Title of the Invention: Novel heterocyclic derivatives
Abstract Title: 2-Arylazole derivatives as antiprotozoal agents

2-Arylazole derivatives of formula (I) or salts or solvates thereof. R¹ and R² are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, hydroxalkyl or aminoalkyl. Y is O or S. R³ is hydrogen, alkyl, halogen or aryl. S, T, V, W and X are independently N or C-R⁴, with the proviso that at least three of S, T, V, W and X are C-R⁴; or two adjacent groups selected from S, T and V form an optionally substituted phenyl ring. R⁴ is hydrogen, alkyl, halogen, -CH₂-R⁵, -OR⁶, -SR⁶ or aryl. R⁵ is cycloalkyl, alkenyl, alkynyl, aryl or heteroaryl, which may be substituted with various substituents. R⁶ is alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heteroaryl, which may be substituted with various substituents. Preferably Y = O; X = C-R⁴; R² = H, CH₃; one of R¹ and R² is H and the other 1-methylhexyl.

Examples also relate to 2-thiophenoxazoles, 2-benzothiophenoxazoles, 2-cyclohexyloxazoles, 2-benzoxazoles, 2-benzodioxoloxazoles and 2-benzonitrileoxazoles; and to oxazole derivatives wherein R¹ and R² together with the nitrogen they are attached to form a piperdine, morpholine or piperazine ring. The compounds may be useful in the treatment of protozoal infections including American trypanosomiasis, African trypanosomiasis, sleeping sickness, Kala-Azar, leishmaniasis, trichomoniasis, Chagas disease and malaria.
Novel Heterocyclic Derivatives

FIELD OF THE INVENTION

[0001] The present invention relates to novel 2-arylazole derivatives, compositions containing them, processes for their preparation and their use as pharmaceutically active agents.

BACKGROUND OF THE INVENTION

[0002] Human or non-human mammalian diseases attributable to infection of the individual by a parasite, especially those prevalent in developing countries in regions of the world such as sub-Saharan Africa, India, Southeast Asia, Central and Southern America, are poorly treated with existing medicaments. For example, treatment of African sleeping sickness, a disease caused by infection of an individual with Trypanosoma brucei parasites, is currently compromised by the poor efficacy, high toxicity and difficult administration requirements of existing drugs such as eflornithine, melarsoprol and suramin. Similarly, treatment of Chagas disease, a disease caused by infection of an individual with Trypanosoma cruzi parasites, is compromised by the ineffectiveness of current drugs such as nifurtimox and benznidazole. Existing therapies for diseases caused by Leishmania sp. parasites, visceral and cutaneous leishmaniasis, including treatment by drugs such as meglumine antimonite, sodium stibogluconate and amphotericin B also suffer from potential toxicity and limited efficacy of these agents. Therefore, there exists a need for new pharmaceutical agents for the effective and safe treatment of these tropical diseases.

[0003] The present invention also seeks to provide compounds, stereoisomeric forms and/or pharmaceutically acceptable salts of the 2-arylazole family which can be used as pharmaceutically active agents, especially for prophylaxis and/or treatment of tropical diseases caused by leishmania, trypanosome, protozoa, and plasmodium falciparum such as South American trypanosomiasis, African trypanosomiasis, sleeping sickness, Kala-Azar, visceral leishmaniasis, Baghdad boil or Aleppo boil, cutaneous leishmaniasis (CL), espundia, Chagas disease, mucocutaneous
leishmaniasis (MCL), trichomoniasis, urogenital trichomoniasis, giardiasis, lamblia
dysentery, amoebiasis, primary amebic meningoencephalitis (PAM), keratitis or
meningitis, coccidiosis, sarcosporidiosis, toxoplasmosis, malaria tropica, malaria
tertiana, malaria quartana, pneumocystis carinii, pneumonia, pneumocystosis,
Balantidium dysentery, and oriental sore.

**SUMMARY OF THE INVENTION**

[0004] The invention provides novel 2-arylazole derivatives of formula (I):

![Chemical Structure](image)

(1)

[0005] wherein R₁ and R² are independently hydrogen, alkyl, cycloalkyl, alkenyl,
alkynyl, hydroxyalkyl, alkoxyalkyl or aminoalkyl;

[0006] R₃ is hydrogen, alkyl, halogen, or aryl;

[0007] S, T, V, W and X are independently C-R⁴ or N; with the proviso that at
least three of S, T, V, W and X are independently C-R⁴; or two adjacent groups
selected from S, T and V together form an optionally substituted phenyl ring;

[0008] R⁴ is independently hydrogen, alkyl, halogen, -CH₂R⁵, -OR⁶, -SR⁶ or aryl;

[0009] R⁵ is cycloalkyl, alkenyl or alkynyl, each of which is unsubstituted or
substituted, or optionally substituted aryl or heteroaryl, whereby the substituents are
independently selected from the group consisting of cyano, nitro, halogen, alkyl,
haloalkyl, alkylthio, arylthio, alkoxy, alkanoyl, alkanoyloxy, alkanoylamino,
aminocarbonyl, alkoxy carbonyl, alkenoyl, alkynoyl, aroyl, alkylsulfinyl and
alkylsulfonyl;

[0010] R⁶ is alkyl, cycloalkyl, alkenyl or alkynyl, each of which is unsubstituted
or substituted, or optionally substituted aryl or heteroaryl, whereby the substituents
are independently selected from the group consisting of cyano, nitro, halogen, alkyl, haloalkyl, alkylthio, arylthio, alkoxy, alkanoyl, alkanoyloxy, alkanoylamino, aminocarbonyl, alkoxy carbonyl, alkenoyl, alkynoyl, aroyl, alkylsulfinyl and alkylsulfonyl;

[0011] Y is oxygen or sulfur;

[0012] or a pharmaceutically acceptable salt or solvate thereof.

[0013] These compounds are useful as pharmaceutically active agents, especially for prophylaxis and/or treatment of tropical diseases caused by Trypanosoma sp., Leishmania sp., Balantidium coli, Eimeria sp., Entamoeba histolytica, Giardia intestinalis, Isospora belli, Naegleria fowleri, Plasmodium sp. and Trichomonas vaginalis such as African trypanosomiasis, Chagas disease, visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), diffuse cutaneous leishmaniasis, Balantidium dysentery, coccidiosis, amoebiasis, giardiasis, primary amebic meningoencephalitis (PAM), malaria and trichomoniasis.

DETAILED DESCRIPTION

Definitions

[0014] “Alkyl” refers to both straight and branched carbon chains; references to individual alkyl groups are specific for the straight chain (e.g. butyl = n-butyl). In one embodiment of alkyl, the number of carbons atoms is 1-20, in another embodiment of alkyl, the number of carbon atoms is 1-8 carbon atoms and in yet another embodiment of alkyl, the number of carbon atoms is 1-4 carbon atoms. Other ranges of carbon numbers are also contemplated depending on the location of the alkyl moiety on the molecule;

[0015] “Alkenyl” refers to both straight and branched carbon chains which have at least one carbon-carbon double bond. In one embodiment of alkenyl, the number of double bonds is 1-3, in another embodiment of alkenyl, the number of double bonds is one. In one embodiment of alkenyl, the number of carbons atoms is 2-20, in another embodiment of alkenyl, the number of carbon atoms is 2-8 and in yet another embodiment of alkenyl, the number of carbon atoms is 2-4. Other ranges of carbon-
carbon double bonds and carbon numbers are also contemplated depending on the location of the alkenyl moiety on the molecule;

[0016] “Alkynyl” refers to both straight and branched carbon chains which have at least one carbon-carbon triple bond. In one embodiment of alkynyl, the number of triple bonds is 1-3; in another embodiment of alkynyl, the number of triple bonds is one. In one embodiment of alkynyl, the number of carbons atoms is 2-20, in another embodiment of alkynyl, the number of carbon atoms is 2-8 and in yet another embodiment of alkynyl, the number of carbon atoms is 2-4. Other ranges of carbon-carbon double bonds and carbon numbers are also contemplated depending on the location of the alkenyl moiety on the molecule;

[0017] “Aryl” refers to a C₆-C₁₀ aromatic ring structure. In one embodiment of aryl, the moiety is phenyl, naphthyl, tetrahydronaphthyl, phenylecyclopropyl and indanyl; in another embodiment of aryl, the moiety is phenyl.

