Abstract:

Title:

Compositions

World Intellectual Property Organization
International Bureau

20 May 2011 (26.05.2011)

(51) International Patent Classification:

C07F 5/02 (2006.01) A61P 33/10 (2006.01)
A61K 31/69 (2006.01)

(21) International Application Number:

PCT/US2010/0575 15

(22) International Filing Date:

19 November 2010 (19.11.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/263,298 20 November 2009 (20.11.2009) US

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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(Hi))
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hj))

Published:

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

(54) Title: BORON-CONTAINING SMALL MOLECULES AS ANTIHELMINTH AGENTS

(57) Abstract: This invention provides, among other things, novel compounds useful for treating helminth infections, pharmaceutical compositions containing such compounds, as well as combinations of these compounds with at least one additional therapeutically effective agent.
BORON-CONTAINING SMALL MOLECULES AS ANTIHELMINTH AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Pat. App. No. 61/263,298, filed November 20, 2009, which is incorporated by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Boron-containing molecules, such as oxaboroles, useful as antimicrobials have been described previously, such as in U.S. Pat. Pubs. US20060234981 and US20070155699. Generally speaking, an oxaborole has the following structure and substituent numbering system:

![Oxaborole Structure](image)

It has now been discovered that certain classes of oxaboroles are surprisingly effective antihelminth agents. This, and other uses of these oxaboroles are described herein.

SUMMARY OF THE INVENTION

[0003] This invention provides, among other things, novel compounds useful for treating infections by worms, pharmaceutical compositions containing such compounds, as well as combinations of these compounds with at least one additional therapeutically effective agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] FIG. 1 provides a description of in vitro screening of 29 oxaboroles against the adult worms of B. malayi. The chart showed 15 compounds which killed adult worms of B. malayi in 1 to 2 days, compared to 16 to 19 days for the positive control albendazole.
FIG. 2 shows that one of the most potent compounds, J15, kills 100% of worms when administered at 0.01 mM in 24 h compared to J13 which loses efficacy at 10 mM.

FIG. 3 shows the structure activity relationship of certain oxaboroles against adult B. malayi in vitro.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Abbreviations

As used herein, the singular forms "a," "an," and "the" include plural references unless the context clearly dictates otherwise. For example, reference to "an active agent" includes a single active agent as well as two or more different active agents in combination. It is to be understood that present teaching is not limited to the specific dosage forms, carriers, or the like, disclosed herein and as such may vary.

The abbreviations used herein generally have their conventional meaning within the chemical and biological arts.

The following abbreviations have been used: Ac is acetyl; AcOH is acetic acid; ACTBr is cetyltrimethylammonium bromide; AIBN is azobisisobutyronitrile or 2,2’ azobisisobutyronitrile; aq. is aqueous; Ar is aryl; Bn is, in general, benzyl [see Cbz for one example of an exception]; (BnS)2 is benzyl disulfide; BnSH is benzyl thiol or benzyl mercaptan; BnBr is benzyl bromide; Boc is tert-butoxy carbonyl; Boc2O is di-tert-butyldicarbonate; Bz is, in general, benzoyl; BzOOH is benzoyl peroxyde; Cbz or Z is benzyloxycarbonyl or carboxybenzyl; Cs2C03 is cesium carbonate; CSA is camphor sulfonic acid; CTAB is cetyltrimethylammonium bromide; Cy is cyclohexyl; DABCO is 1,4-diazabicyclo[2.2.2]octane; DCM is dichloromethane or methylene chloride; DHP is dihydropyran; DIAD is diisopropyl azodicarboxylate; DIEA or DIPEA is N,N-diisopropylethylamine; DMAP is 4-(dimethylamino)pyridine; DME is 1,2-dimethoxyethane; DMF is N,N-dimethylformamide; DMSO is dimethylsulfoxide; equiv or eq. is equivalent; EtOAc is ethyl acetate; EtOH is ethanol; Et2O is diethyl ether; EDCI is -(S-dimethylaminopropyl) -(N’-ethylcarbodiimide hydrochloride; ELS is evaporative light scattering; equiv or eq is equivalent; h is hours; HATU is 0-(7-azabenzotriazol-1-yl)-N,N,N’,N’-tetramethyluronium hexafluorophosphate; HOBt is
\(N\)-hydroxybenzotriazole; HC1 is hydrochloric acid; HPLC is high pressure liquid chromatography; ISCO Companion is automated flash chromatography equipment with fraction analysis by UV absorption available from Presearch; KOAc or AcOK is potassium acetate; \(K_2CO_3\) is potassium carbonate; \(L1AIH_4\) or LAH is lithium aluminum hydride; LDA is lithium diisopropylamide; LHMDS is lithium bis(trimethylsilyl) amide; KHMDS is potassium bis(trimethylsilyl) amide; LiOH is lithium hydroxide; m-CPBA is 3-chloroperoxybenzoic acid; MeCN or ACN is methyl cyanide or cyanomethane or ethanenitrile or acetonitrile which are all names for the same compound; MeOH is methanol; \(MgSO_4\) is magnesium sulfate; mins or min is minutes; Mp or MP is melting point; \(NaCNBH_3\) is sodium cyanoborohydride; NaOH is sodium hydroxide; \(Na_2S0_4\) is sodium sulfate; NBS is N-bromosuccinimide; \(NH_4Cl\) is ammonium chloride; NIS is N-iodosuccinimide; \(N_2\) is nitrogen; NMM is \(N\)-methylmorpholine; \(n-BuLi\) is \(n\)-butyllithium; overnight is O/N; \(PdCl_2(pddf)\) is \(1,1'\)-Bis(diphenylphosphino) ferrocene)dichloropalladium(II); \(Pd/C\) is the catalyst known as palladium on carbon; \(Pd_2(dba)_3\) is an organometallic catalyst known as tris(dibenzylideneacetone) dipalladium(0); \(Ra\) Ni or Raney Ni is Raney nickel; Ph is phenyl; PMB is \(2\)-methoxybenzyl; \(PrOH\) is 1-propanol; \(iPrOH\) is 2-propanol; \(POCl_3\) is phosphorus chloride oxide; PTSA is \(p\)-toluenesulfonic acid; Pyr. or Pyr or Py as used herein means Pyridine; RT or rt or r.t. is room temperature; sat. is saturated; Si-amine or Si-NH\(_2\) is amino-functionalized silica, available from SiliCycle; Si-pyr is pyridyl-functionalized silica, available from SiliCycle; TEA or Et_3N is triethylamine; TFA is trifluoroacetic acid; Tf_2O is trifluoromethanesulfonic anhydride; THF is tetrahydrofuran; TFAA is trifluoroacetic anhydride; THP is tetrahydropyran; TMSI is trimethylsilyl iodide; \(H_2O\) is water; \(dInO\) \(2\)-PhSO\(_2\)Cl is dinitrophenyl sulfonyl chloride; 3-F-4-N0 \(2\)-PhSO\(_2\)Cl is 3-fluoro-4-nitrophenylsulfonyl chloride; 2-MeO-4-N0 \(2\)-PhSO\(_2\)Cl is 2-methoxy-4-nitrophenylsulfonyl chloride; and \((EtO)_2POCH_2COOEt\) is the triester of phosphonoacetic acid known as triethyl phosphonoacetate.

