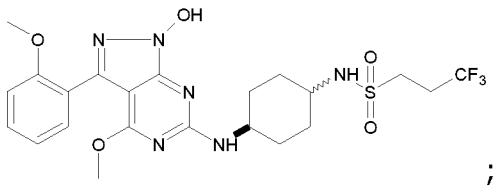
The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of Formula (I).

Salts may be formed using techniques well-known in the art, for example by precipitation from solution followed by filtration, or by evaporation of the solvent.

Typically, a pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of Formula (I) with a suitable acid (such as hydrobromic, hydrochloric, sulfuric, maleic, *p*-toluenesulfonic, methanesulfonic, naphthalenesulfonic or succinic acids), optionally

in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration.

The compound of Formula (I) may also be prepared as the N-oxide. Examples of N-oxides of the compound of Formula (I) are as follows: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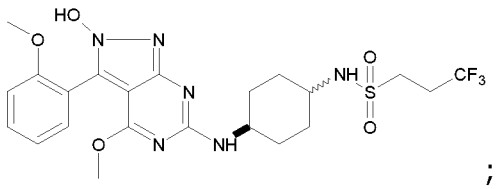
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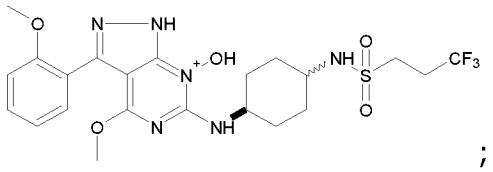
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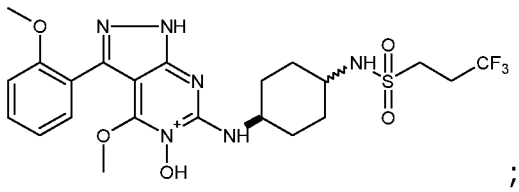
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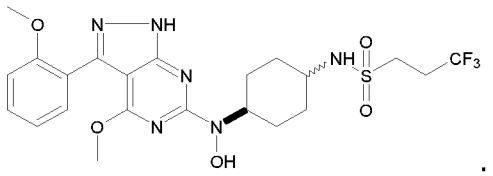
and/or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It will be appreciated that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallised. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvents with high boiling points and/or solvents with a high propensity to form hydrogen bonds such as water, ethanol, *iso*-propyl alcohol, and *N*-methyl pyrrolidinone may be used to form solvates. Methods for the identification of solvated compounds include, but are not limited to, NMR and microanalysis. Accordingly compounds of Formula (I) may exist as solvates. As used herein, the term solvate encompasses solvates of both a free base compound as well as any salt thereof.

The compounds of the invention may be in crystalline or amorphous form. Furthermore, some of the crystalline forms of the compounds of the invention may exist as polymorphs, all of which are included within the scope of the present invention. The most thermodynamically stable polymorphic form or forms of the compounds of the invention are of particular interest. In one aspect of the invention, the compound of Formula (I) is crystalline.

Polymorphic forms of compounds of the invention may be characterised and differentiated using a number of conventional analytical techniques, including, but not limited

to, X-ray powder diffraction (XRPD), infrared spectroscopy (IR), Raman spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and solid-state nuclear magnetic resonance (ssNMR).

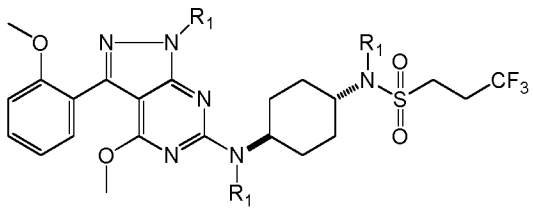
The compounds of the invention may also be prepared as an amorphous molecular dispersion of drug substance in a polymer matrix such as HPMCAS (hydroxypropylmethylcellulose acetate succinate) using a process such as spray-dried dispersion (SDD). Such a technique is employed to improve properties such as stability and solubility.

Compounds of Formula (I) may exist in the form of isotopic variations. An isotopic variation of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of a compound of Formula (I) or a salt or solvate thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of Formula (I), or a pharmaceutically salt thereof, can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples hereafter using appropriate isotopic variations of suitable reagents.

It will be appreciated from the foregoing, that compounds of Formula (I) and salts thereof may exist as solvates or hydrates.

It will be appreciated by those skilled in the art that certain derivatives of the compounds of Formula (I), whilst not necessarily possessing pharmacological activity as such, may be administered and thereafter metabolised in the body to form compounds of Formula (I) which compounds are pharmacologically active. Such derivatives are herein referred to as "prodrugs" and are included within the scope of the invention. Examples of suitable derivatives are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard,

Elsevier, 1985, Chapter 1. Examples of prodrugs of compounds of Formula (I) are shown in Formula (II):



(II).

wherein

each R_1 is independently selected from H, $C(O)OL_1R_2$, $CL_1R_3OL_1R_2$, $C(O)L_1R_2$ or $P(O)(OL_1R_2)(OL_1R_3)$;

each L_1 is independently selected from a bond or X;

X is C_{1-6}alkylene, C_{1-6}haloalkylene, C_{4-6}heterocyclylene, phenylene or C_{5-6}heteroarylene, each of which is optionally substituted by 1 to 4 substituents independently selected from Z;

Z is H, halo, $C(O)L_1R_2$, $C(O)OL_1R_2$, $C(O)NHL_1R_2$, $C(O)N(L_1R_2)(L_1R_3)$, NH_2, OL_1R_2, $NH(L_1R_2)$, $N(L_1R_2)(L_1R_3)$, or $P(O)(OL_1R_2)(OL_1R_3)$;

either

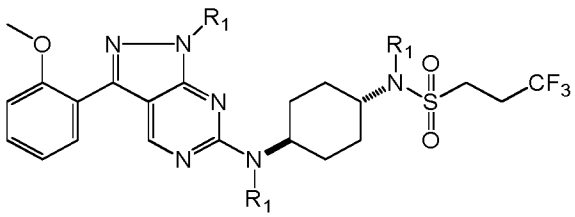
a) Each R_2 and R_3 is independently selected from H or Y;

Y is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{4-6}heterocyclyl, phenyl or C_{5-6}heteroaryl, each of which is optionally substituted by 1 to 4 substituents independently selected from Z;

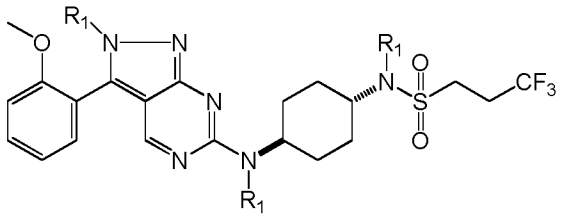
or

b) R_2 and R_3 are bound together to form a linker group L_1, so as to form together with the atoms to which they are attached a C_{4-6}cycloalkyl or , C_{4-6}heterocyclyl group.