[0018] “Alkoxy” refers to -O-alkyl, wherein alkyl is as defined above;

[0019] “Alkanoyl” refers to formyl (-C(=O)H) and -C(=O)-alkyl, wherein alkyl is as defined above;

[0020] “Alkanoyloxy” refers to -O-C(=O)-alkyl, wherein alkanoyl is as defined above;

[0021] “Alkanoylamino” refers to -NH₂-C(=O)-alkyl, wherein alkanoyl is as defined above and the amino (NH₂) moiety can be substituted by alkyl as defined above;

[0022] “Aminocarbonyl” refers to -NH₂-C(=O), wherein the amino (NH₂) moiety can be substituted by alkyl as defined above;

[0023] “Alkoxy carbonyl” refers to -C(=O)-O-alkyl, wherein alkoxy is as defined above;

[0024] “Alkenoyl” refers to -C(=O)-alkenyl, wherein alkenyl is as defined above;

[0025] “Alkynoyl” refers to -C(=O)-alkynyl, wherein alkynyl is as defined above;

[0026] “Aroyl” refers to -C(=O)-aryl, wherein aryl is as defined above;
“Alkylsulfanyl” refers to -S(=O)-alkyl, wherein alkyl is as defined above;

“Alkylsulfonyl” refers to –SO₂-alkyl, wherein alkyl is as defined above;

“Cyclo” as a prefix (e.g. cycloalkyl, cycloalkenyl, cycloalkynyl) refers to a saturated or unsaturated cyclic ring structure having from three to twelve carbon atoms in the ring the scope of which is intended to be separate and distinct from the definition of aryl above. In one embodiment of cyclo, the range of ring sizes is 4-10 carbon atoms; in another embodiment of cyclo the range of ring sizes is 3-4. Other ranges of carbon numbers are also contemplated depending on the location of the cyclo moiety on the molecule;

“Halogen” means the atoms fluorine, chlorine, bromine and iodine. The designation of “halo” (e.g. as illustrated in the term haloalkyl) refers to all degrees of substitutions from a single substitution to a perhalo substitution (e.g. as illustrated with methyl as chloromethyl (-CH₂Cl), dichloromethyl (-CHCl₂), trichloromethyl (-CCl₃));

“Heterocycle”, “heterocyclic” or “heterocyclo” refer to fully saturated or unsaturated, including aromatic (i.e. ‘hetaryl’) cyclic groups, for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothieryl, triazolyl,
triazinyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoazolyl, benzodioxolyl, benzothienyl, quinuclidinyl, quinoliny1, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxaliny1, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl), dihydrosoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzoldolyl, phenanthroliny1, acridiny1, phenanthridiny1, xanthenyl and the like.

[0032] “Pharmaceutically acceptable salt” refers to any salt of a compound of this invention which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. The compounds of the present invention may be basic and may form salts with organic or inorganic acids. Examples of suitable acids for such acid addition salt formation are hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, citric acid, oxalic acid, malonic acid, salicylic acid, p-aminosalicylic acid, malic acid, fumaric acid, succinic acid, ascorbic acid, maleic acid, sulfuric acid, nitric acid, formic acid, propionic acid, gluconic acid, lactic acid, tartaric acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, methanesulfonic acid, ethanesulfonic acid, nitrous acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, p-toluenesulfonic acid, naphthysulfonic acid, sulfanilic acid, camphorsulfonic acid, mandelic acid, o methylmandelic acid, benzenesulfonic acid, adipic acid, d-o-tolyltartric acid, tartaric acid, (o, m, p)-toluic acid, naphthylamine sulfonic acid, and other mineral or carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. In case, the compound bear acidic substituents, the formation of salts with inorganic or organic bases may be possible. Examples of such bases are sodium or potassium hydroxide, ammonium hydroxide, tetraalkylammonium hydroxide, lysine or arginine and the like. Salts may be prepared in a conventional manner using methods well known in the art, for
example, by treatment of a solution of the compound of the general formula (I) with a 
solution of an acid, selected out of the group mentioned above.

[0033] Some of the compounds of the present invention may be crystallized or 
recrystallized from solvents such as aqueous and organic solvents. In such cases 
solvates may be formed. This invention includes within its scope stoichiometric 
solvates including hydrates as well as compounds containing variable amounts of 
water that may be produced by processes such as lyophilisation.

[0034] In the case of chiral substituents, compounds of the general formula (I) 
may exist in the form of optical isomers, e.g. enantiomers, diastereomers and mixtures 
of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, 
in particular the pure isomeric forms. The different isomeric forms may be separated 
or resolved one from the other by conventional methods, or any given isomer may be 
obtained by conventional synthetic methods or by stereospecific or asymmetric 
syntheses. Where a compound according to the general formula (I) contains an alkene 
moiety, the alkene can be presented as a cis or trans isomer or mixture thereof. When 
an isomeric form of a compound of the invention is provided substantially free of 
other isomers, it will preferably contain less than 5% w/w, more preferably less than 
2% w/w and especially less than 1% w/w of the other isomer(s).

[0035] In a first embodiment of the invention there are provided compounds 
of formula (I) wherein:

[0036] R¹ is C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ alkoxyalkyl, or 
C₁₋₁₀ aminoalkyl;

[0037] R² is hydrogen;

[0038] R³ is hydrogen or methyl; and

[0039] Y is oxygen.

[0040] In a second embodiment of the invention, there are provided compounds of 
formula (I) wherein:

[0041] R¹ is C₁₋₁₀ alkyl or cycloalkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ alkoxyalkyl, or 
C₁₋₁₀ aminoalkyl;
R² is hydrogen;
R³ is hydrogen or methyl; and
Y is sulfur.

In a third embodiment of the invention, there are provided compounds of formula (I) wherein:

R¹ is C₁₀ alkyl or cycloalkyl, C₁₀ hydroxyalkyl, C₁₀ alkoxyalkyl, or C₁₀ aminoalkyl;
R² is hydrogen;
R³ is hydrogen or methyl;
Y is oxygen.
T, V, W, and X are independently C-R¹;
S is nitrogen;
R⁴ is independently hydrogen, alkyl, -CH₂R⁵⁻, -OR⁶ or -SR⁶.

In a fourth embodiment of the invention, there are provided compounds of formula (I) wherein:

R¹ is C₁₀ alkyl or cycloalkyl, C₁₀ hydroxyalkyl, C₁₀ alkoxyalkyl, or C₁₀ aminoalkyl;
R² is hydrogen;
R³ is hydrogen or methyl;
Y is oxygen.
S, V, W, and X are independently C-R¹;
T is nitrogen;
R⁴ is independently hydrogen, alkyl, -CH₂R⁵⁻, -OR⁶ or -SR⁶.

In a fifth embodiment of the invention, there are provided compounds of formula (I) wherein:
[0062] R¹ is C₁₀ alkyl or cycloalkyl, C₁₀ hydroxyalkyl, C₁₀ alkoxyalkyl, or C₁₀ aminoalkyl;

[0063] R² is hydrogen;

[0064] R³ is hydrogen or methyl;

[0065] Y is oxygen;

[0066] S, T, V, W, and X are independently C-R⁴;

[0067] R⁴ is independently hydrogen, alkyl, -CH₂R⁵, -OR⁶ or -SR⁶.

[0068] In a sixth embodiment of the invention, there are provided compounds of formula (I) wherein:

[0069] R¹ is C₁₀ alkyl or cycloalkyl, C₁₀ hydroxyalkyl, C₁₀ alkoxyalkyl, or C₁₀ aminoalkyl;

[0070] R² is hydrogen;

[0071] R³ is hydrogen;

[0072] Y is oxygen

[0073] S, T, V, W, and X are independently C-R⁴;

[0074] R⁴ is independently hydrogen, alkyl, -CH₂R⁵, -OR⁶ or -SR⁶.

[0075] In a seventh embodiment of the invention, there are provided compounds of formula (I) wherein:

[0076] R¹ is C₁₀ alkyl or cycloalkyl, C₁₀ hydroxyalkyl, C₁₀ alkoxyalkyl, or C₁₀ aminoalkyl;

[0077] R² is hydrogen;

[0078] R³ is hydrogen;

[0079] Y is sulfur;

[0080] S, T, V, W, and X are independently C-R⁴;

[0081] R⁴ is independently hydrogen, alkyl, -CH₂R⁵, -OR⁶ or -SR⁶;
R^5 is cycloalkyl, which is unsubstituted or substituted, or optionally substituted aryl or heteroaryl, whereby the substituents are independently selected from the group consisting of cyano, nitro, halogen, alkyl, alkylthio, alkoxy, alkoxy carbonyl, aroyl, alkylsulfinyl and alkylsulfonyl; and

R^6 is alkyl, or optionally substituted aryl or heteroaryl, whereby the substituents are independently selected from the group consisting of cyano, nitro, halogen, alkyl, alkylthio, alkoxy, alkoxy carbonyl, aroyl, alkylsulfinyl and alkylsulfonyl.