[0010] "Compound of the invention," as used herein refers to the compounds discussed herein, salts (e.g. pharmaceutically acceptable salts), prodrugs, solvates and hydrates of these compounds.

[0011] "Combination of the invention," as used herein refers to the compounds and antibiotics discussed herein as well as acids, bases, salt forms (such as
pharmaceutically acceptable salts), prodrugs, solvates and hydrates of these compounds and antibiotics.

[0012] "Boron containing compounds", as used herein, refers to the compounds of the invention that contain boron as part of their chemical formula.

[0013] MIC, or minimum inhibitory concentration, is the point where the compound stops more than 50% of cell growth, preferably 60%> of cell growth, preferably 70%> of cell growth, preferably 80%> of cell growth, preferably 90%> of cell growth, relative to an untreated control.

[0014] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents, which would result from writing the structure from right to left, e.g., -CH₂O - is intended to also recite -OCH₂-.

[0015] The term "poly" as used herein means at least 2. For example, a polyvalent metal ion is a metal ion having a valency of at least 2.

[0016] "Moiety" refers to a radical of a molecule that is attached to the remainder of the molecule.

[0017] The symbol \(-\text{\rightward}\), whether utilized as a bond or displayed perpendicular to a bond, indicates the point at which the displayed moiety is attached to the remainder of the molecule.

[0018] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e. C\textsubscript{1}-C\textsubscript{10} means one to ten carbons). In some embodiments, the term "alkyl" means a straight or branched chain, or combinations thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl
groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers.

[0019] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by -CH₂CH₂CH₂CH₂-, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0020] The term "alkenylene" by itself or as part of another substituent means a divalent radical derived from an alkene.

[0021] The term "cycloalkylene" by itself or as part of another substituent means a divalent radical derived from a cycloalkyl.

[0022] The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from an heteroalkane.

[0023] The term "heterocycloalkylene" by itself or as part of another substituent means a divalent radical derived from an heteroalkane.

[0024] The term "arylene" by itself or as part of another substituent means a divalent radical derived from an aryl.

[0025] The term "heteroarylene" by itself or as part of another substituent means a divalent radical derived from heteroaryl.

[0026] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0027] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom. In some embodiments, the term "heteroalkyl," by itself or in combination with another term, means a stable straight or
branched chain, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom. In an exemplary embodiment, the heteroatoms can be selected from the group consisting of B, O, N and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) B, O, N and S may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to,

-CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)₂-CH₃, -CH₂-S-CH₂-CH₃,
-CH₂-CH₂-S(0)-CH₃, -CH₂-CH₂-S(0)₂-CH₃, -CH=CH₀-CH₃, -CH₂-CH=N-OCH₃,
and -CH=CH-N(CH₃)₂-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkylenamino, alkylendiamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(0)₂R' - represents both -C(0)₂R' - and -R'C(0)₂ -.

[0028] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0029] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C1-C4)alkyl" is mean to include, but
not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0030] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, substituent that can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms. In an exemplary embodiment, the heteroatom is selected from B, N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, 6-quinolyl, dioxaborolane, dioxaborinane and dioxaborepane. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0031] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxyethyl, 2-pyridyloxymethyl, 3-(1-naphthoxy)propyl, and the like).

[0032] Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0033] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkylnyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically
referred to as "alkyl group substituents," and they can be one or more of a variety of
groups selected from, but not limited to: -R', -OR', =0, =NR', =N-OR', =NR'R'',
-SR', -halogen, -SiR'R''R''', -OC(0)R', -C(0)R', -C0_2 R', -CONR'R'',
-OC(0)NR'R'', -NR'C(0)R', -NR'-C(0)NR'R''', -NR'C(0) _2 R',
-NR'""-C(NR'R'R'')=NR''', -NR""-C(NR'R'R'')=NR''', -S(0)R', -S(0) 2 R',
-S(0) 2 NR'R'', -NR'S0 2 R', -CN, -N0 2, -N3, -CH(Ph)_2, fluoro(Ci-C i)
alkoxy, and fluoro(Ci-C i)alkyl, in a number ranging from zero to (2m'+1), where m' is the total
number of carbon atoms in such radical. R', R'', R''' and R'''' each preferably
independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted
or unsubstituted aryl, e.g., aryl substituted with 1-3 halogens, substituted or
unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a
compound of the invention includes more than one R group, for example, each of the
R groups is independently selected as are each R', R'', R''' and R''''' groups
when more than one of these groups is present. When R' and R'' are attached to the
same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or
7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-
pyrrolidinyl and 4-morpholinyi. From the above discussion of substituents, one of
skill in the art will understand that the term "alkyl" is meant to include groups
including carbon atoms bound to groups other than hydrogen groups, such as
haloalkyl (e.g., -CF_3 and -CH_2 CF_3) and acyl (e.g., C(0)CH_3, -C(0)CF_3,
-C(0)CH_2 OCH_3, and the like).

[0034] Similar to the substituents described for the alkyl radical, substituents for the
aryl and heteroaryl groups are generically referred to as "aryl group substituents."
The substituents are selected from, for example: -R', -OR', =0, =NR', =N-OR',
-NR'R'', -SR', -halogen, -SiR'R''R''', -OC(0)R', -C(0)R', -C0_2 R', -CONR'R'',
-OC(0)NR'R'', -NR'C(0)R', -NR'-C(0)NR'R''', -NR'C(0) _2 R',
-NR""-C(NR'R'R'')=NR''', -NR""-C(NR'R'R'')=NR''', -S(0)R', -S(0) 2 R',
-S(0) 2 NR'R'', -NR'S0 2 R', -CN, -N0 2, -N3, -CH(Ph)_2, fluoro(Ci-C i)
alkoxy, and fluoro(Ci-C i)alkyl, in a number ranging from zero to the total number of open
valences on the aromatic ring system; and where R', R'', R''' and R'''' are
preferably independently selected from hydrogen, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and
substituted or unsubstituted heteroaryl. When a compound of the invention includes
more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R''' groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula \(-T-C(0)-(CRR')_q-U-,\)
wherein T and U are independently -NR-, -0-, -CRR' or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula \(-A-(CH_2)_r-B-,\)
wherein A and B are independently -CRR', -0-, -NR-, -S-, -S(O)-, -S(0) 2-, -S(0) 2NR'- or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula \(-(CRR'_{s-X}-(CR''R'')_{d})-,\)
where s and d are independently integers of from 0 to 3, and X is -0-, -NR', -S-, -S(O), -S(0) 2-, or -S(0) 2NR'. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen or substituted or unsubstituted (Ci-C6)alkyl.