Further examples of prodrugs of compounds of Formula (I) are shown in compounds of Formula (III) or (IV), or a pharmaceutically acceptable salt thereof:



(III), or



(IV)

wherein

each R_1 is independently selected from H, $C(O)OL_1R_2$, $CH(L_1R_3)OL_1R_2$, $CH_2OL_1R_2$, $C(L_1R_3)(L_1R_4)OL_1R_2$, $C(O)L_1R_2$, $C(O)C(L_1R_2)=C(L_1R_3)L_1R_4$ $P(O)(OL_1R_2)(OL_1R_3)$, $C(O)OL_1OP(O)(OL_1R_2)(OL_1R_3)$, or $C(O)OL_1OC(O)L_1$-$L_1OP(O)(OL_1R_2)(OL_1R_3)$;

each L_1 is independently selected from a bond or X;

X is C_{1-6}alkylene, C_{2-6}alkenylene, C_{2-6}alkynylene, C_{4-7}cycloalkylene, C_{5-7}cycloalkenylene, C_{4-7}heterocycloalkylene, C_5-C_7heterocycloalkenylene, phenylene or C_{5-6}heteroarylene; each of which is optionally substituted by 1 to 6 substituents independently selected from Z;

each Z is independently selected from halo, $C(O)L_1R_2$, $C(O)OL_1R_2$, $C(O)NHL_1R_2$, $C(O)N(L_1R_2)(L_1R_3)$, OL_1R_2, $N(L_1R_2)(L_1R_3)$, CN, $S(L_1R_2)$, $S(O)(L_1R_2)$, $SO_2(L_1R_2)$ or $P(O)(OL_1R_2)(OL_1R_3)$;

either

a) each R_2, R_3 and R_4 is independently selected from H or Y;

or

b) each R_2, R_3 and R_4 is independently selected from Y, wherein two of said R_2, R_3 and R_4 are bound together through an additional L_1 group so as to form a cyclic group;

Y is Z or C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{4-7}cycloalkyl, C_{5-7}cycloalkenyl, C_{4-7}heterocycloalkyl, C_5-C_7heterocycloalkenyl, phenyl or C_{5-6}heteroaryl, each of which is optionally substituted by 6 substituents independently selected from Z.

In one embodiment of Formula (III) or of Formula (IV), each R_1 is independently selected from H, $C(O)OL_1R_2$, $CH(L_1R_3)OL_1R_2$, $CH_2OL_1R_2$, $C(L_1R_3)(L_1R_4)OL_1R_2$, $C(O)L_1R_2$, $P(O)(OL_1R_2)(OL_1R_3)$, $C(O)OL_1OP(O)(OL_1R_2)(OL_1R_3)$, or $C(O)OL_1OC(O)L_1$-$L_1OP(O)(OL_1R_2)(OL_1R_3)$.

As used herein for Formula (II), the term "C_{1-6}alkyl" means a straight or branched alkyl containing at least one, and at most six, carbon atoms. Examples of C_{1-6}alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, neopentyl, or hexyls.

As used herein for Formula (II), the term "C_{1-6}haloalkyl" means C_{1-6}alkyl wherein one or more of the hydrogen atoms are replaced with halo.

As used herein for Formula (II), the term "C_{1-6}alkylene" means a divalent radical of C_{1-6}alkyl. Examples of C_{1-6}alkylene include, but are not limited to, methylene, ethylene, isopropylene, n-butylene, isobutylene, tert-butylene, pentylene, neopentylene, or hexylenes.

As used herein for Formula (II), the term "C_{1-6}haloalkylene" means a means a divalent radical of C_{1-6}haloalkyl as defined herein.

As used herein for Formula (II), the term "C_{4-6}cycloalkyl" means a non-aromatic carbocyclic ring containing at least four and at most six carbon atoms. Examples of C_{4-6}cycloalkyl groups include cyclobutyl, cyclopentyl and cyclohexyl.

As used herein for Formula (II), the term "C_{4-6}heterocyclyl" means a saturated ring containing at least four and at most six atoms, which includes one or more (e.g. 2) ring heteroatoms selected from nitrogen, oxygen and sulfur. Examples of C_{4-6}heterocyclyl groups include, but are not limited to, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, morpholinyl, 1,4-dioxanyl, thiomorpholinyl, 1,4-oxathianyl and 1,4-dithanyl. The point of attachment to the rest of the molecule may be by any suitable carbon or nitrogen atom.

As used herein for Formula (II), the term "C_{4-6}heterocyclylene" means a divalent radical of a C_{4-6}heterocyclyl group as defined herein.

As used herein for Formula (II), the term "C_{5-6}heteroaryl" refers to an optionally substituted aromatic ring comprising five or six heteroatoms selected from N, O and S. Examples of C_{5-6}heteroaryl groups include, but are not limited to, furanyl, thiophenyl, pyrrolyl, pyridyl, pyrimidyl, imidazolyl and isoxazolyl. Optional heteroaryl substituents include halo, and alkyl.

As used herein for Formula (II), the term "C_{5-6}heteroarylene" means a divalent radical of C_{5-6}heteroaryl as defined herein.

As used herein for Formula (II), the term "phenylene" means a means a divalent radical of phenyl.

As used herein for Formula (II), the term "halo" refers to fluoro, chloro, bromo or iodo.

As used herein for Formula (III) or Formula (IV), the term "C_{1-6}alkyl" means a straight or branched saturated hydrocarbon group containing at least one, and at most six, carbon atoms. Examples of C_{1-6}alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, neopentyl, or hexyls.

As used herein for Formula (III) or Formula (IV), the term "C_{1-6}alkylene" means a divalent radical of C_{1-6}alkyl as defined herein. Examples of C_{1-6}alkylene include, but are not limited to, methylene, ethylene, n-propylene, isopropylene, n-butylene, isobutylene, tert-butylene, pentylene, neopentylene, or hexylenes.

As used herein for Formula (III) or Formula (IV), the term "C_{2-6}alkenyl" means a straight or branched unsaturated hydrocarbon group containing at least two, and at most six, carbon atoms, wherein the hydrocarbon group has one or more positions of unsaturation each of which is present as a double bond. Examples of C_2-C_6alkenyl include, but are not limited to, ethenyl (-CH=CH-), propenyl (-CH_2-CH=CH-), isopropenyl, butenyl, pentenyl, hexenyl, 1-propenyl, 2-butenyl and 2-methyl-2-butenyl.

As used herein for Formula (III) or Formula (IV), the term "C_{2-6}alkenylene" means a divalent radical of C_{2-6}alkenyl as defined herein. Examples of C_2-C_6alkenylene include, but are not limited to, ethenylene, n-propenylene, isopropenylene, n-butenylene, isobutenylene, tert-butenylene, pentenylene, neopentenylene, or hexenylenes.

As used herein for Formula (III) or Formula (IV), the term "C_{2-6}alkynyl" means a straight or branched unsaturated hydrocarbon group containing at least two, and at most six, carbon atoms, wherein the hydrocarbon group has one or more positions of unsaturation each of which is present as a triple bond. Examples of C_2-C_6alkynyl include, but are not limited to, ethynyl (-CH≡CH-), propynyl (-CH_2-CH≡CH-), butynyl, pentynyl, hexynyl, 1-propynyl, 2-butynyl and 2-methyl-2-butynyl.

As used herein for Formula (III) or Formula (IV), the term "C_{2-6}alkynylene" means a divalent radical of C_{2-6}alkynyl as defined herein. Examples of C_2-C_6alkenylene include, but are not limited to, ethynylene, n-propynylene, n-butynylene, isobutynylene, tert-butynylene, pentynylene, neopentynylene, or hexynylenes.

As used herein for Formula (III) or Formula (IV), the term "C_{4-7}cycloalkyl" means a non-aromatic carbocyclic saturated ring containing at least four and at most seven carbon atoms. Examples of C_{4-7}cycloalkyl groups include, but are not limited to, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein for Formula (III) or Formula (IV), the term "C_{4-7}cycloalkylene" means a divalent radical of C_{4-7}cycloalkyl as defined herein.

As used herein for Formula (III) or Formula (IV), the term "C_{5-7}cycloalkenyl" means a non-aromatic carbocyclic unsaturated ring containing at least five and at most seven carbon atoms. Examples of C_{5-7}cycloalkenyl groups include, but are not limited to, cyclopentenyl, cyclohexenyl and cycloheptenyl.

As used herein for Formula (III) or Formula (IV), the term "C_{5-7}cycloalkenylene" means a divalent radical of C_{5-7}cycloalkenyl as defined herein.