In a further embodiment of the present invention Y is oxygen. In a still further embodiment of the present invention S, T, V, W, and X are independently C-R^4. In a still further embodiment of the present invention R^1 is C_{1-10} alkyl, C_{3-12} cycloalkyl, C_{1-10} hydroxyalkyl, C_{1-10} alkoxyalkyl or C_{1-10} aminoalkyl. In a still further embodiment of the present invention R^2 is hydrogen. In a still further embodiment of the present invention R^3 is hydrogen or alkyl. In a still further embodiment of the present invention R^4 is independently hydrogen, alkyl, -CH_2R^5, -OR^6 or -SR^6.

In a further embodiment of the invention, the compound of formula (I) is selected from:

1. [2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-(1R,2R,5S)-2,6,6-trimethyl bicyclo[3.1.1]hept-3-yl)-amine

2. [2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine

3. Adamantan-2-yl-[2-(4-ethoxyphenyl)-oxazol-4-ylmethyl]-amine

4. Bicyclo[2.2.1]hept-2-yl-[2-(4-ethoxyphenyl)-oxazol-4-ylmethyl]-amine

5. [2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-(1-methyl-hexyl)-amine

6. ((1S,2R,5S)-6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-[2-(4-ethoxyphenyl)-oxazol-4-ylmethyl]-amine

7. [2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-(1-propyl-butyl)-amine

8. (1-Methylhexyl)-(2-phenyl-oxazol-4-ylmethyl)-amine
9. (1-Methylhexyl)-(2-o-tolyl-oxazol-4-ylmethyl)-amine
10. (1-Methylhexyl)-(2-m-tolyl-oxazol-4-ylmethyl)-amine
11. (1-Methylhexyl)-(2-p-tolyl-oxazol-4-ylmethyl)-amine
12. [2-(3-Ethoxyphenyl)-oxazol-4-ylmethyl]-(1-methyl-hexyl)-amine
13. [2-(2-Chlorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
14. [2-(3-Chlorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
15. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
16. 2-[(1-Methylhexylamino)-methyl]-oxazol-2-yl]-phenol
17. [2-(3-Methoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
18. [2-(4-Methoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
19. [2-(3,4-Dichlorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
20. [2-(3-Fluorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
21. [2-(4-tert-Butylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
22. (1-Methylhexyl)-(2-naphthalen-2-y1-oxazol-4-ylmethyl)-amine
23. [2-(2-Fluorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
24. [2-(4-Fluorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
25. (1-Methylhexyl)-(2-naphthalen-1-y1-oxazol-4-ylmethyl)-amine
26. [2-(2-Ethoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
27. (1-Methylhexyl)-[2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethyl]-amine
28. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
29. [2-(4-Bromophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
30. (1-Methylhexyl)-[2-(2-trifluoromethoxyphenyl)-oxazol-4-ylmethyl]-amine
31. (1-Methylhexyl)-[2-(3-trifluoromethoxyphenyl)-oxazol-4-ylmethyl]-amine
32. (1-Methylhexyl)-[2-(4-trifluoromethoxyphenyl)-oxazol-4-ylmethyl]-amine
33. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-(1R)-1-methylhexyl)-amine
34. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-(1S)-1-methylhexyl)-amine
35. [2-(4-Isopropoxy-phenyl)-oxazol-4-ylmethyl]-1-(1-methylhexyl)-amine
36. [2-(4-Butoxy-phenyl)-oxazol-4-ylmethyl]-1-(1-methylhexyl)-amine
37. (2-Biphenyl-4-yl-oxazol-4-ylmethyl)-(1-methylhexyl)-amine
38. (1-Methylhexyl)-[2-(4-trifluoromethylsulfanyl-phenyl)-oxazol-4-ylmethyl]-amine
39. (1-Methylhexyl)-(2-thiophen-2-yl-oxazol-4-ylmethyl)-amine
40. (2-Benzol[b]thiophen-2-yl-oxazol-4-ylmethyl)-(1-methylhexyl)-amine
41. [2-(2,4-Difluorophenyl)-oxazol-4-ylmethyl]-1-(1-methylhexyl)-amine
42. [2-(3,4-Difluorophenyl)-oxazol-4-ylmethyl]-1-(1-methylhexyl)-amine
43. [2-(3,5-Difluorophenyl)-oxazol-4-ylmethyl]-1-(1-methylhexyl)-amine
44. [2-(2,5-Difluorophenyl)-oxazol-4-ylmethyl]-1-(1-methylhexyl)-amine
45. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-(1R,2R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)-amine
46. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-ylmethyl)-amine
47. Bicyclo[2.2.1]hept-2-yl-[2-(4-chlorophenyl)-oxazol-4-ylmethyl]-amine
48. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-3,3,5-trimethyl-cyclohexyl)-amine
49. Adamantan-2-y1-[2-(4-chlorophenyl)-oxazol-4-ylmethyl]-amine
[00135] 50. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-cyclopentyl-amine
[00136] 51. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-cyclohexyl-amine
[00137] 52. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-cycloheptyl-amine
[00138] 53. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-cyclohexyl-methyl-amine
[00139] 54. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-(1-propyl-butyl)-amine
[00140] 55. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-((R)-1-cyclohexyl-ethyl)-amine
[00141] 56. [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-((S)-1-cyclohexyl-ethyl)-amine
[00142] 57. Adamantan-2-yl-[2-(4-butyl-phenyl)-oxazol-4-ylmethyl]-amine
[00143] 58. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine
[00144] 59. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(\((1R,2R,3R,5S)-2,6,6\)-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine
[00145] 60. Adamantan-2-yl-[2-(4-bromophenyl)-oxazol-4-ylmethyl]-amine
[00146] 61. [2-(4-Bromophenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine
[00147] 62. [2-(4-Bromophenyl)-oxazol-4-ylmethyl]-(\((1R,2R,3R,5S)-2,6,6\)-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine
[00148] 63. Adamantan-2-yl-(2-biphenyl-4-yl-oxazol-4-ylmethyl)-amine
[00149] 64. [2-(2,3-Difluorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
[00150] 65. [2-(2,6-Difluorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
[00151] 66. Adamantan-2-yl-[2-(4-tert-butyl-phenyl)-oxazol-4-ylmethyl]-amine
[00153] 68. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-cycloheptyl-amine
[00154] 69. [2-(4-Bromophenyl)-oxazol-4-ylmethyl]-cycloheptyl-amine

[00155] 70. [2-(4-tert-Butylphenyl)-oxazol-4-ylmethyl]-cycloheptyl-amine

[00156] 71. [2-(4-Butoxy-phenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine

[00157] 72. [2-(4-Butoxy-phenyl)-oxazol-4-ylmethyl]-(1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine

[00158] 73. [2-(4-Butoxy-phenyl)-oxazol-4-ylmethyl]-(1S,2R,5S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amine

[00159] 74. [2-(4-Butoxy-phenyl)-oxazol-4-ylmethyl]-cycloheptyl-amine

[00160] 75. (2-Biphenyl-4-yl-oxazol-4-ylmethyl)-(3,3,5-trimethyl-cyclohexyl)-amine

[00161] 76. (2-Biphenyl-4-yl-oxazol-4-ylmethyl) -((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine

[00162] 77. (2-Biphenyl-4-yl-oxazol-4-ylmethyl) -((1S,2R,5S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amine

[00163] 78. (2-Biphenyl-4-yl-oxazol-4-ylmethyl)-cycloheptyl-amine

[00164] 79. Adamantan-2-yl-[2-(4-butoxyphenyl)-oxazol-4-ylmethyl]-amine

[00165] 80. Cycloheptyl-[2-(4-ethoxyphenyl)-oxazol-4-ylmethyl]-amine

[00166] 81. Adamantan-2-yl-[2-(4-pentloxyphenyl)-oxazol-4-ylmethyl]-amine

[00167] 82. [2-(4-Penloxyphenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine

[00168] 83. [2-(4-Penloxyphenyl)-oxazol-4-ylmethyl] -((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine

[00169] 84. ((1S,2R,5S)-6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-[2-(4-penloxyphenyl)-oxazol-4-ylmethyl]-amine

[00170] 85. Cycloheptyl-[2-(4-penloxyphenyl)-oxazol-4-ylmethyl]-amine

[00171] 86. (1-Methylhexyl)-[2-(4-propoxyphenyl)-oxazol-4-ylmethyl]-amine
87. Adamantan-2-yl-[2-(4-propoxyphenyl)-oxazol-4-ylmethyl]-amine
88. [2-(4-Propoxyphenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine
89. Cycloheptyl-[2-(4-propoxyphenyl)-oxazol-4-ylmethyl]-amine
90. (1-Methylhexyl)-[2-(4-pentyloxyphenyl)-oxazol-4-ylmethyl]-amine
91. [2-(4-Propoxyphenyl)-oxazol-4-ylmethyl]-(1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-amine
92. (1S,2R,5S)-6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethyl]-[2-(4-propoxyphenyl)-oxazol-4-ylmethyl]-amine
93. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(3-pyrrolidin-1-yl-propyl)-amine
94. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(3-piperidin-1-yl-propyl)-amine
95. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(1-methyl-pyrrolidin-2-yl-ethyl)-amine
96. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(2,6-dimethoxybenzyl)-amine
97. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(4-methylbenzyl)-amine
98. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(4-methoxybenzyl)-amine
99. (1-Methylhexyl)-[2-(2-phenoxyphenyl)-oxazol-4-ylmethyl]-amine
100. (1-Methylhexyl)-[2-(3-phenoxyphenyl)-oxazol-4-ylmethyl]-amine
101. (1-Methylhexyl)-[2-(4-phenoxyphenyl)-oxazol-4-ylmethyl]-amine
102. [2-(4-Decyloxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
103. {2-[2-(2,2-Dimethyl-propoxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine
104. [2-(4-Cyclohexyloxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
[00190] 105. [2-(4-Cyclohexyloxyphenyl)-oxazol-4-ylmethyl]-((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine

[00191] 106. Cycloheptyl-[2-(4-cyclohexyloxyphenyl)-oxazol-4-ylmethyl]-amine

[00192] 107. [2-(4-Ethylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

[00193] 108. Cycloheptyl-[2-(4-isoproxyphenyl)-oxazol-4-ylmethyl]-amine

[00194] 109. [2-(4-Isoproxyphenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine

[00195] 110. [2-(4-Isoproxyphenyl)-oxazol-4-ylmethyl]-((1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine

[00196] 111. ((1S,2R,5S)-6,6-Dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-[2-(4-isoproxyphenyl)-oxazol-4-ylmethyl]-amine

[00197] 112. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-ethyl-amine

[00198] 113. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(1-methyl-butyl)-amine

[00199] 114. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-pentyl-amine

[00200] 115. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-isopropyl-amine

[00201] 116. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-propyl-amine

[00202] 117. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(1-ethyl-propyl)-amine

[00203] 118. sec-Butyl-[2-(4-butylphenyl)-oxazol-4-ylmethyl]-amine

[00204] 119. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-hexyl-amine

[00205] 120. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-cyclobutyl-amine

[00206] 121. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-cyclopentyl-amine

[00207] 122. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-cyclopropyl-amine

[00208] 123. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(1phenyl-ethyl)-amine

[00209] 124. (R)-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(1phenyl-ethyl)-amine

[00210] 125. Benzyl-[2-(4-butylphenyl)-oxazol-4-ylmethyl]-amine

[00211] 126. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-phenethyl-amine
127. Butyl-[2-(4-butyphenyl)-oxazol-4-ylmethyl]-amine
128. [2-(4-Buthphenyl)-oxazol-4-ylmethyl]-cyclohexyl-amine
129. [2-(4-Cyclopentoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
130. [2-(4-Isobutoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
131. [2-(4-sec-Butoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
132. 1-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-4-methyl-piperazine
133. {2-[4-(2-Ethoxy-ethoxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine
134. (1-Methylhexyl)-[2-(4-nitrophenyl)-oxazol-4-ylmethyl]-amine
135. [2-(4-Cyclobutoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
136. {2-[4-(1-Ethyl-propoxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine
137. [2-(4-Methoxybenzyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
138. (2,6-Dimethoxybenzyl)-[2-(4-isopropoxyphenyl)-oxazol-4-ylmethyl]-amine
139. (2-Cyclohexyl-oxazol-4-ylmethyl)-(1-methylhexyl)-amine
140. [2-(4-Difluoromethoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
141. (1-Methylhexyl)-{2-[4-(1,1,2,2-tetrafluoro-ethoxy)phenyl]-oxazol-4-ylmethyl}-amine
142. [2-(4-Cyclohexylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
143. [2-(4-Isopropylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
144. (1-Methylhexyl)-[2-(4-pentylphenyl)-oxazol-4-ylmethyl]-amine
145. [2-(3,4-Dimethylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine
146. [2-(4-Butoxy-3-Fluorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

147. [2-(4-Butoxyphenyl)-oxazol-4-ylmethyl]-(2,2-dimethyl-propyl)-amine

148. {2-[4-(2,2-Dimethyl-propoxy)phenyl]-oxazol-4-ylmethyl}-(2,2-dimethyl-propyl)-amine

149. [2-(4-Benzylxoyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

150. [2-(3,5-Bis-trifluoromethylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

151. [2-(3,5-DiMethoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

152. 1-(4-Hydroxy-3-{4-[(1-Methylhexylamino)-methyl]-oxazol-2-yl}phenyl)-ethanone

153. 4-Chloro-2-{4-{1-Methylhexylamino}-methyl}-oxazol-2-yl]-phenol

154. [2-(4-tert-Butylphenyl)-oxazol-4-ylmethyl]-(2,6-dimethoxybenzyl)-amine

155. [2-(4-Butoxyphenyl)-oxazol-4-ylmethyl]-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine

156. [2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-[2-(4-pentyloxyphenyl)-oxazol-4-ylmethyl]-amine

157. N’-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-N,N-dimethyl-propane-1,3-diamine

158. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amine

159. N’-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-N,N-dimethyl-ethane-1,2-diamine

160. {2-[4-(4-Chlorobenzylxoy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine
161. (1-Methylhexyl)-[2-(4-phenethyloxyphenyl)-oxazol-4-ylmethyl]-amine

162. 2-(4-{4-[(1-Methylhexylamino)-methyl]-oxazol-2-yl}-phenoxy)-1-phenyl-ethanone

163. {2-[4-(4-Methylbenzyloxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine

164. 2-{4-[(1-Methylhexylamino)-methyl]-oxazol-2-yl}-benzonitrile

165. [2-(2,4-Dichlorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

166. [2-(2,6-Dichlorophenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

167. (1-Methylhexyl)-[2-(4-p-tolylxophenyl)-oxazol-4-ylmethyl]-amine

168. {2-[4-(4-Chloro-phenoxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine

169. {2-[4-(4-Methoxy-phenoxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine

170. {2-[4-(4-Fluoro-phenoxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine

171. [2-(3-Methoxy-4-methylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

172. {2-[4-(4-Fluorobenzyloxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine

173. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(3-morpholin-4-yl-propyl)-amine

174. N'-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-N,N-diethyl-propane-1,3-diamine

175. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-[2-(3H-imidazol-4-yl)-ethyl]-amine

176. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(3-imidazol-1-yl-propyl)-amine
177. (1-Benzyl-piperidin-4-yl)-[2-(4-buty1phenyl)-oxazol-4-ylmethyl]-amine

178. N’-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-2,2-dimethyl-propane-1,3-diamine

179. N’-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-2,2,N,N-tetramethyl-propane-1,3-diamine

180. {2-[4-(3,4-Dichlorobenzyloxy)phenyl]-oxazol-4-ylmethyl}-(1-methylhexyl)-amine

181. (3-{{2-(4-Butylphenyl)-oxazol-4-ylmethyl]-amino}propyl}-carbamic acid tert-butyl ester

182. 1-Amino-3-{{2-(4-Butylphenyl)-oxazol-4-ylmethyl]-amino}propan-2-ol

183. [2-(4-Cyclopentyl oxyphenyl)-oxazol-4-ylmethyl]-[2-(1-methylpyrrolidin-2-yl)-ethyl] -amine