"Ring" as used herein, means a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. A ring includes fused ring moieties. The number of atoms in a ring is typically defined by the number of members in the ring. For example, a "5- to 7-membered ring" means there are 5 to 7 atoms in the encircling arrangement. Unless otherwise specified, the ring optionally includes a heteroatom. Thus, the term "5- to 7-membered ring" includes, for example phenyl, pyridinyl and piperidinyl. The term "5- to 7-membered heterocycloalkyl ring", on the other hand, would include pyridinyl and piperidinyl, but not phenyl. The term "ring" further includes a ring system comprising more than one "ring", wherein each "ring" is independently defined as above.

As used herein, the term "heteroatom" includes atoms other than carbon (C) and hydrogen (H). Examples include oxygen (O), nitrogen (N) sulfur (S), silicon (Si), germanium (Ge), aluminum (Al) and boron (B).
The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include triflate, chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The symbol "R" is a general abbreviation that represents a substituent group that is selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted heterocycloalkyl groups.

By "effective" amount of a drug, formulation, or permeant is meant a sufficient amount of an active agent to provide the desired local or systemic effect. A "Topically effective," "pharmaceutically effective," or "therapeutically effective" amount refers to the amount of drug needed to effect the desired therapeutic result.

The term "pharmaceutically acceptable salt" is meant to include a salt of a compound of the invention which is prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric,
lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977)). Certain specific compounds of the invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0042] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compounds in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0043] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein readily undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an ex vivo environment.

[0044] Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the invention. Certain compounds of the invention may exist in multiple crystalline or amorphous forms.

[0045] Certain compounds of the invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are encompassed within the scope of the invention. The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr, J. Chem. Ed. 1985, 62: 114-120. Solid and broken wedges are used to denote the absolute configuration of a stereocenter unless otherwise noted. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are included.
Compounds of the invention can exist in particular geometric or stereoisomeric forms. The invention contemplates all such compounds, including cis- and trans-isomers, (-)- and (+)-enantiomers, (R)- and (S)-enantiomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, such as enantiomerically or diastereomerically enriched mixtures, as falling within the scope of the invention. Additional asymmetric carbon atoms can be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Optically active (R)- and (S)-isomers and d and l isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If, for instance, a particular enantiomer of a compound of the invention is desired, it can be prepared by asymmetric synthesis, or by derivatization with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as an amino group, or an acidic functional group, such as a carboxyl group, diastereomeric salts can be formed with an appropriate optically active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers. In addition, separation of enantiomers and diastereomers is frequently accomplished using chromatography employing chiral, stationary phases, optionally in combination with chemical derivatization (e.g., formation of carbamates from amines).

The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" refers to any formulation or carrier medium that provides the appropriate delivery of an effective amount of an active agent as defined herein, does not interfere with the effectiveness of the biological activity of the active agent, and
that is sufficiently non-toxic to the host or patient. Representative carriers include water, oils, both vegetable and mineral, cream bases, lotion bases, ointment bases and the like. These bases include suspending agents, thickeners, penetration enhancers, and the like. Their formulation is well known to those in the art of cosmetics and topical pharmaceuticals. Additional information concerning carriers can be found in Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott, Williams & Wilkins (2005) which is incorporated herein by reference.

[0050] The term "excipients" is conventionally known to mean carriers, diluents and/or vehicles used in formulating drug compositions effective for the desired use.

[0051] The term "topical administration" refers to the application of a pharmaceutical agent to the external surface of the skin, nail, hair, claw or hoof, such that the agent crosses the external surface of the skin, nail, hair, claw or hoof and enters the underlying tissues. Topical administration includes application of the composition to intact skin, nail, hair, claw or hoof, or to a broken, raw or open wound of skin, nail, hair, claw or hoof. Topical administration of a pharmaceutical agent can result in a limited distribution of the agent to the skin and surrounding tissues or, when the agent is removed from the treatment area by the bloodstream, can result in systemic distribution of the agent.

[0052] The terms "effective amount" or a "therapeutically effective amount" of a drug or pharmacologically active agent refers to a nontoxic but sufficient amount of the drug or agent to provide the desired effect. In the oral dosage forms of the present disclosure, an "effective amount" of one active of the combination is the amount of that active that is effective to provide the desired effect when used in combination with the other active of the combination. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

[0053] The phrases "active ingredient", "therapeutic agent", "active", or "active agent" mean a chemical entity which can be effective in treating a targeted disorder, disease or condition.
The phrase "pharmaceutically acceptable" means moieties or compounds that are, within the scope of medical judgment, suitable for use in humans without causing undesirable biological effects such as undue toxicity, irritation, allergic response, and the like, for example.

The phrase "oral dosage form" means any pharmaceutical composition administered to a subject via the oral cavity. Exemplary oral dosage forms include tablets, capsules, films, powders, sachets, granules, solutions, solids, suspensions or as more than one distinct unit (e.g., granules, tablets, and/or capsules containing different actives) packaged together for co-administration, and other formulations known in the art. An oral dosage form can be one, two, three, four, five or six units. When the oral dosage form has multiple units, all of the units are contained within a single package, (e.g. a bottle or other form of packaging such as a blister pack). When the oral dosage form is a single unit, it may or may not be in a single package. In a preferred embodiment, the oral dosage form is one, two or three units. In a particularly preferred embodiment, the oral dosage form is one unit.

The phrase "unit", as used herein, refers to the number of discrete objects to be administered which comprise the dosage form. In some embodiments, the dosage form includes a compound of the invention in one capsule. This is a single unit. In some embodiments, the dosage form includes a compound of the invention as part of a therapeutically effective dosage of a cream or ointment. This is also a single unit. In some embodiments, the dosage form includes a compound of the invention and another active ingredient contained within one capsule, or as part of a therapeutically effective dosage of a cream or ointment. This is a single unit, whether or not the interior of the capsule includes multiple discrete granules of the active ingredient. In some embodiments, the dosage form includes a compound of the invention in one capsule, and the active ingredient in a second capsule. This is a two unit dosage form, such as two capsules or tablets, and so such units are contained in a single package. Thus the term 'unit' refers to the object which is administered to the animal, not to the interior components of the object.