As used herein for Formula (III) or Formula (IV), the term "C_{4-7}heterocycloalkyl" means a saturated ring containing at least four and at most seven atoms, which includes at least one heteroatom in the ring selected from nitrogen, oxygen and sulfur. Examples of C_{4-7}heterocycloalkyl groups include, but are not limited to, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,4-dioxanyl, thiomorpholinyl, 1,4-oxathianyl, 1,4-dithanyl, dioxepanyl, azepanyl, oxepanyl and diazepanyl. The point of attachment to the rest of the molecule may be by any suitable carbon or nitrogen atom.

As used herein for Formula (III) or Formula (IV), the term "C_{4-7}heterocycloalkylene" means a divalent radical of a C_{4-7}heterocycloalkyl group as defined herein.

As used herein for Formula (III) or Formula (IV), the term "C_5-C_7heterocycloalkenyl" means a non-aromatic unsaturated ring containing at least five and at most seven atoms, which includes at least one heteroatom in the ring selected from nitrogen, oxygen and sulfur. Examples of C_5-C_7heterocycloalkenyl groups include, but are not limited to, dihydropyranyl, dihydrofuranyl, dihydrothiophenyl, pyrrolinyl, azepinyl, oxepinyl, thiepiny, dioxepinyl, dihydropyrrolyl, dihydropyrazolyl, dihydroimidazolyl, dihydrooxazolyl, dihydrothiazolyl and dihydrothiopyranyl.

As used herein for Formula (III) or Formula (IV), the term "C_5-C_7heterocycloalkenylene" means a divalent radical of C_5-C_7heterocycloalkenyl as defined herein.

As used herein for Formula (III) or Formula (IV), the term "C_{5-6}heteroaryl" refers to an aromatic ring containing at least five and at most six atoms, and comprising at least one heteroatom in the ring selected from nitrogen, oxygen and sulfur. Examples of C_{5-6}heteroaryl groups include, but are not limited to, furanyl, thiophenyl, pyrrolyl, pyridyl, pyrimidyl, imidazolyl and isoxazolyl. The point of attachment to the rest of the molecule may be by any suitable carbon or nitrogen atom.

As used herein for Formula (III) or Formula (IV), the term "C_{5-6}heteroarylene" means a divalent radical of C_{5-6}heteroaryl as defined herein.

As used herein for Formula (III) or Formula (IV), the term "phenylene" means a means a divalent radical of phenyl.

As used herein for Formula (III) or Formula (IV), the term "halo" refers to fluoro, chloro, bromo or iodo.

Accordingly, in one aspect of the invention there is provided a compound of Formula (II), (III) or (IV), or a pharmaceutically acceptable salt thereof. In another aspect there is provided a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt thereof. In a further aspect there is provided a compound of Formula (III). In another aspect there is provided a compound of Formula(IV). In another aspect there is provided a compound of Formula(II).

In another aspect of the invention there is provided a pharmaceutical composition comprising a compound of Formula (II), (III) or (IV), or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier.

In a further aspect there is provided a combination comprising (a) a compound of Formula (II), (III) or (IV), or a pharmaceutically acceptable salt thereof, and (b) at least one additional therapeutic agent.

In another aspect there is provided a compound of Formula (II), (III) or (IV), or a pharmaceutically acceptable salt thereof, for use in therapy or for use as a medicament in therapy.

In yet another aspect there is provided a compound of Formula (II), (III) or (IV), or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of leishmaniasis.

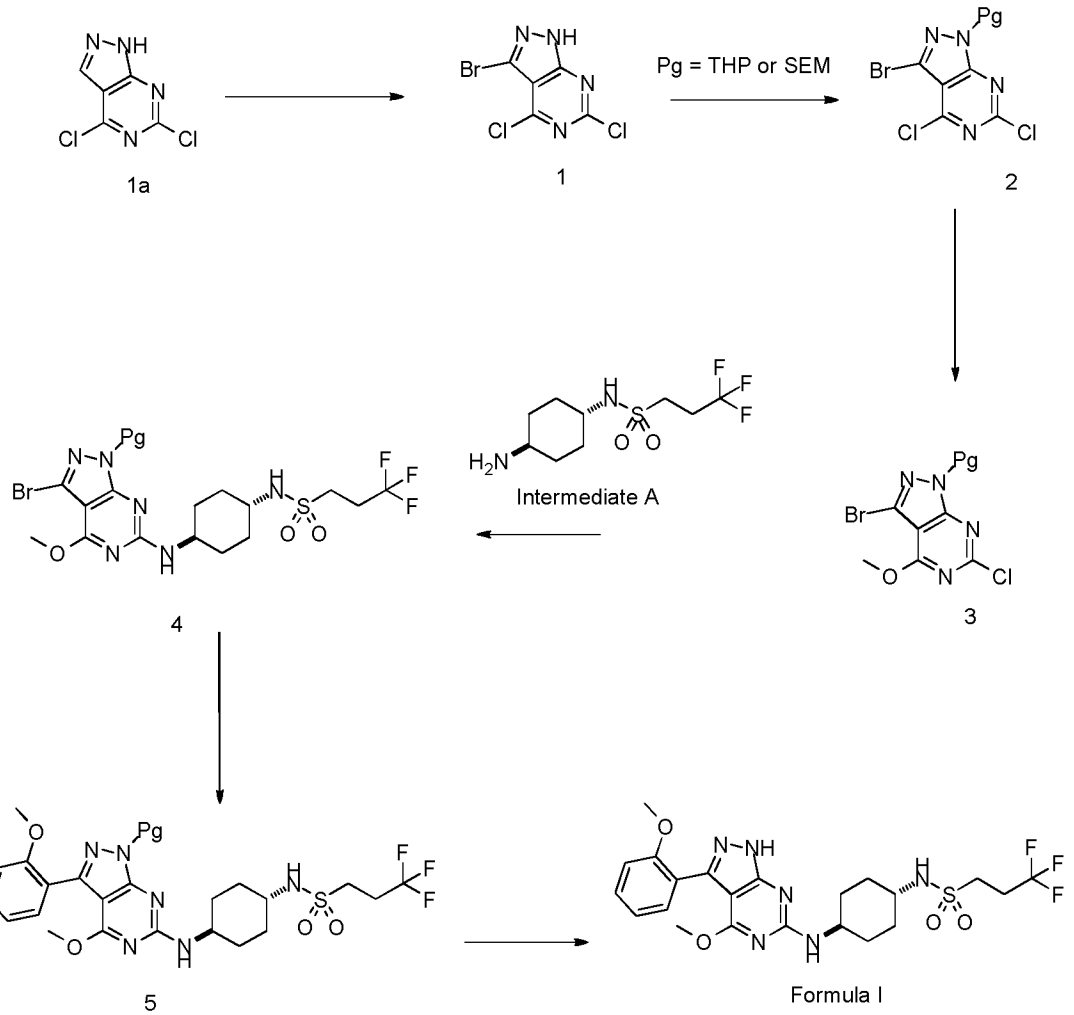
In a further aspect, there is provided the use of a compound of Formula (II), (III) or (IV), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of leishmaniasis.

In another aspect, there is provided a method of treatment or prevention of leishmaniasis, which method comprises administering to a mammal in need thereof, a therapeutically effective amount of a compound a compound of Formula (II), (III) or (IV), or a pharmaceutically acceptable salt thereof.

Compound Preparation

The compound of Formula (I) and salts thereof, may be prepared by the methodology described hereinafter, constituting further aspects of this invention.

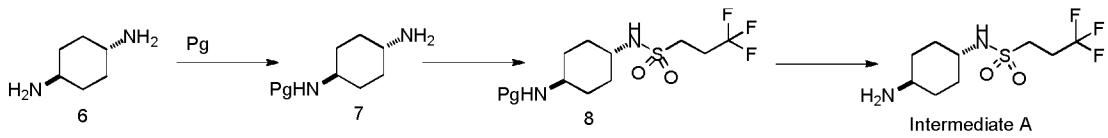
The general procedures which can be used to synthesise the compound of Formula (I) are summarised in reaction Schemes 1 and 2 are illustrated in the Examples.