184. [2-(4-Butoxy-3-methylphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

185. [2-(4-Butoxy-3-Methoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

186. [2-(3-Butoxyphenyl)-oxazol-4-ylmethyl]-(1-methylhexyl)-amine

187. N’-[2-(4-Methoxyphenyl)-5-methyl-oxazol-4-ylmethyl]-N,N-dimethyl-propane-1,3-diamine

188. [2-(4-Methoxyphenyl)-5-methyl-oxazol-4-ylmethyl]–[2-(1-methylpyrrolidin-2-yl)-ethyl] -amine

189. [2-(3-Methoxyphenyl)-5-methyl-oxazol-4-ylmethyl]-[2-(1-methylpyrrolidin-2-yl)-ethyl] -amine

190. [2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-(5-methyl-2-p-tolyl-oxazol-4-ylmethyl)-amine
191. \([2-(1-Methyl-pyrroloidin-2-yl)-ethyl]-(5-methyl-2-m-tolyl-oxazol-4-ylmethyl)-amine\)

192. \([2-(4-Methoxyphenyl)-5-methyl-oxazol-4-ylmethyl]-(1-methylhexyl)-amine\)

193. \([2-(3-Methoxyphenyl)-5-methyl-oxazol-4-ylmethyl]-(1-methylhexyl)-amine\)

194. \((1-Methylhexyl)-(5-methyl-2-p-tolyl-oxazol-4-ylmethyl)-amine\)

195. \((1-Methylhexyl)-(5-methyl-2-m-tolyl-oxazol-4-ylmethyl)-amine\)

196. \([2-(2-Fluorophenyl)-5-methyl-oxazol-4-ylmethyl]-(1-methylhexyl)-amine\)

197. \((2-Benzol[1,3]dioxol-5-yl-oxazol-4-ylmethyl)-(1-methylhexyl)-amine\)

198. \(Benzyl-[2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-amine\)

199. \(Bis-[2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-methyl-amine\)

200. \([2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-(1R,2S,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine\)

201. \(Adamantan-1-yl-[2-(4-Ethoxyphenyl)-oxazol-4-ylmethyl]-amine\)

202. \(Bis-[2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-(1R)-1-methylhexyl)-amine\)

203. \(Adamantan-1-yl-[2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-amine\)

204. \([2-(4-Chlorophenyl)-oxazol-4-ylmethyl]phenyl-amine\)

205. \([2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-diethyl-amine\)

206. \(1-[2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-piperidin\)

207. \(Adamantan-2-yl-[2-(3-chloro-thiophen-2-yl)-oxazol-4-ylmethyl]-amine\)

208. \([2-(3-Chloro-thiophen-2-yl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine\)
209. [2-(3-Chloro-thiophen-2-yl)-oxazol-4-ylmethyl]-(1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl-amine

210. [2-(4-tert-Butylphenyl)-oxazol-4-ylmethyl]-(3,3,5-trimethyl-cyclohexyl)-amine

211. [2-(4-tert-Butylphenyl)-oxazol-4-ylmethyl]-(1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl-amine

212. [2-(4-Bromophenyl)-oxazol-4-ylmethyl]-(1S,2R,5S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amine

213. [2-(4-tert-Butylphenyl)-oxazol-4-ylmethyl]-(1S,2R,5S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amine

214. [2-(3-Chloro-thiophen-2-yl)-oxazol-4-ylmethyl]-(1S,2R,5S)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amine

215. [2-(3-Chloro-thiophen-2-yl)-oxazol-4-ylmethyl]-cycloheptyl-amine

216. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-(4-chlorobenzyl)-amine

217. [2-(4-Decyloxyphenyl)-oxazol-4-ylmethyl]-(1R,2R,3R,5S)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amine

218. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-pyridin-2-ylmethyl-amine

219. [2-(4-Butylphenyl)-oxazol-4-ylmethyl]-pyridin-3-ylmethyl-amine

220. 4-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-morpholine

221. 1-[2-(4-Butylphenyl)-oxazol-4-ylmethyl]-4phenyl-piperazine

222. N'-[2-(4-Isobutoxyphenyl)-oxazol-4-ylmethyl]-N,N-dimethyl-propane-1,3-diamine

223. N'-[2-(4-Cyclopentyloxyphenyl)-oxazol-4-ylmethyl]-N,N-dimethyl-propane-1,3-diamine

224. N'-[2-(4-Isopropylphenyl)-oxazol-4-ylmethyl]-N,N-dimethyl-propane-1,3-diamine
[00310] 225. N,N-Dimethyl-N’-[2-(4-phenethyloxyphenyl)-oxazol-4-ylmethyl]-propane-1,3-diamine

[00311] 226. N’-[2-(4-sec-Butoxyphenyl)-oxazol-4-ylmethyl]-N,N-dimethyl-propane-1,3-diamine

[00312] 227. N’-[2-[4-(1-Ethylpropoxy)phenyl]-oxazol-4-ylmethyl]-N,N-dimethyl-propane-1,3-diamine

[00313] 228. [2-(2-Fluorophenyl)-5-methyl-oxazol-4-ylmethyl]-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine

[00314] The numbers 1 to 228 are assigned to these compounds for reference and identification hereafter.

[00315] The compounds of the invention can be prepared, isolated or obtained by any method apparent to those of skill in the art. Exemplary methods of preparation are described in detail in the examples below.

[00316] The compounds of the invention can be prepared, isolated or obtained by any method apparent to those of skill in the art. Exemplary methods of preparation are described in detail in the examples below.

[00317] According to a feature of the present invention compounds of formula (I) can be obtained by treatment of an 2-aryloxazol-4-ylmethylene chloride of formula (II), with an appropriate substituted amine, wherein R¹ and R² are as defined above, optionally in the presence of a solvent and a non-nucleophilic base, for example, as illustrated in the reaction scheme below:

\[
\text{Cl} \quad \text{R¹} \quad \text{R²} \quad \text{Triethylamine} \quad \text{Solvent}
\]

[00318] It will be appreciated by those skilled in the art that alternatives to triethylamine (e.g. potassium or cesium carbonate, sodium hydride, diisopropylethylamine) may be employed, and that a variety of solvents (e.g.
tetrahydrofuran, dimethyformamide, acetonitrile) may be used (or by using an excess of $R^1R^2NH$, that this may act as both solvent and base), and that the choice of exact reaction conditions will be dictated by the properties of the individual components of the reaction, for example, solubility of the either the chloromethylarylazole and/or amine in the solvent to be employed.

**Pharmaceutical Compositions and Methods of Administration**

[00319] According to a further feature of the invention there are provided compositions which comprise a 2-arylazole derivative of formula (I) or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient, carrier or diluent. The composition of the invention can also be in a variety of forms which include, but are not limited to, oral formulations, injectable formulations, and topical, dermal or subdermal formulations.

[00320] The composition of the invention may be in a form suitable for oral use, for example, as dietary supplements, troches, lozenges, chewables, tablets, hard or soft capsules, emulsions, aqueous or oily suspensions, aqueous or oily solutions, dispersible powders or granules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, bittering agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[00321] Tablets may contain the active ingredient in admixture with non-toxic, pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.
Formulations for oral use may be hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. Capsules may also be soft gelatin capsules, wherein the active ingredient is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The compositions of the invention may also be in the form of oil-in-water or water-in-oil emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening agents, bittering agents, flavoring agents, and/or preservatives.

In one embodiment of the formulation, the composition of the invention is in the form of a microemulsion. Microemulsions are well suited as the liquid carrier vehicle. Microemulsions are quaternary systems comprising an aqueous phase, an oily phase, a surfactant and a cosurfactant. They are translucent and isotropic liquids.

Microemulsions are composed of stable dispersions of microdroplets of the aqueous phase in the oily phase or conversely of microdroplets of the oily phase in the aqueous phase. The size of these microdroplets is less than 200 nm (1000 to 100,000 nm for emulsions). The interfacial film is composed of an alternation of surface-active (SA) and co-surface-active (Co-SA) molecules which, by lowering the interfacial tension, allows the microemulsion to be formed spontaneously.

In one embodiment of the oily phase, the oily phase can be formed from mineral or vegetable oils, from unsaturated polyglycosylated glycerides or from triglycerides, or alternatively from mixtures of such compounds. In one embodiment of the oily phase, the oily phase comprises of triglycerides; in another embodiment of the oily phase, the triglycerides are medium-chain triglycerides, for example, C₈-C₁₀ caprylic/capric triglyceride. In another embodiment of the oily phase will represent a
% v/v range selected from the group consisting of about 2 to about 15%; about 7 to about 10%; and about 8 to about 9% v/v of the microemulsion.