The term, "prodrug", as defined herein, is a derivative of a parent drug molecule that exerts its pharmacological effect only after chemical and/or enzymatic conversion to its active form in vivo. Prodrugs include those designed to circumvent
problems associated with delivery of the parent drug. This may be due to poor physicochemical properties, such as poor chemical stability or low aqueous solubility, and may also be due to poor pharmacokinetic properties, such as poor bioavailability or poor half-life. Thus, certain advantages of prodrugs may include improved chemical stability, absorption, and/or PK properties of the parent carboxylic acids. Prodrugs may also be used to make drugs more "patient friendly," by minimizing the frequency (e.g., once daily) or route of dosing (e.g., oral), or to improve the taste or odor if given orally, or to minimize pain if given parenterally.

[0058] In some embodiments, the prodrugs are chemically more stable than the active drug, thereby improving formulation and delivery of the parent drug, compared to the drug alone.

[0059] Prodrugs for carboxylic acid analogs of the invention may include a variety of esters. In an exemplary embodiment, the pharmaceutical compositions of the invention include a carboxylic acid ester. In an exemplary embodiment, the prodrug is suitable for treatment /prevention of those diseases and conditions that require the drug molecule to cross the blood brain barrier. In an exemplary embodiment, the prodrug enters the brain, where it is converted into the active form of the drug molecule. In one embodiment, a prodrug is used to enable an active drug molecule to reach the inside of the eye after topical application of the prodrug to the eye.

Additionally, a prodrug can be converted to its parent compound by chemical or biochemical methods in an ex vivo environment. For example, a prodrug can be slowly converted to its parent compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0060] "Antihelminth", as used herein, is a compound which can kill or inhibit the growth of a helminth. The term antihelminth is broad enough to encompass acids, bases, salt forms (such as pharmaceutically acceptable salts), prodrugs, solvates and hydrates of the antihelminth compound.

[0061] The term "microbial infection" or "infection by a microorganism" refers to any infection of a host by an infectious agent including, but not limited to, bacteria (see, e.g., Harrison's Principles of Internal Medicine, pp. 93-98 (Wilson et al., eds., 12th ed. 1991); Williams et al., J. of Medicinal Chem. 42:1481-1485 (1999), herein each incorporated by reference in their entirety).
"Biological medium," as used herein refers to both in vitro and in vivo biological milieus. Exemplary in vitro "biological media" include, but are not limited to, cell culture, tissue culture, homogenates, plasma and blood. In vivo applications are generally performed in mammals, preferably humans.

"Inhibiting" and "blocking," are used interchangeably herein to refer to the partial or full blockade of an enzyme, such as a beta-lactamase.

The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include triflate, chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

Boron is able to form dative bonds with oxygen, sulfur or nitrogen under some circumstances in this invention. Dative bonds are usually weaker than covalent bonds. In situations where a boron is covalently bonded to at least one oxygen, sulfur or nitrogen, and is at the same time datively bonded to an oxygen, sulfur or nitrogen, respectively, the dative bond and covalent bond between the boron and the two identical heteroatoms can interconvert or be in the form of a resonance hybrid. There is potential uncertainty surrounding the exact nature and extent of electron sharing in these situations. Generally, in boron compounds comprising both covalent and coordinate covalent (dative) bonds, the electrons in such bonds may be partially or fully delocalized.

Embodiments of the invention also encompass compounds that are poly- or multi-valent species, including, for example, species such as dimers, trimers, tetramers and higher homologs of the compounds of use in the invention or reactive analogues thereof.

"Salt counterion", as used herein, refers to positively charged ions that associate with a compound of the invention when the boron is fully negatively or partially negatively charged. Examples of salt counterions include H⁺, H₃Ot⁺, ammonium, potassium, calcium, magnesium and sodium.
The compounds comprising a boron bonded to a carbon and three heteroatoms (such as three oxygens described in this section) can optionally contain a fully negatively charged boron or partially negatively charged boron, due to the nature of the dative bond between the boron and one of the oxygens. Due to the negative charge, a positively charged counterion may associate with this compound, thus forming a salt. Examples of positively charged counterions include H\(^+\), H\(_2\)O\(^+\), calcium, sodium, ammonium and potassium. The salts of these compounds are implicitly contained in descriptions of these compounds.

Introduction

The present invention provides novel boron compounds. The novel compounds, as well as pharmaceutical compositions containing such compounds or combinations of these compounds with at least one additional therapeutically effective agent, can be used for, among other things, treating worm infections.

The Compounds

III. a) Cyclic Boronic Esters

In one aspect, the invention provides a compound of the invention. In an exemplary embodiment, the invention is a compound described herein. In an exemplary embodiment, the invention is a compound according to a formula described herein.

In an exemplary embodiment, the compound has a structure which is:

wherein X is N or CH; R\(^5\) is H or halogen and R\(^1\) or R\(^2\) is selected from the group consisting of: alkoxy, optionally substituted with a substituted or unsubstituted phenyl; alkoxy, optionally substituted with a substituted or unsubstituted heteroaryl; alkyamino, optionally substituted with a substituted or unsubstituted phenyl; alkyamino, optionally substituted with a substituted or unsubstituted heteroaryl; -NHC(0)R\(^1\)\(^2\), wherein R\(^1\)\(^2\) is unsubstituted phenyl or unsubstituted heteroaryl; -NHS(0)2R\(^1\)\(^2\), wherein R\(^1\)\(^2\) is unsubstituted phenyl or unsubstituted heteroaryl; -NHC(0)R\(^1\)\(^2\), wherein R\(^1\)\(^2\) is unsubstituted alkyl; -C(0)NHR\(^1\)\(^2\), wherein R\(^1\)\(^2\) is unsubstituted alkyl, or a hydrate, solvate or salt thereof.
In an exemplary embodiment, the compound has a structure which is:

wherein $R^5$ is $H$ or halogen and $R^1$ or $R^2$ is selected from the group consisting of:

- alkoxy, optionally substituted with a substituted or unsubstituted phenyl; alkoxy,
- optionally substituted with a substituted or unsubstituted heteroaryl; alkylamino,
- optionally substituted with a substituted or unsubstituted phenyl; alkylamino,
- optionally substituted with a substituted or unsubstituted heteroaryl; $\text{-NHC(O)R}^{11}$, wherein $R^{11}$ is unsubstituted phenyl or unsubstituted heteroaryl; $\text{-NHS(O)R}^{11}$, wherein $R^{11}$ is unsubstituted phenyl or unsubstituted heteroaryl; $\text{-NHC(O)R}^{12}$, wherein $R^{12}$ is unsubstituted alkyl; $\text{-C(O)NHR}^{12}$, wherein $R^{12}$ is unsubstituted alkyl, or a hydrate, solvate or salt thereof.