Scheme 1

Also disclosed herein is a process for the preparation of an N-protected (N-Pg) variant of a compound of Formula I from an intermediate compound A or a salt thereof and the corresponding N-protected compound of Formula 4 wherein the N-Pg group may be any suitable N-protecting group such as for example a THP or SEM group. For the avoidance of doubt, any suitable salt of intermediate compound A may be used, and an exemplary salt is the TFA salt of *N*-((1,4-*trans*)-4-aminocyclohexyl)-3,3,3-trifluoropropane-1-sulfonamide as utilised in the Examples herein.

The general procedures which may be used to synthesise Intermediate A are summarised in reaction Scheme 2.



Scheme 2

Scheme 1: Compounds of Formula (I) in Scheme 1 may be prepared from 4,6-dichloro-1*H*-pyrazolo[3,4-d]pyrimidine (1a). Compound (1a) may be subjected to bromination using a suitable brominating agent, such as *N*-bromosuccinimide, to provide compound (1). The pyrazole NH of compound (1) may be protected with a suitable protecting group Pg such as THP or SEM, under suitable conditions, to give (2). One of the chloro groups on the pyrimidine ring may be replaced by a methoxy group using with a suitable reagent such as sodium methoxide to provide (3). Compound (3) may be reacted with Intermediate A in the presence of a suitable base, such as DIPEA, to provide (4). Compound (4) may be subjected to a coupling reaction, for example a Suzuki or a Buchwald reaction, with a suitable reagent, such as 2-methoxyphenylboronic acid, to introduce a 2-methoxyphenyl group, in the presence of a suitable palladium catalyst, to give compound (5). Compound (5) may be subjected to deprotection using a suitable reagent to give the compound of Formula (I).

Scheme 2: Intermediate A in Scheme 2 may be made from cyclohexane-1,4-diamine (14). Compound (14) may be protected with a suitable protecting group (Pg) (such as Boc) to give compound (15) followed by sulfonylation of the remaining free NH_2 to give (16). Compound (16) may then be deprotected under suitable conditions to give Intermediate A.

Compounds 1a and 6 (Aldrich Sigma) are commercially available.

Examples of other protecting groups (Pg) that may be employed in the synthetic routes described herein and the means for their removal can be found in *T. W. Greene 'Protective Groups in Organic Synthesis', 4th Edition, J. Wiley and Sons, 2006,* incorporated herein by reference as it provides such procedures.

For any of the hereinbefore described reactions or processes, conventional methods of heating and cooling may be employed, for example temperature-regulated oil-baths or temperature-regulated hot-blocks, and ice/salt baths or dry ice/acetone baths respectively. Conventional methods of isolation, for example extraction from or into aqueous or non-aqueous solvents may be used. Conventional methods of drying organic solvents, solutions, or extracts, such as shaking with anhydrous magnesium sulfate, or anhydrous sodium sulfate, or passing through a hydrophobic frit, may be employed. Conventional methods of purification, for example crystallisation and chromatography, for example silica chromatography or reverse-phase chromatography, may be used as required. Crystallisation may be performed using conventional solvents such as ethyl acetate, methanol, ethanol, or

butanol, or aqueous mixtures thereof. It will be appreciated that specific reaction times temperatures may typically be determined by reaction-monitoring techniques, for example thin-layer chromatography and LC-MS.

Methods of Use

It will be appreciated by those skilled in the art that references herein to treatment refer to the treatment of established conditions. However, the compounds of Formula (I) and pharmaceutically acceptable salts thereof may, depending on the condition, also be useful in the prevention (prophylaxis) of certain diseases.

As used herein, unless otherwise indicated, "treat", "treating" or "treatment" in reference to a disease means: (1) to ameliorate the disease or one or more of the biological manifestations of the disease (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the disease or (b) one or more of the biological manifestations of the disease, (3) to alleviate one or more of the symptoms or effects associated with the disease, (4) to slow the progression of the disease or one or more of the biological manifestations of the disease, and/or (5) to diminish the likelihood of severity of a disease or biological manifestations of the disease.

As used herein, unless otherwise indicated, "prevent", "preventing" or "prevention" means the prophylactic administration of a drug to diminish the likelihood of the onset of or to delay the onset of a disease or biological manifestation thereof. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a disorder or biological manifestation thereof, or to delay the onset of such disorder or biological manifestation thereof.

Thus, in one embodiment, there is provided the treatment or prevention of a disease. In another embodiment, there is provided the treatment of a disease. In a further embodiment, there is provided the prevention of a disease.

There is thus provided as a further aspect of the invention a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy. There is further provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament in therapy, which therapy is human or veterinary.

It will be appreciated that, when a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used in therapy, it is used as an active therapeutic agent.

There is also therefore provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of leishmaniasis, particularly visceral leishmaniasis.

In one embodiment of the invention there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of cutaneous leishmaniasis.

There is further provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of leishmaniasis, particularly visceral leishmaniasis.

There is further provided a method of treatment or prevention of leishmaniasis, particularly visceral leishmaniasis, which method comprises administering to a human subject in need thereof, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention there is provided a method of treatment or prevention of cutaneous leishmaniasis, which method comprises administering to a mammal in need thereof, a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compositions and formulations

While it is possible that, for use in the methods of the invention, the compound of Formula (I) or a pharmaceutically acceptable salt thereof may be administered as the bulk substance, it is usually preferable to present the active ingredient in a pharmaceutical formulation, for example, wherein the agent is in admixture with at least one pharmaceutically acceptable carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

The term "carrier" refers to a diluent, excipient, and/or vehicle with which an active compound is administered. The pharmaceutical compositions of the invention may contain combinations of more than one carrier. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition. The choice of pharmaceutical carrier can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise, in addition to the

carrier, any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilizing agent(s).

The phrase "pharmaceutically acceptable", as used herein, refers to salts, molecular entities and other ingredients of compositions that are generally physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). Suitably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government for use in mammals, and more particularly in humans, or listed in the U.S. Pharmacopoeia or other generally recognized texts, for example the International Union of Pure and Applied Chemistry (IUPAC) Handbook of Pharmaceutical Salts, 2011 Edition.

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the present application includes both one and more than one such excipient.

The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with formulation of antibacterials, such as anti-tubercular agents, or formulation of antimalarial agents.

The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. In one aspect, the invention is directed to a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In another aspect the invention is directed to a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and together with at least one or more pharmaceutically acceptable carrier. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention further provides a pharmaceutical composition as defined herein for use as a medicament, for example for use as a medicament for use in the treatment or prevention of leishmaniasis, such as for use as a medicament for use in the treatment or prevention of visceral leishmaniasis.

A therapeutically effective amount of the compound of the present invention can be determined by methods known in the art. The therapeutically effective quantities will depend on the age and on the general physiological condition of the subject, the route of administration and the pharmaceutical formulation used. The therapeutic doses will generally

be between about 1 and 2000 mg/day, for example between about 500 mg and 2000 mg/day. The daily dose as employed for human treatment will range from 1 to 2000 mg, which may be administered in one or two daily doses, for example, depending on the route of administration and the condition of the subject. When the composition comprises dosage units, each unit will contain 1 mg to 2000 mg of active ingredient. When the dosage form is a tablet, the total weight of the tablet is suitably 1000mg or lower.

The present invention is further related to a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

The present invention is further related to a pharmaceutical composition for the treatment of leishmaniasis, particularly visceral leishmaniasis (VL), comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof.

The present invention is yet further related to a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier.

The present invention is even further related to a pharmaceutical composition comprising a) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and b) one or more pharmaceutically acceptable carriers.

The present invention is even further related to a pharmaceutical composition comprising a) 1 to 2000 mg of the compound of Formula (I) or a pharmaceutically acceptable salt thereof, and b) 1 mg and 2000 mg of one or more pharmaceutically acceptable carriers.