[00327] The aqueous phase includes, for example, water or glycol derivatives, such as propylene glycol, glycol ethers, polyethylene glycols or glycerol. In one embodiment of the glycol derivatives, the glycol is selected from the group consisting of propylene glycol, diethylene glycol monoethyl ether, dipropylene glycol monoethyl ether and mixtures thereof. Generally, the aqueous phase will represent a proportion from about 1 to about 4% v/v in the microemulsion.

[00328] Surfactants for the microemulsion include diethylene glycol monoethyl ether, dipropylene glycol monomethyl ether, polyglycolyzed C8-C10 glycerides or polyglyceryl-6 dioleate. In addition to these surfactants, the cosurfactants include short-chain alcohols, such as ethanol and propanol.

[00329] Some compounds are common to the three components discussed above, for example, aqueous phase, surfactant and cosurfactant. However, it is well within the skill level of the practitioner to use different compounds for each component of the same formulation. In one embodiment for the amount of surfactant/cosurfactant, the cosurfactant to surfactant ratio will be from about 1/7 to about 1/2. In another embodiment for the amount of cosurfactant, there will be from about 25 to about 75% v/v of surfactant and from about 10 to about 55% v/v of cosurfactant in the microemulsion.

[00330] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, atachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as sucrose, saccharin or aspartame, bittering agents, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid, or other known preservatives.

[00331] Aqueous suspensions may contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose,
hydroxy-propylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxylethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide, with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents and/or bittering agents, such as those set forth above.

[00332] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, bittering, flavoring and coloring agents, may also be present.

[00333] Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring agent(s) and/or coloring agent(s).

[00334] The compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene
glycols may also be used. Preservatives, such as phenol or benzyl alcohol, may be used.

[00335] In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00336] Topical, dermal and subdermal formulations can include emulsions, creams, ointments, gels or pastes.

[00337] Organic solvents that can be used in the invention include but are not limited to: acetyltributyl citrate, fatty acid esters such as the dimethyl ester, diisobutyl adipate, acetone, acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone (e.g. N-methylpyrrolidone), diethylene glycol monoethyl ether, ethylene glycol and diethyl phthalate, or a mixture of at least two of these solvents.

[00338] As vehicle or diluent, mention may be made of plant oils such as, but not limited to soybean oil, groundnut oil, castor oil, corn oil, cotton oil, olive oil, grape seed oil, sunflower oil, etc.; mineral oils such as, but not limited to, petrolatum, paraffin, silicone, etc.; aliphatic or cyclic hydrocarbons or alternatively, for example, medium-chain (such as C₈-C₁₂) triglycerides.

[00339] Dosage forms may contain from about 0.5 mg to about 5 g of an active agent. In one embodiment of the dosage form, the dosage is from about 1 mg to about 500 mg of an active agent, typically about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg.

[00340] In one embodiment of the invention, the active agent is present in the formulation at a concentration of about 0.05 to 10% weight/volume. In another embodiment of the invention, the active agent is present in the formulation as a
concentration from about 0.1 to 2% weight/volume. In yet another embodiment of the invention, the active agent is present in the formulation as a concentration from about 0.25 to about 1.5% weight/volume. In still another embodiment of the invention, the active agent is present in the formulation as a concentration about 1% weight/volume.

[00341] According to a further feature of the invention there is provided a method of treating or preventing infection in a subject, the method comprising administering to the subject a therapeutically effective amount of 2-arylzazole derivative of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

[00342] The compounds of the invention are especially useful for the prophylaxis and/or treatment of South American trypanosomiasis, African trypanosomiasis, sleeping sickness, Kala-Azar, visceral leishmaniasis, Baghdad boil or Aleppo boil, cutaneous leishmaniasis (CL), esplundia, Chagas disease, mucocutaneous leishmaniasis (MCL), trichomoniasis, urogenital trichomonosis, giardiasis, lamblia dysentery, amoebiasis, primary amebic meningoencephalitis (PAM), keratitis or meningitis, coccidiosis, sarcosporidosis, toxoplasmosis, Malaria tropica, Malaria tertiana, Malaria quartana, pneumocystis carinii, pneumonia, pneumocystosis, Balantidium dysentery, and oriental sore.

[00343] The pharmaceutical preparation comprising the 2-arylzazole derivatives of the invention, for delivery to a human or other mammal, is preferably in unit dosage form, in which the preparation is subdivided into unit doses containing an appropriate quantity of the active component. The unit dosage form can be a packaged preparation containing discrete quantities of the preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet or lozenge itself, or it can be an appropriate number of any of these in packaged form.

[00344] The quantity of active component in a unit dose preparation may be varied or adjusted from about 0.1 mg to about 1000 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.
In therapeutic use for the treatment of a parasitic infection in a human or other mammal, the compounds utilized in the pharmaceutical method of the invention are administered at an initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. The dosages may be varied depending on the requirements of the patient, for example, the size of the human or mammal being treated, the severity of the condition being treated, the route of administration, and the potency of the compound being used. Determination of the proper dosage and route of administration for a particular situation is within the skill of the practitioner. Generally, the treatment will be initiated with smaller dosages which are less than the optimum dose of the compound, which can be increased in small increments until the optimum effect under the particular circumstances of the infection is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following Examples illustrate the synthesis of representative compounds used in the present invention and the following Reference Examples illustrate the synthesis of intermediates in their preparation. These examples are not intended, nor are they to be construed, as limiting the scope of the invention. It will be clear that the invention may be practiced otherwise than as particularly described herein. Numerous modifications and variations of the present invention are possible in view of the teachings herein and, therefore, are within the scope of the invention.

**Abbreviations**

- CH₂Cl₂: dichloromethane
- EtOAc: ethyl acetate
- ELS: Evaporative Light Scattering
- HCO₂H: formic acid
- MeOH: Methanol
- THF: tetrahydrofuran

The following are registered trade marks: Teflon, Tygon, Supelco, All temperatures are given in degrees Centigrade. Room temperature means 20 to 25°C. Reagents were purchased from commercial sources or prepared following standard literature procedures. Unless otherwise noted, reactions were carried out under a positive pressure of nitrogen. Reaction vessels were sealed with either rubber septa or Teflon screw caps. Nitrogen was introduced through Tygon tubing, fitted with a large
bore syringe needle. Concentration under vacuum refers to the removal of solvent on a Büchi Rotary Evaporator.

[00348] Analytical HPLC was performed using a Supelco® discovery C18 15 cm x 4.6 mm / 5 µm column coupled with an Agilent 1050 series VWD UV detector at 210 nm. Conditions: Solvent A: H₂O/1% acetonitrile/0.1% HCO₂H; Solvent B: methanol.

[00349] Proton magnetic resonance (¹H NMR) spectra were recorded on a Varian INOVA® NMR spectrometer [400 MHz (¹H) or 500 MHz (³¹P)]. All spectra were determined in the solvents indicated. Although chemical shifts are reported in ppm downfield of tetramethylsilane, they are referenced to the residual proton peak of the respective solvent peak for ¹H NMR. Interproton coupling constants are reported in Hertz (Hz).

[00350] LCMS spectra were obtained using a ThermoFinnigan® AQA MS ESI instrument utilizing a Phenomenex® Aqua 5 micron C18 125 Å 50 x 4.60 mm column. The spray setting for the MS probe was at 350 µL/min with a cone voltage at 25 mV and a probe temperature at 450 °C. The spectra were recorded using ELS and UV (254 nm) detection. Alternatively, LCMS spectra were obtained using an Agilent® 1200SL HPLC equipped with a 6130 mass spectrometer operating with electrospray ionization.