In an exemplary embodiment, the compound has a structure which is:

wherein $R^5$ is $H$ or halogen and $R^1$ is selected from the group consisting of:

- alkoxy, optionally substituted with a substituted or unsubstituted phenyl; alkoxy,
- optionally substituted with a substituted or unsubstituted heteroaryl; alkylamino,
- optionally substituted with a substituted or unsubstituted phenyl; alkylamino,
- optionally substituted with a substituted or unsubstituted heteroaryl; $\text{-NHC(O)R}^{11}$, wherein $R^{11}$ is unsubstituted phenyl or unsubstituted heteroaryl; $\text{-NHS(O)R}^{11}$, wherein $R^{11}$ is unsubstituted phenyl or unsubstituted heteroaryl; $\text{-NHC(O)R}^{12}$, wherein $R^{12}$ is unsubstituted alkyl; $\text{-C(O)NHR}^{12}$, wherein $R^{12}$ is unsubstituted alkyl, or a hydrate, solvate or salt thereof.

In an exemplary embodiment, the compound has a structure which is:

wherein $R^5$ is $H$ or halogen and $R^1$ or $R^2$ is selected from the group consisting of:

- alkoxy, optionally substituted with a substituted or unsubstituted phenyl; alkoxy,
- optionally substituted with a substituted or unsubstituted heteroaryl; alkylamino,
- optionally substituted with a substituted or unsubstituted phenyl; alkylamino,
optionally substituted with a substituted or unsubstituted heteroaryl; -NHC(0)R^{11},
wherein R^{11} is unsubstituted phenyl or unsubstituted heteroaryl; -NHS(0)2R^{11},
wherein R^{11} is unsubstituted phenyl or unsubstituted heteroaryl; -NHC(0)R^{12},
wherein R^{12} is unsubstituted alkyl; -C(0)NHR^{12}, wherein R^{12} is unsubstituted alkyl,
or a hydrate, solvate or salt thereof.

[0075] In an exemplary embodiment, the compound has a structure according to the formula:

wherein R^5 is H or halogen and R^1 is alkoxy, substituted with a substituted or
unsubstituted heteroaryl. In an exemplary embodiment, said heteroaryl is selected
from the group consisting of pyridinyl, imidazolyl, thiazolyl and pyrimidinyl. In an
exemplary embodiment, R^5 is H or halogen and R^1 is methoxy or ethoxy or propoxy,
substituted with pyridinyl, imidazolyl, thiazolyl and pyrimidinyl. In an exemplary
embodiment, R^5 is H or halogen and R^1 is methoxy or ethoxy or propoxy, substituted
with a substituted or unsubstituted heteroaryl. In an exemplary embodiment, R^5 is H
or halogen and R^1 is methoxy or ethoxy or propoxy, substituted with a substituted or
unsubstituted pyridinyl or substituted or unsubstituted imidazolyl or substituted or
unsubstituted thiazolyl or substituted or unsubstituted pyrimidinyl. In an exemplary
embodiment, R^5 is as described herein and R^1 is pyridinylmethoxy. In an exemplary
embodiment, R^5 is as described herein and R^1 is pyridin-2-ylmethoxy. In an
exemplary embodiment, R^5 is as described herein and R^1 is pyridin-3-ylmethoxy. In
an exemplary embodiment, R^5 is as described herein and R^1 is pyridin-4-ylmethoxy.
In an exemplary embodiment, R^5 is as described herein and R^1 is imidazolylmethoxy.
In an exemplary embodiment, R^5 is as described herein and R^1 is imidazol-2-
ylmethoxy. In an exemplary embodiment, R^5 is as described herein and R^1 is
thiazolylmethoxy. In an exemplary embodiment, R^5 is as described herein and R^1 is
thiazol-2-ylmethoxy. In an exemplary embodiment, R^5 is as described herein and R^1
is pyrimidinylmethoxy. In an exemplary embodiment, R^5 is as described herein and
R^1 is pyrimidin-6-ylmethoxy. In an exemplary embodiment, R^5 is as described herein
and R^1 is methoxy substituted with a substituted or unsubstituted heteroaryl. In an
exemplary embodiment, R^5 is as described herein and R^1 is ethoxy substituted with a
substituted or unsubstituted phenyl. In an exemplary embodiment, R^5 is as described
herein and $R^1$ is propoxy substituted with a substituted or unsubstituted phenyl. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is butoxy substituted with a substituted or unsubstituted phenyl. In an exemplary embodiment, $R^1$ is as described herein and $R^5$ is H. In an exemplary embodiment, $R^1$ is as described herein and $R^5$ is F.

[0076] In an exemplary embodiment, the compound has a structure according to the formula:

$$\text{Structure}$$

wherein $R^5$ is H or halogen and $R^1$ is alkoxy, substituted with a substituted or unsubstituted phenyl. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is benzoxy. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is methoxy substituted with a substituted phenyl. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is ethoxy substituted with a substituted or unsubstituted phenyl. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is propoxy substituted with a substituted or unsubstituted phenyl. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is butoxy substituted with a substituted or unsubstituted phenyl. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is alkoxy, substituted with an aminomethylsubstituted phenyl. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is alkoxy, substituted with a phenyl which is substituted with a mono-unsubstituted alkyaminomethyl moiety. In an exemplary embodiment, $R^5$ is as described herein and $R^1$ is alkoxy, substituted with a phenyl with is substituted with a di-unsubstituted alkyaminomethyl moiety. In an exemplary embodiment, $R^1$ is as described herein and $R^5$ is H. In an exemplary embodiment, $R^1$ is as described herein and $R^5$ is F.
In an exemplary embodiment, the compound has a structure according to the formula:

wherein \( R^5 \) is H or halogen and \( R^{4a} \) is alkylene, and \( R^{21} \) and \( R^{22} \) are each independently selected from H or methyl or ethyl or unsubstituted \( C_3 \) alkyl or unsubstituted \( C_4 \) alkyl or unsubstituted \( C_5 \) alkyl or unsubstituted \( C_6 \) alkyl. In an exemplary embodiment, \( R^5 \) is H or halogen and \( R^{4a} \) is methylene or ethylene or propylene, and \( R^{21} \) and \( R^{22} \) are each independently selected from H or methyl or ethyl or unsubstituted \( C_3 \) alkyl or unsubstituted \( C_4 \) alkyl or unsubstituted \( C_5 \) alkyl or unsubstituted \( C_6 \) alkyl. In an exemplary embodiment, \( R^5 \) is H or halogen and \( R^{4a} \) is methylene or ethylene or propylene, and \( R^{21} \) is H and \( R^{22} \) is H. In an exemplary embodiment, \( R^5 \) is H or halogen and \( R^{4a} \) is methylene or ethylene or propylene, and \( R^{21} \) is H and \( R^{22} \) is H or methyl or ethyl or unsubstituted \( C_3 \) alkyl or unsubstituted \( C_4 \) alkyl or unsubstituted \( C_5 \) alkyl or unsubstituted \( C_6 \) alkyl. In an exemplary embodiment, \( R^5 \) is H or halogen and \( R^{4a} \) is methylene or ethylene or propylene, and \( R^{21} \) and \( R^{22} \) are each independently selected from H or methyl or ethyl or unsubstituted \( C_3 \) alkyl or unsubstituted \( C_4 \) alkyl or unsubstituted \( C_5 \) alkyl or unsubstituted \( C_6 \) alkyl. In an exemplary embodiment, \( R^5 \) is H or F and \( R^{4a} \) is methylene, and \( R^{21} \) and \( R^{22} \) are each independently selected from H or methyl or ethyl or unsubstituted \( C_3 \) alkyl or unsubstituted \( C_4 \) alkyl or unsubstituted \( C_5 \) alkyl or unsubstituted \( C_6 \) alkyl. In an exemplary embodiment, \( R^5 \) is H or F and \( R^{4a} \) is methylene, and \( R^{21} \) and \( R^{22} \) are each independently selected from H or methyl or ethyl or unsubstituted \( C_3 \) alkyl. In an exemplary embodiment, \( R^5 \) is H or F and \( R^{4a} \) is methylene, and \( R^{21} \) and \( R^{22} \) are each independently selected from methyl or ethyl or unsubstituted \( C_3 \) alkyl.
[0078] In an exemplary embodiment, the compound has a structure according to the formula:

wherein \( R^1 \) is halogen and \( R^5 \) is H or halogen. In an exemplary embodiment, when \( R^1 \) is Cl, \( R^5 \) is not H. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^1 \) is F. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^1 \) is Cl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^1 \) is Br. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^1 \) is I. In an exemplary embodiment, \( R^1 \) is as described herein and \( R^5 \) is F.

[0079] In an exemplary embodiment, the compound has a structure according to the formula:

wherein \( R^3 \) is H or unsubstituted alkyl and \( R^5 \) is H or halogen. In an exemplary embodiment, when \( R^3 \) is methyl, \( R^5 \) is not H. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is unsubstituted \( \text{Ci-C}_6 \) alkyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is H. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is methyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is ethyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is unsubstituted \( \text{C}_3 \) alkyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is isopropyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is unsubstituted \( \text{C}_4 \) alkyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is t-butyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is unsubstituted \( \text{C}_5 \) alkyl. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^3 \) is unsubstituted \( \text{C}_6 \) alkyl. In an exemplary embodiment, \( R^3 \) is as described herein and \( R^5 \) is H. In an exemplary embodiment, \( R^3 \) is as described herein and \( R^5 \) is F.

[0080] In an exemplary embodiment, the compound has a structure according to the formula:
wherein R^5 is H or halogen. In an exemplary embodiment, R^5 is H. In an exemplary
embodiment, R^5 is F.

[0081] In an exemplary embodiment, the compound has a structure according to
the formula:

wherein R^5 is H or halogen. In an exemplary embodiment, R^5 is H. In an exemplary
embodiment, R^5 is F.

[0082] In an exemplary embodiment, the compound has a structure according to
the formula:

wherein R^5 is H or halogen. In an exemplary embodiment, R^5 is H. In an exemplary
embodiment, R^5 is F.

[0083] In an exemplary embodiment, the compound has a structure according to
the formula:

wherein R^5 is H or halogen. In an exemplary embodiment, R^5 is halogen. In an
exemplary embodiment, R^5 is F.

[0084] In an exemplary embodiment, the compound has a structure according to
the formula:

wherein R^1 is halogen and R^5 is H or halogen. In an exemplary embodiment, when R^1
is Cl, R^5 is not H. In an exemplary embodiment, R^5 is as described herein and R^1 is F.
In an exemplary embodiment, R^5 is as described herein and R^1 is Cl. In an exemplary
embodiment, R^5 is as described herein and R^1 is Br. In an exemplary embodiment, R^5
is as described herein and R^1 is I. In an exemplary embodiment, R^1 is as described
herein and $R^5$ is H. In an exemplary embodiment, $R^1$ is as described herein and $R^5$ is F.

[0085] In an exemplary embodiment, the compound has a structure according to the formula:

![Chemical Structure 1]

wherein $R^3$ is H or unsubstituted alkyl and $R^5$ is H or halogen. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is unsubstituted $\mathrm{C}_1$-$\mathrm{C}_6$ alkyl. In an exemplary embodiment, when $R^3$ is methyl, $R^5$ is not H. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is H. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is methyl. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is ethyl. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is unsubstituted $\mathrm{C}_3$ alkyl. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is unsubstituted $\mathrm{C}_4$ alkyl. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is unsubstituted $\mathrm{C}_5$ alkyl. In an exemplary embodiment, $R^5$ is as described herein and $R^3$ is unsubstituted $\mathrm{C}_6$ alkyl. In an exemplary embodiment, $R^3$ is as described herein and $R^5$ is H. In an exemplary embodiment, $R^3$ is as described herein and $R^5$ is F.

[0086] In an exemplary embodiment, the compound has a structure according to the formula:

![Chemical Structure 2]

wherein $R^8$ is unsubstituted alkylene and $R^5$ is H or halogen. In an exemplary embodiment, when $R^8$ is ethylene, $R^5$ is not H. In an exemplary embodiment, $R^5$ is as described herein and $R^8$ is unsubstituted $\mathrm{C}_1$-$\mathrm{C}_6$ alkylene. In an exemplary embodiment, $R^5$ is as described herein and $R^8$ is methylene. In an exemplary embodiment, $R^5$ is as described herein and $R^8$ is ethylene. In an exemplary embodiment, $R^5$ is as described herein and $R^8$ is propylene. In an exemplary embodiment, $R^5$ is as described herein and $R^8$ is butylene. In an exemplary embodiment, $R^5$ is as described herein and $R^8$ is pentylene. In an exemplary embodiment, $R^5$ is as described herein and $R^8$ is hexylene. In an exemplary
embodiment, \( R^8 \) is as described herein and \( R^5 \) is H. In an exemplary embodiment, \( R^8 \) is as described herein and \( R^5 \) is F.