It will be appreciated that pharmaceutical compositions for use in accordance with the present invention may be in the form of oral, parenteral, transdermal, inhalation, sublingual, topical, implant, nasal, or enterally administered (or other mucosally administered) suspensions, capsules or tablets, which may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. In one aspect, the pharmaceutical composition is formulated for oral administration.

The pharmaceutical compositions of the invention include those in a form adapted for oral use in mammals including humans.

The pharmaceutical compositions of the invention include those in a form adapted for oral use and may be used for the treatment of leishmaniasis, particularly visceral leishmaniasis, in mammals including humans.

The compound of the invention can be administered for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications for example as a single or sole-therapeutic agent or may be administered as part of a combination therapy as detailed herein.

The composition may be formulated for administration by any convenient route. For the treatment of leishmaniasis, particularly visceral leishmaniasis (VL), the compositions may be in the form of tablets, capsules, powders, granules, lozenges, aerosols or liquid preparations, for oral use.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulfate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

The compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be the sole therapeutic agent in the compositions of the invention, or it may be present in the formulation in combination with one or more additional therapeutic agents.

The invention thus provides in a further aspect, a combination comprising (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and (b) at least one additional therapeutic agent. The combination optionally further comprises at least one pharmaceutically acceptable carrier. In one aspect of the invention there is provided a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier and one or more additional therapeutic agents.

The present invention further provides a combination of (a) and (b) as defined herein for use as a medicament, for example for use as a medicament for use in the treatment or prevention of leishmaniasis, such as for use as a medicament for use in the treatment or prevention of visceral leishmaniasis.

Examples of such one or more additional therapeutic agents are anti-leishmania agents, including, but not limited to, miltefosine, paromomycin, sodium stibugluconate, meglumine antimoniate, amphotericin B deoxycholate or liposomal amphotericin B. In one aspect of the invention for oral treatment the additional therapeutic agent is miltefosine. Such chemotherapy is determined by the judgment of the treating physician using preferred drug combinations. In addition to the aforementioned, future anti-leishmania therapeutic agents emerging from clinical studies may also be employed as the one or more additional therapeutic agents in a combination with a compound of Formula (I).

In another aspect, the invention provides a combination comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, together with one or more additional therapeutic agents, such as an anti-leishmaniasis agent, an anti-AIDS or anti-HIV agent, or an anti-TB agent.

In a further aspect, the one or more additional therapeutic agent is, for example, an agent useful for the treatment of leishmaniasis in a mammal, therapeutic vaccines, anti-leishmaniasis agents and/or agents for the treatment of HIV / AIDS.

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and further therapeutic agent(s) may be employed in combination by administration simultaneously in a unitary pharmaceutical composition including both agents. Alternatively, the combination may be administered separately in separate pharmaceutical compositions, each including one of the agents in a sequential manner wherein, for example, the compound of Formula (I) or a pharmaceutically acceptable salt, thereof is administered first and the other agent second and *vice versa*. Such sequential administration may be close in time (e.g. simultaneously) or remote in time. For example, administration of the other agent several minutes to several dozen minutes after the administration of the first agent, and administration of the other agent several hours to several days after the administration of the first agent are within the scope of the invention, wherein the lapse of time is not limited. For example, one agent may be administered once a day, and the other agent may be administered 2 or 3 times a day, or one agent may be administered once a week, and the other agent may be administered once a day.

When administration is sequential, either the compound of the present invention or one or more additional therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition. When combined in the same formulation it will be appreciated that the compound and agents must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any

convenient formulation, conveniently in such manner as are known for such compounds in the art.

During a treatment regime, it will be appreciated that administration of each agent of the combination may be repeated one or more times.

Furthermore, the agents may be administered in the same or different dosage forms, e.g. one agent may be administered topically and the other compound may be administered orally. Suitably, both agents are administered orally.

The combinations may be presented as a combination kit. By the term "combination kit" "or kit of parts" as used herein is meant the pharmaceutical composition or compositions that are used to administer the combination according to the invention. When the agents of the combination are administered simultaneously, the combination kit can contain the agents in a single pharmaceutical composition, such as a tablet, or in separate pharmaceutical compositions. When the agents are not administered simultaneously, the combination kit will contain each agent in separate pharmaceutical compositions either in a single package or in separate pharmaceutical compositions in separate packages. The combination kit can also be provided with instructions, such as dosage and administration instructions. Such dosage and administration instructions can be of the kind that are provided to a doctor, for example by a drug product label, or they can be of the kind that are provided by a doctor, such as instructions to a patient.

In one aspect, the one or more additional therapeutic agent is a therapeutic vaccine. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, may thus be administered in conjunction with vaccination against leishmaniasis infection. Existing veterinary vaccines include canileish and leishmune.

The compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be either i) administered to an individual who has previously been vaccinated against leishmaniasis infection; ii) administered to an individual who is subsequently vaccinated against leishmaniasis infection; or iii) may be co-administered with a vaccine against leishmaniasis infection, either by administering the compound of the invention and the vaccine together in the same dosage form or co-administering the compound of the invention and the vaccine in separate dosage forms.

When a compound of Formula (I), or a pharmaceutically acceptable salt thereof is used in combination with one or more additional therapeutic agents, the dose of the compound or agent may differ from that when the compound or agent is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention and the one or more additional therapeutic

agents required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

Abbreviations

In describing the invention, chemical elements are identified in accordance with the Periodic Table of the Elements. Abbreviations and symbols utilized herein are in accordance with the common usage of such abbreviations and symbols by those skilled in the chemical arts. The following abbreviations are used herein:

ACN	Acetonitrile
AIDS	Acquired Immune Deficiency Syndrome
Boc	tert-butyloxycarbonyl
aq.	Aqueous
$CDCl_3$	Deuterated chloroform
CD_3OD	Deuterated methanol
CO_2	Carbon dioxide
Conc.	Concentrated
DAD	Diode array detection
DAPI	4′,6-Diamidino-2-phenylindole
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated dimethylsulfoxide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
g	grams
h	hours
H_2	Hydrogen
H_2O	Water
HCl	Hydrochloric acid
HIV	Human Immunodeficiency Virus
HPLC	high performance liquid chromatography

L	litres
Lawesson's reagent	2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide
M	Molar
MeOH	Methanol
min	Minutes
mL	Millilitre
mmol	Millimolar
MOM	Methoxymethyl ether
MS	Mass spectrum
Na_2CO_3	Sodium bicarbonate
$NaHCO_3$	Sodium hydrogen carbonate
$NaHSO_3$	Sodium bisulfite or Sodium hydrogen sulfite
Na_2SO_4	Sodium sulfate
NaOH	Sodium hydroxide
NH_4OH	Ammonium Hydroxide
NMR	Nuclear Magnetic Resonance spectroscopy
PBS	Phosphate buffered saline
PBS-A	Bovine serum albumin
Pd/C	Palladium on Carbon
Pg	Protecting group
PMA	Phorbol 12-myristate 13-acetate
quant.	Quantitative
RT	Room Temperature
sat.	Saturated
SEM	2-(Trimethylsilyl)ethoxy]methyl
$SOCl_2$	thionyl chloride
sol.	Solution
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin layer chromatography

wt% Weight percentage

Examples

The following Examples illustrate the invention, as guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the invention. While particular embodiments of the invention are described, the skilled artisan will appreciate that various changes and modifications can be made. References to preparations carried out in a similar manner to, or by the general method of, other preparations, may encompass variations in routine parameters such as time, temperature, workup conditions, minor changes in reagent amounts etc.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded, and chemical shifts are reported in parts per million (ppm) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. Mass spectra were obtained using electrospray (ES) ionization techniques. All temperatures are reported in degrees centigrade.