[00351] Silica gel chromatography was carried out on a Teledyne ISCO CombiFlash® Companion Flash Chromatography System with a variable flow rate from 5-100 mL/min. The columns used were Teledyne ISCO RediSep® Disposable Flash Columns (4, 12, 40, 80, or 120 g prepacked silica gel), which were run with a maximum capacity of 1 g crude sample per 10 g silica gel. Samples were preloaded on Celite in Analogix® Sample Loading Cartridges with frits (1/in, 1/out). The eluent was 0-100% EtOAc in heptane or 0-10% MeOH in CH₂Cl₂ as a linear gradient over the length of the run (14-20 minutes). Peaks were detected by variable wavelength UV absorption (200-360 nm). The resulting fractions were analyzed, combined as appropriate, and evaporated under reduced pressure to provide purified material.
HPLC purification was performed using a 50 mm Varian Dynamax® HPLC 21.4 mm Microsorb Guard-8 C18 column, Dyonex Chromeleon® operating system coupled with a Varian Prostar® 320 UV-vis detector (254 nm) and a Sedex55 ELS detector. Conditions: Solvent A: H2O/1% acetonitrile/0.1% HCO2H; Solvent B: methanol. The appropriate solvent gradient for purification was determined based on the results of analytical HPLC experiments. The resulting fractions were analyzed, combined as appropriate, and evaporated under reduced pressure to provide purified material.

The following experimental sections illustrate procedures for the preparation of intermediates and methods for the preparation of products according to this invention. It should be evident to those skilled in the art that appropriate substitution of both the materials and methods disclosed herein will produce the examples illustrated below and those encompassed by the scope of the invention.

Example 1

To a solution of 4-chloromethyl-2-(4-ethoxyphenyl)-oxazole (50 mg, 0.21 mmol), prepared according to Reference Example 1 below, in dry acetonitrile (10 mL) was added triethylamine (0.3 mL, 2.1 mmol) and 2-aminoheptane (0.1 mL, 0.63 mmol). The reaction was heated to 78°C for 16 hours, and then cooled to room temperature. The solution was concentrated to dryness by rotary evaporation, and the resultant material was partitioned between dichloromethane (20 mL) and aqueous sodium hydroxide (1M, 10 mL). The organic layer was dried over sodium sulfate and evaporated. The crude product was chromatographed on silica gel to yield the [2-(4-ethoxyphenyl)-oxazol-4-ylmethyl]-1-(methyl-hexyl)-amine (Compound 5) as a clear oil. Calculated for C_{19}H_{28}N_{2}O_{3}: 316. Observed; 317 (M+H)+. 1H NMR (400 MHz, chloroform-d) δ ppm 0.83 - 0.93 (m, 3 H) 1.09 (d, J=6.2 Hz, 3 H) 1.21 - 1.38 (m, 7 H) 1.44 (t, J=6.9 Hz, 3 H) 1.48 - 1.56 (m, 1 H) 1.68 (br. s., 2 H) 2.71 (tq, J=6.2, 6.0 Hz, 1 H) 3.66 - 3.87 (m, 2 H) 4.09 (q, J=7.0 Hz, 2 H) 6.90 - 7.00 (m, 2 H) 7.52 (t, J=0.9 Hz, 1 H) 7.90 - 7.99 (m, 2 H).

By proceeding in a similar manner, the following compounds were prepared:
[00356] (1-Methylhexyl)-(2-phenyl-oxazol-4-ylmethyl)-amine [Compound 8];
Calculated for C_{17}H_{22}N_{2}O; 272. Observed; 273 (M+H)+. ¹H NMR (400 MHz,
chloroform-d) δ ppm 0.85 - 0.93 (m, 3 H) 1.10 (d, J=6.2 Hz, 3 H) 1.23 - 1.41 (m, 7 H)
1.44 - 1.59 (m, 2 H) 2.72 (tq, J=6.2, 6.0 Hz, 1 H) 3.71 - 3.88 (m, 2 H) 7.42 - 7.51 (m,
3 H) 7.58 (s, 1 H) 8.00 - 8.07 (m, 2 H).

[00357] (1-Methylhexyl)-(2-thiophen-2-yl-oxazol-4-ylmethyl)-amine [Compound
39]; Calculated for C_{13}H_{22}N_{2}OS; 278. Observed; 279 (M+H)+. ¹H NMR (400 MHz,
chloroform-d) δ ppm 0.85 - 0.93 (m, 3 H) 1.09 (d, J=6.2 Hz, 3 H) 1.22 - 1.38 (m, 7 H)
1.42 - 1.56 (m, 1 H) 1.66 (br. s., 1 H) 2.70 (tq, J=6.2, 5.9 Hz, 1 H) 3.68 - 3.84 (m, 2
H) 7.11 (dd, J=5.1, 3.7 Hz, 1 H) 7.42 (dd, J=4.9, 1.2 Hz, 1 H) 7.51 (s, 1 H) 7.66 (dd,
J=3.7, 1.2 Hz, 1 H).

[00358] [2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-cyclohexyl-amine [Compound
51]; Calculated for C_{16}H_{19}ClN_{2}O; 290. Observed; 291 (M+H)+. ¹H NMR (400 MHz,
chloroform-d) δ ppm 1.01 - 1.38 (m, 5 H) 1.52 - 1.69 (m, 2 H) 1.69 - 1.83 (m, 2 H)
1.85 - 2.05 (m, 2 H) 2.52 (tt, J=10.3, 3.7 Hz, 1 H) 3.80 (d, J=1.0 Hz, 2 H) 7.36 - 7.50
(m, 2 H) 7.57 (s, 1 H) 7.89 - 8.07 (m, 2 H).

[00359] (2-Cyclohexyl-oxazol-4-ylmethyl)-(1-methylhexyl)-amine [Compound
139]; Calculated for C_{17}H_{30}N_{2}O; 278. Observed; 279 (M+H)+. ¹H NMR (400 MHz,
methanol-d4) δ ppm 0.91 - 0.96 (m, 3 H) 1.26 - 1.49 (m, 10 H) 1.35 (d, J=6.4 Hz, 3
H) 1.51 - 1.65 (m, 3 H) 1.70 - 1.86 (m, 4 H) 2.01 - 2.10 (m, 2 H) 2.85 (tt, J=11.1, 3.7
Hz, 1 H) 3.24 - 3.34 (m, 1 H) 4.10 - 4.20 (m, 2 H) 7.92 (s, 1 H).

[00360] (1-Methylhexyl)-[2-(4-p-tolyloxyphenyl)-oxazol-4-ylmethyl]-amine
[Compound 167]; Calculated for C_{24}H_{30}N_{2}O; 378. Observed; 379 (M+H)+. ¹H
NMR (400 MHz, chloroform-d) δ ppm 0.86 - 0.93 (m, 3 H) 1.07 - 1.12 (m, 3 H) 1.23
- 1.40 (m, 7 H) 1.46 - 1.56 (m, 1 H) 1.60 (br. s., 1 H) 2.66 - 2.77 (m, 1 H) 3.67 - 3.86
(m, 2 H) 6.94 - 6.99 (m, 2 H) 7.00 - 7.05 (m, 2 H) 7.14 - 7.22 (m, 2 H) 7.54 (s, 1 H)
7.92 - 8.02 (m, 2 H).

[00361] Bis-[2-(4-chlorophenyl)-oxazol-4-ylmethyl]-(R)-1-methylhexyl)-amine
[Compound 202]; Calculated for C_{27}H_{20}Cl_{2}N_{2}O; 497. Observed; 498 (M+H)+. ¹H
NMR (400 MHz, chloroform-d) δ ppm 0.85 (t, J=7.0 Hz, 3 H) 1.06 (d, J=6.6 Hz, 3 H)
1.14 - 1.44 (m, 7 H) 1.51 - 1.65 (m, 1 H) 2.89 (sxt, J=6.6 Hz, 1 H) 3.62 - 3.83 (m, 4 H) 7.38 - 7.46 (m, 4 H) 7.70 (s, 2 H) 7.91 - 8.00 (m, 4 H).

**[00362]** 2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-phenyl-amine [Compound 204]; Calculated for C_{16}H_{13}ClN_{2}O; 284. Observed; 285 (M+H)+. 1H NMR (400 MHz, chloroform-d) δ ppm 4.34 (s, 2 H) 6.66 - 6.74 (m, 2 H) 6.73 - 6.81 (m, 1 H) 7.15 - 7.25 (m, 2 H) 7.39 - 7.49 (m, 2 H) 7.60 (s, 1 H) 7.94 - 8.01 (m, 2 H).

**[00363]** 1-[2-(4-Chlorophenyl)-oxazol-4-ylmethyl]-piperidine [Compound 206]; Calculated for C_{15}H_{17}ClN_{2}O; 276. Observed; 277 (M+H)+. 1H NMR (400 MHz, chloroform-d) δ ppm 1.39 - 1.49 (m, 2 H) 1.61 (quin, J=5.7 Hz, 4 H) 2.48 (br. s., 4 H) 3.49 (d, J=0.8 Hz, 2 H) 7.38 - 7.46 (m, 2 H) 7.57 (s, 1 H) 7.95 - 8.01 (m, 2 H).

**[00364]** N'-(2-(4-Isopropylphenyl)-oxazol-4-ylmethyl]-N,N-dimethylpropane-1,3-diamine [Compound 224]; Calculated for C_{18}H_{27}N_{2}O; 301. Observed; 302 (M+H)+. 1H NMR (400 MHz, chloroform-d) δ ppm 1.24 (d, J=6.8 Hz, 6 H) 2.29 - 2.40 (m, 2 H) 2.92 (quin, J=6.9 Hz, 1 H) 3.04 (t, J=6.2 Hz, 2 H) 3.39 (s, 6 H) 3.83 -3.91 (m, 2 H) 4.94 (s, 2 H) 7.27 (d, J=8.4 Hz, 2 H) 7.87 (d, J=8.4 Hz, 2 H) 8.49 (s, 1 H).

**[00365]** By proceeding in a similar manner to the reactions described in Example 1 above, Compounds 1-4, 6-7, 9-38, 40-50, 52-138, 140-166, 168-201, 203, 205, 207-223, and 225-228 were also prepared.

**Reference Example 1**

**[00366]** 4-Chloromethyl-2-(4-ethoxyphenyl)-oxazole. To a disposable 40 mL glass reaction vial was added 1,3-dichloroacetone (3.07 g, 24.2 mmol) and 4-ethoxybenzamidine (2g, 12.1 mmol). The reaction was submerged into a preheated oil bath (130°C), at which time the heterogeneous solid mixture melted into a brown oil. The reaction was stirred for two hours, and then cooled to room temperature. The resultant material was dissolved in CH_{2}Cl_{2} (100 mL) and washed with aqueous sodium hydroxide (1M, 50 mL) and brine (50 mL). The organic portion was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed on silica gel to provide 4-chloromethyl-2-(4-ethoxyphenyl)-oxazole as a white crystalline solid (1.3g). Calculated for C_{12}H_{12}ClNO_{2}; 237. Observed; 228
(M+H)+. $^1$H NMR (400 MHz, chloroform-d) δ ppm 1.45 (t, J=6.9 Hz, 3 H) 4.09 (q, J=7.0 Hz, 2 H) 4.57 (d, J=0.8 Hz, 2 H) 6.96 (ddd, J=9.3, 2.7, 2.4 Hz, 2 H) 7.65 (t, J=0.9 Hz, 1 H) 7.97 (ddd, J=9.3, 2.8, 2.5 Hz, 2 H).

**Trypanosome Strain and Cultivation**

[00367] All experiments were conducted with the bloodstream-form trypanosome *T. brucei brucei* 427 strain. Parasites were cultured in T-25 vented cap flasks and kept in humidified incubators at 37°C and 5% CO$_2$. The parasite culture media was complete HMI- 9 medium (c.f. Hirumi, Journal of Parasitology 1989, Volume 75, page 985 *et seq*) containing 10% FBS, 10% Serum Plus medium and penicillin/streptomycin. To ensure log growth phase, trypanosomes were sub-cultured at appropriate dilutions every 2-3 days.
**In Vitro Drug Sensitivity Assays**

Log phase cultures were diluted 1:10 in HMI-9 and 10 μL was counted using hemocytometer to determine parasite concentration. Parasites were diluted to 2 x 105/mL in HMI-9 to generate a 2-fold working concentration for assay. Compounds to be tested were serially diluted in DMSO and 0.5 μL added to 49.5 μL HMI-9 in triplicate 96-well plates using a Biomek® NX liquid handler. Parasites from the diluted stock were added to each well (50 μL) using a Multidrop 384 dispenser to give a final concentration of 1.0x105/ml parasites in 0.4% for DMSO. Trypanosomes were incubated with compounds for 72 hrs at 37°C with 5% CO2. Resazurin® (20 μL of 12.5 mg/ml stock) from Sigma-Aldrich was added to each well and plates were incubated for an additional 2-4 hrs. Assay plates were read using an EnVision plate reader at an excitation wavelength of 544 nm and emission of 590 nm. Triplicate data points were averaged to generate sigmoidal dose response curve and determine IC\textsubscript{50} values using XLfit® curve fitting software from IDBS (Guildford, UK).

Under these assay conditions, Compounds 1 to 228 of the invention gave an IC\textsubscript{50} value in the range of from 0.07 to >5 μg/ml.
CLAIMS

1. A 2-arylazole derivative of formula (I):

   ![Chemical Structure](image)

   (I)

   wherein R¹ and R² are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl or aminoalkyl;

   R³ is hydrogen, alkyl, halogen, or aryl;

   S, T, V, W and X are independently C-R⁴ or N; with the proviso that at least three of S, T, V, W and X are independently C-R⁴; or two adjacent groups selected from S, T and V together form an optionally substituted phenyl ring;

   R⁴ is independently hydrogen, alkyl, halogen, -CH₂R⁵, -OR⁶, -SR⁶ or aryl;

   R⁵ is cycloalkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted, or optionally substituted aryl or heteroaryl, whereby the substituents are independently selected from the group consisting of cyano, nitro, halogen, alkyl, haloalkyl, alkylthio, arylthio, alkoxy, alkanoyl, alkanoyloxy, alkanoylamino, aminocarbonyl, alkoxy carbonyl, alkenoyl, alkynoyl, aroyl, alkylsulfanyl and alkylsulfonyl;

   R⁶ is alkyl, cycloalkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted, or optionally substituted aryl or heteroaryl, whereby the substituents are independently selected from the group consisting of cyano, nitro, halogen, alkyl, haloalkyl, alkylthio, arylthio, alkoxy, alkanoyl, alkanoyloxy, alkanoylamino, aminocarbonyl, alkoxy carbonyl, alkenoyl, alkynoyl, aroyl, alkylsulfanyl and alkylsulfonyl;

   Y is oxygen or sulfur;

   or a pharmaceutically acceptable salt or solvate thereof.
2. The compound according to Claim 1 in which Y is oxygen.

3. The compound according to Claim 1 or 2 in which S, T, V, W, and X are independently C-R^4.

4. The compound according to Claim 1, 2 or 3 in which R^1 is C_{1-10} alkyl, C_{3-12} cycloalkyl, C_{1-10} hydroxyalkyl, C_{1-10} alkoxyalkyl or C_{1-10} aminoalkyl.

5. The compound according to Claim 1, 2, 3 or 4 in which R^2 is hydrogen.

6. The compound according to any one of Claims 1 to 5 in which R^3 is hydrogen or alkyl.

7. The compound according to Claim 1 which is selected from Compound Numbers 1 to 228.

8. A composition comprising a 2-arylazole derivative as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier or diluent.

9. A method of treating or preventing infection in a subject, the method comprising administering to the subject a therapeutically effective amount of a 2-arylazole derivative of formula (I) as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof.

10. The use of a 2-arylazole derivative of formula (I) as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, for
prophylaxis and/or treatment of South American trypanosomiasis, African trypanosomiasis, sleeping sickness, Kala-Azar, visceral leishmaniasis, Baghdad boil or Aleppo boil, cutaneous leishmaniasis (CL), espundia, Chagas disease, mucocutaneous leishmaniasis, trichomoniasis, urogenital trichomonosis, giardiasis, lamblia dysentery, amoebiasis, primary amebic meningoencephalitis (PAM), keratitis or meningitis, coccidiosis, sarcosporidiosis, toxoplasmosis, Malaria tropica, Malaria tertiana, Malaria quartana, pneumocystis carinii, pneumonia, pneumocystosis, Balantidium dysentery, or oriental sore.
Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

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<th>Category</th>
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<th>Identity of document and passage or figure of particular relevance</th>
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Categories:

| X | Document indicating lack of novelty or inventive step |
| Y | Document indicating lack of inventive step if combined with one or more other documents of same category. |
| & | Member of the same patent family |
| A | Document indicating technological background and/or state of the art. |
| P | Document published on or after the declared priority date but before the filing date of this invention. |
| E | Patent document published on or after, but with priority date earlier than, the filing date of this application. |

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC:

Worldwide search of patent documents classified in the following areas of the IPC

The following online and other databases have been used in the preparation of this search report.
### International Classification:

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