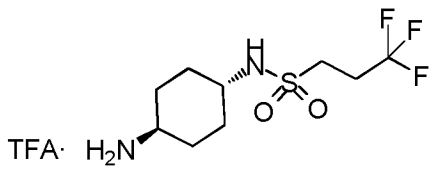
Reactions involving metal hydrides (including sodium hydride) and organo-metallic reagents are carried out under argon or nitrogen unless otherwise specified.

In the following Intermediates and Examples, where the relative stereochemistry of the compound has been identified, this is indicated both in the name and structure of the compound.

In certain of the following Intermediates and Examples, starting materials are identified by reference to other Intermediate or Example numbers. This does not signify that the actual material (or "batch") obtained from any particular Intermediate or Example was necessarily used in a subsequent step exemplified herein, but is used as a short-hand means of denoting the relevant compound name.

Intermediates

Intermediate A, TFA salt: *N*-((1,4-*trans*)-4-aminocyclohexyl)-3,3,3-trifluoropropane-1-sulfonamide, TFA salt



(a) *tert*-Butyl ((1r,4r)-4-aminocyclohexyl)carbamate (compound 7, wherein Pg is Boc)

In a 10 L reactor, a solution of (1,4-*trans*)-cyclohexane-1,4-diamine (compound 6) (89 g, 779 mmol, Aldrich Sigma) in Et_2O (2 L) was cooled to 5 °C, then a solution of di-*tert*-butyl dicarbonate (170 g, 779 mmol) in Et_2O (1 L) was added dropwise over 2 h. The reaction mixture was stirred at 5 °C for 2 h and at RT overnight. To the reaction mixture, 10% citric acid solution (3 L) was added and stirred for 30 min. The insoluble solid was filtered off, and the phases were separated. The aqueous layer was washed with Et_2O (1 L). The aqueous phase was cooled to 10 °C and basified with solid NaOH (pH 14), then extracted with DCM (2 x 2 L). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to give a white solid (110 g, 66% yield).

This was combined with another batch (210 g) of this compound (compound 7) then re-purified by flash column chromography (2-5% MeOH/ DCM) to afford a white solid (compound 23) (297 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 – 4.28 (1H, m), 3.48-3.28 (1H, m), 2.68 – 2.57 (1H, m), 2.01 – 1.89 (2H, m), 1.89 – 1.69 (2H, m), 1.35 (9H, s) and 1.28 – 1.05 (4H, m).

(b) <u>*tert*-butyl ((1,4-*trans*)-4-(3,3,3-trifluoropropylsulfonamido)cyclohexyl)-carbamate (compound 8)</u>

This reaction was performed in two batches. To a suspension of *tert*-Butyl ((1,4-*trans*)-4-aminocyclohexyl)carbamate (compound 7, wherein Pg is tert-butyl) (30 g, 140 mmol) in THF (1.33 L), cooled at -78 °C, *n*-butyllithium (56 mL, 140 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 20 min and at -10 °C for 10 min. After cooling to -78 °C, 3,3,3-trifluoropropane-1-sulfonyl chloride (17.64 mL, 140 mmol, purchased from Matrix) was added. After stirring for 1.5 h, it was allowed to warm to RT and stirred for 20 min. The reaction mixture was diluted with H_2O (500 mL), followed by addition of a solution 2M HCl (20 mL) and was extracted with EtOAc (400 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give a white solid (43.5 g, 83% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (1H, d), 6.77 – 6.70 (1H, m), 3.30 – 3.23 (2H, m), 3.17 – 3.01 (2H, m), 2.70 – 2.56 (2H, m), 1.87 – 1.67 (4H, m), 1.36 (9H, s) and 1.31 – 1.13 (4H, m).

(c) <u>*N*-((1,4-*trans*)-4-aminocyclohexyl)-3,3,3-trifluoropropane-1-sulfonamide, TFA salt (Intermediate A, TFA salt)</u>

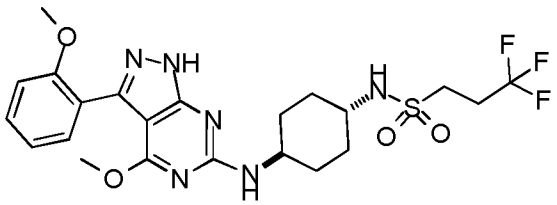
TFA (182 mL, 2377 mmol) was added to a solution of *tert*-butyl ((1,4-*trans*)-4-(3,3,3-trifluoropropylsulfonamido)cyclohexyl)carbamate (compound 8) (89 g, 238 mmol) in DCM (732 mL), cooled to 0 °C. The reaction mixture was stirred at RT overnight. The mixture was concentrated to dryness and co-evaporated with Et_2O (100 mL) to give a white solid (Intermediate A, TFA salt) (93.5 g, quant. yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (3H, br s), 7.43 (1H d), 3.34 – 3.24 (2H, m), 3.16 – 3.05 (1H, m), 2.99 – 2.86 (1H, m), 2.72 – 2.56 (2H, m), 1.95 – 1.84 (4H, m) and 1.43 – 1.21 (4H, m).

Final Compounds

Example 1

Final Compound 3: 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide (Formula I)



3-Bromo-4,6-dichloro-1*H*-pyrazolo[3,4-d]pyrimidine (compound 1)

This reaction was run five times with 1 g each batch. The amounts shown are a total of each of the five batches.

To a solution of 4,6-dichloro-1*H*-pyrazolo[3,4-d]pyrimidine (compound 1a) (5 g, 26.5 mmol, Chemshuttle) in ACN (100 mL) was added *N*-bromosuccinimide (5.18 g, 29.1 mmol). The reaction was heated in a microwave at 100 ºC over 15 minutes. ACN was removed under vacuum. The remaining residue was partitioned between EtOAc (150 mL) and water (300mL H_2O + 100 mL NaCl). The aqueous layer was extracted wit EtOAc (150 mL). Organic layers were combined, washed water (100 mL H_2O + 20 mL NaCl) X 3, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was triturated with water (30 mL) x3 and dried *in vacuo* at 45ºC to afford a solid 3-bromo-4,6-dichloro-1*H*-pyrazolo[3,4-d]pyrimidine (compound 1) (6.5 g, 92% yield).

Method A

(a) 3-bromo-6-chloro-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound 3, wherein Pg is SEM)

To a suspension of 3-bromo-4,6-dichloro-1*H*-pyrazolo[3,4-d]pyrimidine (compound 1) (5.94 g, 22.17 mmol) in dichloromethane (206 ml), cooled at 0 °C. DIPEA (11.31 ml, 66.5 mmol) was added dropwise and the resulting solution was stirred at 0 °C over 5 min. After this time, 2-(trimethylsilyl)ethoxymethyl chloride (4.67 ml, 26.6 mmol) was added dropwise and the resulting solution was stirred at 0 °C over 3 h. H_2O (200 mL) was added to the reaction and the phases were separated. The aqueous layer was extracted with DCM (1 x 100

mL). The organic layers were combined, dried with Na_2SO_4, filtered and concentrated to give an orange oil, that was purified by flash column chromatography (EtOAc/cyclohexane 0-20%) to afford a yellow oil (compound 2). This material (6.35 g) was then suspended in MeOH (224 ml). Sodium methoxide solution in MeOH (25 wt%, 3.99 ml, 17.54 mmol) was then added and the resulting solution was stirred at room temperature over 2 h. The mixture was partitioned between EtOAc (200 mL) and H_2O (300 mL + 50 mL NaCl). The layers were separated and the organic layer was washed with (200 mL H_2O + 50 mL NaCl) X 3. The resulting organic phase was dried with Na_2SO_4, filtered and concentrated to afford a white solid [3-bromo-6-chloro-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound 3, wherein Pg is SEM)] (5.71 g, 65.4% yield over two steps).

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.62 (2H,s), 4.14 (3H, s), 3.59 (2H, t), 0.84 (2H, t) and -0.07 (9H, s).

(b) *N*-((1,4-*trans*)-4-((3-bromo-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)-3,3,3-trifluoropropane-1-sulfonamide (compound 4, wherein Pg is SEM)

To a suspension of 3-bromo-6-chloro-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound 3, wherein Pg is SEM) (58.5 g, 134 mmol) in 1,4-dioxane (700 mL), intermediate A (93 g, 241 mmol) and DIPEA (74.7 mL, 428 mmol) were added and the resulting suspension heated at 110 °C for 3 nights. The reaction was partitioned between EtOAc (700 mL) and H_2O (1.2 L) and the aqueous layer extracted with further EtOAc (500 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a brown oil (175 g). Crude material was purified by flash column chromatography (5-25% EtOAc/cyclohexane) to afford a yellow pale powder (compound 4, wherein Pg is SEM) (44.95 g, 53.2% yield).

MS (+ve ion electrospray): *m/z* 631 / 633 [MH^+]

(c) 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide (compound 5, wherein Pg is SEM)

To a solution of *N*-((1,4-*trans*)-4-((3-bromo-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)-3,3,3-trifluoropropane-1-sulfonamide (compound 4, wherein Pg is SEM) (44.9 g, 71.1 mmol) in DMF (600 mL), (2-methoxyphenyl)boronic acid (16.20 g, 107 mmol), potassium carbonate (49.1 g, 355 mmol) and tetrakis(triphenylphosphine)palladium (0) (8.22 g, 7.11 mmol) were added. The resulting suspension was purged with N_2 and heated at 130 °C for 4.5 h. The reaction was filtered through celite, which was washed EtOAc (8 x 100 mL). The organic layer was

washed with H_2O (2 x 1 L), dried over Na_2SO_4, filtered and concentrated to afford a brown oil (58 g). Crude material was purified by flash column chromatography (5-40% EtOAc/cyclohexane) to give a yellow pale foam (compound 5, wherein Pg is SEM) (40.84 g, 87% yield).

MS (+ve ion electrospray): *m/z* 659 [MH^+]

(d) 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide (Formula I)

To a solution of 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide (compound 5, wherein Pg is SEM) (40.84 g, 57.7 mmol) in MeOH (745 ml) was cooled to 0 °C. Acetyl chloride (44.8 ml, 634 mmol) was added dropwise and the solution was stirred at RT overnight. The reaction was partitioned between DCM (500 mL), sat. aq. sol. $NaHCO_3$ (200 mL) and 2M NaOH (until pH 7). The phases were separated and the aqueous layer was extracted with DCM (350 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (20% (3:1 EtOAc:EtOH)/cyclohexane) to afford a yellow pale solid (12.66g) and a second impure crop (24g). This impure fraction was triturated with Et_2O to give a cream solid. Both solids were combined and triturated with Et_2O to give a white solid (Formula I) (21.45 g, 70.4% yeild).

This was then combined with another batch (21g) of this compound (Formula I) which was dissolved in DCM/MeOH, concentrated, titruated with Et_2O and dried under vacumn at 45 °C over 10 days to give the desired product (37.5g) as a white solid.

^1H NMR (400 MHz, DMSO-d_6) δ 12.89 (1H, br s), 7.43 – 7.29 (3H, m), 7.12 – 6.95 (3H, m), 3.86 (3H, br s), 3.74 – 3.61 (4H, m), 3.38 – 3.25 (2H, m), 3.21 – 3.09 (1H, m), 2.74 – 2.57 (2H, m), 2.02 – 1.86 (4H, m) and 1.44 – 1.28 (4H, m).

MS (+ve ion electrospray): *m/z* 529 [MH^+]

Method B

(a) 3-bromo-4,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound 2, wherein Pg is THP)

3-bromo-4,6-dichloro-1*H*-pyrazolo[3,4-d]pyrimidine (compound 1) (40.0 g, 149 mmol), 3,4-dihydro-2*H*-pyran (41 mL, 447 mmol) and *p*-toluenesulfonic acid monohydrate (5.7 g, 30.0 mmol) were dissolved in THF (650 mL) and heated at 70 °C for 2 h. The solvent was removed under vacuum and the solid residue triturated in Et_2O (300 mL) at 40°C for 2 h. The resulting suspension was allowed to slowly cool down to RT. This residue was washed with Et_2O to give desired product (compound 2, wherein Pg is THP) (41.5 g, 79% yield).

MS (+ve ion electrospray): *m/z* 353 / 351 [MH^+]

(b) 3-bromo-6-chloro-4-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound 3, wherein Pg is THP)

A solution of NaOMe (5.5 g, 102 mmol) in MeOH (500 mL) was added dropwise over 1 h to a solution of 3-bromo-4,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound 2, wherein Pg is THP) (35.8 g, 102 mmol) in MeOH (160 mL). The resulting suspension was stirred for 30 min. Solvent was removed and crude was taken up with EtOAc, washed with sat. aq. sol. $NaHCO_3$ and dried with Na_2SO_4 to give desired product (compound 3, wherein Pg is THP) (35.5 g, quant. yield). This was used in subsequent reactions without further purification.

MS (+ve ion electrospray): *m/z* 349 / 347 [MH^+]

(c) *N*-((1,4-*trans*)-4-((3-bromo-4-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)-3,3,3-trifluoropropane-1-sulfonamide (compound 4, wherein Pg is THP)

DIPEA (20 mL, 115 mmol), followed by intermediate A (7.4 g, 19.1 mmol), were added to a stirred solution of 3-bromo-6-chloro-4-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (compound 3, wherein Pg is THP) (8.6 g, 24.8 mmol) in EtOH (190 mL) at RT under Argon. The solvent was removed under vacumn where EtOAc and sat. aq. sol. $NaHCO_3$ were added and the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were dried with Na_2SO_4, the solvent was removed and the resulting residue was purified by flash column chromatography (7:3 cyclohexane in EtOAc) to afford the desired product (compound 4, wherein Pg is THP) (7.84 g, 65% yield).

MS (+ve ion electrospray): *m/z* 587 / 585 [MH^+]

(d) 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)-cyclohexyl)propane-1-sulfonamide (compound 5, wherein Pg is THP)

N-((1,4-*trans*)-4-((3-bromo-4-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)-3,3,3-trifluoropropane-1-sulfonamide (compound 4, wherein Pg is THP) (3.9 g, 6.6 mmol), 2-methoxyphenylboronic acid (1.37 g, 8.9 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (483 mg, 0.66 mmol), sodium carbonate (2.1 g, 39.6 mmol), DME (160 mL) and H_2O (80 mL) were added in a reaction vessel under argon. The resulting mixture was stirred at 110 °C for 30 min. The reaction mixture was filtered then concentrated under vacuum. The residue was taken up in EtOAc and washed with a sat. aq. sol. NH_4Cl. The layers were separated and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The crude material was purified by

flash column chromatography (6:4 Cyclohexane in EtOAc) to afford desired product (compound 5, wherein Pg is THP) (4.04 g, quant. yield).

MS (+ve ion electrospray): *m/z* 613 [MH^+]

(e) 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide (Formula I)

1.25 M HCl in MeOH (450 mL, 568 mmol) was added to 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide (compound 5, wherein Pg is THP) (5.96 g, 9.7 mmol). The resulting mixture was stirred at 60 °C for 30 min. The reaction mixture was concentrated under vacuum to a final volume of 100 mL. The resulting mixture was then treated with sat. aq. sol. $NaHCO_3$ (300 mL) and extracted with EtOAc (400 mL). The aqueous layer was extracted with EtOAc (2 x). The combined organics layers were dried over Na_2SO_4, and evaporated under vacuum to obtain crude material which was purified by flash column chromatography (Cyclohexane in EtOAc from 3:7 to 1:9) to give desired product (Formula I) (3.5 g, 68% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (1H, br s), 7.29 – 7.43 (3H, m), 7.09 (1H, d), 6.94 – 7.03 (2H, m), 3.83 (3H, s), 3.62 – 3.75 (4H, m), 3.26 – 3.31 (2H, m), 3.17 (1H, br s), 2.59 – 2.73 (2H, m), 1.87 – 2.01 (4H, m) and 1.27 – 1.44 (4H, m).

MS (+ve ion electrospray): *m/z* 529 [MH^+]

Biological Activity

Intramacrophage Leishmania donovani assay

The intramacrophage Leishmania assay was performed exactly as described in de Rycker et al (Antimicrob Agents Chemother. 2013 Jul;57(7):2913-22. doi: 10.1128/AAC.02398-12. Epub 2013 Apr 9. Comparison of a high-throughput high-content intracellular Leishmania donovani assay with an axenic amastigote assay. De Rycker M, Hallyburton I, Thomas J, Campbell L, Wyllie S, Joshi D, Cameron S, Gilbert IH, Wyatt PG, Frearson JA, Fairlamb AH, Gray DW.) . Briefly, 1 µl of compound was pre-dispensed into 384 well sterile intermediary plates. For single point screening, amphotericin B was added to all wells of column 24 as a positive control (final concentration 2 µM) and DMSO to column 23. For potency determinations, ten-point, one in three dilution curves were created with the highest concentration being 50 µM and on each plate a control curve of amphotericin B was included. Controls were as follows: columns 11 and 12: DMSO, columns 23 and 24: amphotericin B (final concentration 2 µM). To the intermediary plates, 100 µl of THP-1 media was added and plates were shaken for >5 min to ensure complete mixing. THP-1 cells (8,000 per well, 50 µl) were plated into black clear-bottom 384 well plates (Corning) in presence of

10 nM PMA. After 20 min at RT, the plates were incubated at 37 °C under 5% CO_2 in a humidified incubator for 75 h. The cells were then washed with 450 µl sterile phosphate buffered saline (PBS) supplemented with 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.1% (w/v) bovine serum albumin (PBS-A) and amastigotes were added to all wells at a multiplicity of infection of 5 (40,000 amastigotes per well). After 40 min at RT, plates were returned to the incubator. Amastigotes were incubated in the presence of macrophages for 16 h. Any remaining extracellular amastigotes were subsequently removed with an overflow wash of 1 mL PBS-A per well (wash buffer is being aspirated from the top of the well as it is being dispensed) followed by addition of 25 µl of the compound pre-dilutions using a Matrix Hydra DT pipetting station. The final dilution of each compound was 200-fold. Plates were incubated for 72 h and then washed (250 µl PBS-A) and fixed (4 % (v/v) formaldehyde-PBS, 30 min, RT). After fixation, the wells were washed with 250 µl PBS, stained (10 µg/mL DAPI, 0.4 µg mL-1 HCS Cellmask Deep Red in PBS + 0.1% (v/v) Triton X-100, 30 min, RT) and washed with 250 µl PBS. Finally, PBS + 0.05% (v/v) thimerosal was added to the wells, the plates were sealed and imaged on a high-content microscope (GE IN Cell 1000 or GE IN Cell 2000) using a 10x objective. Image analysis was carried out with GE IN Cell Analyzer 1000 Workstation using the "Multi Target Analysis" module. Settings for segmentation were as follows: nuclei: minimum area: 142.384 μm^2, sensitivity: 81, method: top-hat; cells: characteristic area: 2500 μm^2, sensitivity: 60, method: multiscale top-hat; organelles (amastigotes): granule size 1 – 3, 3 scales, sensitivity: 90, detection in entire cell. For each well, i) THP-1 cell count (cytotoxicity readout) and ii) average number of amastigotes per cell (potency readout) were calculated, both in terms of pEC_{50} values.

Results of the Intramacrophage *Leishmania donovani* assay

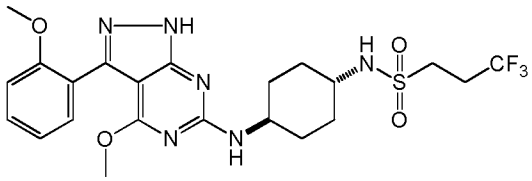
The compound of Formula (I) was tested in the Intramacrophage *Leishmania donovani* assay.

The compound of Formula (I) is found to have an average pEC_{50} value of 6.5 against amastigotes and pEC_{50} value of 4.6 against THP-1 cells in the Intramacrophage *Leishmania donovani* assay.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. The compound 3,3,3-trifluoro-*N*-((1,4-*trans*)-4-((4-methoxy-3-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)cyclohexyl)propane-1-sulfonamide, having the Formula (I):

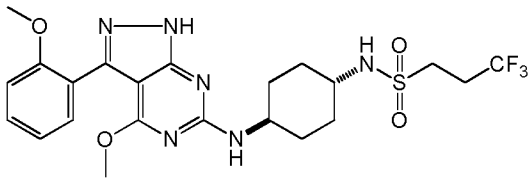


(I)

or a salt thereof.

2. The compound of Formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.

3. The compound of Formula (I) according to claim 1, having the Formula (I):



(I).

4. A pharmaceutical composition comprising a compound according to any of claims 1 to 3, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier.

5. A combination comprising (a) a compound of Formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, and (b) at least one additional therapeutic agent.

6. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for use in therapy.

7. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of leishmaniasis.

8. Use of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of leishmaniasis.

9. A method of treatment or prevention of leishmaniasis, which method comprises administering to a mammal in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof.

10. A compound for use according to claim 7, wherein the leishmaniasis is visceral leishmaniasis.

11. Use of a compound according to claim 8, wherein the leishmaniasis is visceral leishmaniasis.

12. A method of treatment or prevention according to claim 9, wherein the mammal is a human.

13. A method of treatment or prevention according to claim 9 or claim 12, wherein the leishmaniasis is visceral leishmaniasis.

14. A pharmaceutical composition according to claim 4 for use in therapy.

15. A pharmaceutical composition according to claim 4 for use in the treatment or prevention of leishmaniasis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/050124

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P33/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/121107 A1 (HOFFMANN LA ROCHE [CH]; DING QINGJIE [US]; JIANG NAN [US]; ROBERTS JOH) 22 December 2005 (2005-12-22) claims 1-19	1-15
A	RAM VISHNU J ET AL: "Synthesis of functionalized pyrazoles and pyrazolo(3,4-d)pyrimidines as potential leishmanicides", INDIAN JOURNAL OF CHEMISTRY. SECTION B, COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH (C S I R), IN, vol. 34, no. 6, 1 January 1995 (1995-01-01), pages 521-524, XP009188765, ISSN: 0376-4699 page 521, paragraph Biological Actvity - page 522; compounds 4a-e	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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1 March 2016	11/03/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sotoca Usina, E

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	LAURA A. T. CLEGHORN ET AL: "Identification of Inhibitors of the Leishmania cdc2-Related Protein Kinase CRK3", CHEMMEDCHEM, vol. 6, no. 12, 9 December 2011 (2011-12-09), pages 2214-2224, XP055022427, ISSN: 1860-7179, DOI: 10.1002/cmdc.201100344 figure 2; compound Series 6	1-15
A	DE MELLO H ET AL: "Antileishmanial Pyrazolopyridine Derivatives: Synthesis and Structure?Activity Relationship Analysis", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 47, no. 22, 1 January 2004 (2004-01-01), pages 5427-5432, XP002545174, ISSN: 0022-2623, DOI: 10.1021/JM0401006 table 2; compounds 19, 20	1-15
A	ALEX M. ARONOV ET AL: "Selective Tight Binding Inhibitors of Trypanosomal Glyceraldehyde-3-phosphate Dehydrogenase via Structure-Based Drug Design", JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 24, 1 November 1998 (1998-11-01), pages 4790-4799, XP055054326, ISSN: 0022-2623, DOI: 10.1021/jm9802620 Scheme 2; table 3; compounds 7a-o	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2016/050124

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