[0087] In an exemplary embodiment, the compound has a structure according to the formula:

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{formula.png}
\caption{Structure of the compound.}
\end{figure}}
\]

wherein \( R^8 \) is unsubstituted alkylene and \( R^5 \) is H or halogen. In an exemplary embodiment, when \( R^8 \) is ethylene, \( R^5 \) is not H. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is unsubstituted C\textsubscript{6} alkylene. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is not ethylene. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is not methylene, ethylene, and propylene. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is methylene. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is ethylene. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is propylene. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is butylene. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is pentyline. In an exemplary embodiment, \( R^5 \) is as described herein and \( R^8 \) is hexylene. In an exemplary embodiment, \( R^8 \) is as described herein and \( R^5 \) is H. In an exemplary embodiment, \( R^8 \) is as described herein and \( R^5 \) is F.

[0088] In an exemplary embodiment, the compound has a structure according to the formula:

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{formula.png}
\caption{Structure of the compound.}
\end{figure}}
\]

wherein \( R^1 \) is selected from the group consisting of F, Br and I, \( R^8 \) is as described herein, and \( R^5 \) is H or halogen. In an exemplary embodiment, \( R^1 \) and \( R^8 \) are as described herein and \( R^5 \) is H. In an exemplary embodiment, \( R^1 \) and \( R^8 \) are as described herein and \( R^5 \) is F.

[0089] In an exemplary embodiment, the compound has a structure according to the formula:
wherein \( R^8 \) is as described herein, and \( R^5 \) is H or halogen. In an exemplary embodiment, when \( R^8 \) is ethylene, \( R^5 \) is not H. In an exemplary embodiment, \( R^8 \) is unsubstituted alkylene. In an exemplary embodiment, \( R^8 \) is as described herein and \( R^5 \) is H. In an exemplary embodiment, \( R^8 \) is as described herein and \( R^5 \) is F.

[0090] In an exemplary embodiment, the compound has a structure according to the formula:

```
H3C
NC
\[ \text{R}^8 \text{S} \]
\[ \text{N} \]
\[ \text{R}^5 \text{OH} \]
```

wherein \( R^3 \) is H or unsubstituted alkyl, and \( R^5 \) is H or halogen. In an exemplary embodiment, when \( R^3 \) is methyl, \( R^5 \) is not H. In an exemplary embodiment, \( R^3 \) is as described herein. In an exemplary embodiment, \( R^3 \) is as described herein and \( R^5 \) is H. In an exemplary embodiment, \( R^3 \) is as described herein and \( R^5 \) is F.

[0091] In an exemplary embodiment, the compound has a structure which is selected from the group consisting of:

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\[ \text{R}^9 \text{R}^3 \text{R}^{3a} \]
```

wherein \( R^{3a} \) is selected from the group consisting of S, SO and SO₂, \( R^9 \) is selected from the group consisting of hydroxy, unsubstituted alkoxy, nitro, amino and halogen, and \( R^5 \) is H or halogen. In an exemplary embodiment, \( R^9 \) and \( R^5 \) as described herein, and \( R^{3a} \) is S. In an exemplary embodiment, \( R^{3a} \) and \( R^9 \) are as described herein, and \( R^5 \) is F. In an exemplary embodiment, \( R^{3a} \) and \( R^9 \) are as described herein, and \( R^5 \) is H. In an exemplary embodiment, \( R^{3a} \) and \( R^9 \) are as described herein, and \( R^5 \) is F. In an exemplary embodiment, \( R^{3a} \) and \( R^5 \) as described herein, and \( R^9 \) is F. In an exemplary embodiment, \( R^{3a} \) and \( R^5 \) as described herein, and \( R^9 \) is Cl. In an exemplary embodiment, \( R^{3a} \) and \( R^5 \) as described herein, and \( R^9 \) is methoxy. In an exemplary embodiment, \( R^{3a} \) and \( R^5 \) as described herein, and \( R^9 \) is ethoxy. In an exemplary embodiment, \( R^{3a} \) and \( R^5 \) as described herein, and \( R^9 \) is unsubstituted \( C_3 \) alkoxy. In an
exemplary embodiment, \( R^9 \) as described herein, and \( R^9 \) is unsubstituted C-alkoxy. In an exemplary embodiment, \( R^3 \) and \( R^5 \) as described herein, and \( R^9 \) is unsubstituted C-alkoxy. In an exemplary embodiment, \( R^3 \) and \( R^5 \) as described herein, and \( R^9 \) is unsubstituted C-alkoxy. In an exemplary embodiment, \( R^9 \) is described herein, \( R^3 \) is S, and \( R^5 \) is H. In an exemplary embodiment, \( R^9 \) is methoxy, \( R^3 \) is S, and \( R^5 \) is as described herein. In an exemplary embodiment, \( R^3 \) is described herein, and \( R^5 \) is H, and \( R^9 \) is F or Cl or methoxy or ethoxy or unsubstituted C-alkoxy or unsubstituted C-alkoxy or unsubstituted C-alkoxy or unsubstituted C-alkoxy. In an exemplary embodiment, \( R^3 \) is S, and \( R^5 \) is F, and \( R^9 \) is F or Cl or methoxy or ethoxy or unsubstituted C-alkoxy or unsubstituted C-alkoxy or unsubstituted C-alkoxy. In an exemplary embodiment, \( R^9 \) is selected from the group consisting of:

\[
\begin{align*}
\text{(1)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\text{(2)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\text{(3)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\text{(4)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\end{align*}
\]

wherein \( R^3 \), \( R^9 \), and \( R^5 \) are as described herein.

In an exemplary embodiment, the compound has a structure which is selected from the group consisting of:

\[
\begin{align*}
\text{(5)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\text{(6)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\text{(7)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\text{(8)} & \quad \text{R}^9 \quad \text{R}^3 \quad \text{R}^5 \\
\end{align*}
\]

wherein \( R^3 \) is selected from the group consisting of S, SO and \( \text{SO}_2 \), each \( R^9 \) is an independently selected halogen, and \( R^5 \) is H or halogen. In an exemplary embodiment, \( R^3 \) and \( R^5 \) as described herein, and each \( R^9 \) is CI.
In an exemplary embodiment, the compound has a structure selected from the group consisting of:

![Chemical structure]

wherein $R^3$ is selected from the group consisting of $S$, $SO$, and $SO_2$, and $R^5$ is H or halogen. In an exemplary embodiment, $R^5$ as described herein, and $R^3$ is $S$. In an exemplary embodiment, $R^3$ as described herein, and $R^5$ is $F$. In an exemplary embodiment, $R^3$ as described herein, and $R^5$ is H. In an exemplary embodiment, $R^5$ is as described herein, and $R^3$ is $S$. In an exemplary embodiment, $R^3$ is $S$, and $R^5$ is H.

In an exemplary embodiment, the compound is:

![Chemical structure]

In an exemplary embodiment, the invention provides a compound described herein, or a salt, hydrate or solvate thereof, or a combination thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt, hydrate or solvate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt thereof. In an exemplary embodiment, the salt is a pharmaceutically acceptable salt. In an exemplary embodiment, the invention provides a compound described herein, or a hydrate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a solvate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a prodrug thereof. In an exemplary embodiment, the invention provides a salt of a compound described herein. In an exemplary embodiment, the invention provides a pharmaceutically acceptable salt of a compound described herein. In an exemplary embodiment, the invention provides a hydrate of a compound described herein. In an exemplary embodiment, the invention provides a solvate of a compound described herein. In an exemplary embodiment, the invention provides a prodrug of a compound described herein.
In an exemplary embodiment, alkyl is linear alkyl. In another exemplary embodiment, alkyl is branched alkyl.

In an exemplary embodiment, heteroalkyl is linear heteroalkyl. In another exemplary embodiment, heteroalkyl is branched heteroalkyl.

IIIb) Compositions involving stereoisomers

As used herein, the term "chiral", "enantiomerically enriched" or "diastereomerically enriched" refers to a composition having an enantiomeric excess (ee) or a diastereomeric excess (de) of greater than about 50%, preferably greater than about 70% and more preferably greater than about 90%. In general, higher than about 90%, enantiomeric or diastereomeric excess is particularly preferred, e.g., those compositions with greater than about 95%, greater than about 97% and greater than about 99%, ee or de.

When a first compound and a second compound are present in a composition, and the first compound is a non-superimposable mirror image of the second compound, and the first compound is present in the composition in a greater amount than the second compound, then the first compound is referred to herein as being present in "enantiomeric excess".

The term "enantiomeric excess" of a compound z, as used herein, is defined as:

\[ ee_2 = \left( \frac{cone. \text{ } df \text{ } z}{cone. \ text{ } df \text{ } z + cone. \ text{ } df \text{ } y} \right) \times 100 \]

wherein z is a first compound in a composition, y is a second compound in the composition, and the first compound is a non-superimposable mirror image of the second compound.

The term "enantiomeric excess" is related to the older term "optical purity" in that both are measures of the same phenomenon. The value of ee will be a number from 0 to 100, zero being racemic and 100 being enantiomerically pure. A composition which in the past might have been called 98% optically pure is now more precisely characterized by 96%> ee. A 90%> ee reflects the presence of 95% of one enantiomer and 5% of the other(s) in the material in question.

When a first compound and at least one additional compound are present in a composition, and the first compound and each of the additional compounds are
stereoisomers, but not mirror images, of one another, and the first compound is present in the composition in a greater amount than each of the additional compounds, then the first compound is referred to herein as being present in "diastereomeric excess".

[0104] When dealing with mixtures of diastereomers, the term "diastereomeric excess" or "de" is defined analogously to enantiomeric excess. Thus:

\[ de = \left( \frac{\text{cone, } df \text{ major diastereomer} - \text{cone, } df \text{ min or diastereomer(s)}}{\text{cone, } df \text{ major diastereomer} + \text{cone, } df \text{ min or diastereomer(s)}} \right) \times 100 \]

wherein the major diastereomer is a first compound in a composition, and the minor diastereomer(s) is at least one additional compound in the composition, and the major diastereomer and minor diastereomer(s) are stereoisomers, but not mirror images, of one another.

[0105] The value of de will likewise be a number from 0 to 100, zero being an equal mixture of a first diastereomer and the remaining diastereomer(s), and 100 being 100% of a single diastereomer and zero% of the other(s) - i.e.

[0106] Hence, in one embodiment, the invention provides a composition including a first compound of the invention, wherein the first compound of the invention has at least one stereocenter, and at least one stereoisomer of the first compound of the invention. In another embodiment, the invention provides a composition including a first compound of the invention, wherein the first compound of the invention has at least one stereocenter, and a second compound of the invention, wherein the first compound of the invention is a stereoisomer of the second compound of the invention. In another embodiment, the invention provides a composition including a first compound of the invention, wherein the first compound of the invention has at least one stereocenter, and only one stereoisomer of the first compound of the invention.

[0107] In another embodiment, the invention provides a composition including a first compound of the invention, wherein the first compound of the invention has only one stereocenter, and an enantiomer of the first compound of the invention. In another embodiment, the invention provides a composition including a first
compound of the invention, wherein the first compound of the invention has two stereocenters, and an enantiomer of the first compound of the invention. In another embodiment, the invention provides a composition including a first compound of the invention, wherein the first compound of the invention has two stereocenters, and at least one diastereomer of the first compound of the invention. In another embodiment, the invention provides a composition including a first compound of the invention, wherein the first compound of the invention has two stereocenters, and only one diastereomer of the first compound of the invention.

[0108] In situations where the first compound of the invention and its enantiomer are present in a composition, the first compound of the invention can be present in an enantiomeric excess of at least about 80%, or at least about 90%, or at least about 92% or at least about 95%. In another embodiment, where the first compound of the invention and its enantiomer are present in a composition, the first compound of the invention can be present in an enantiomeric excess of at least about 96%, at least about 97%, at least about 98%, at least about 99% or at least about 99.5%. In another embodiment, the first compound of the invention has at least one stereocenter and is enantiomerically pure (enantiomeric excess is about 100%).

[0109] In situations where the first compound of the invention and at least one diastereomer of the first compound of the invention are present in a composition, the first compound of the invention can be present in a diastereomeric excess of at least about 80%, or at least about 90%, or at least about 92% or at least about 95%. In situations where the first compound of the invention and at least one diastereomer of the first compound of the invention are present in a composition, the first compound of the invention can be present in a diastereomeric excess of at least about 96%, at least about 97%, at least about 98%, at least about 99% or at least about 99.5%. In another embodiment, the first compound of the invention has at least two stereocenters and is diastereomERICally pure (diastereomeric excess is about 100%).

[0110] Enantiomeric or diastereomeric excess can be determined relative to exactly one other stereoisomer, or can be determined relative to the sum of at least two other stereoisomers. In an exemplary embodiment, enantiomeric or diastereomeric excess is determined relative to all other detectable stereoisomers, which are present in the mixture. Stereoisomers are detectable if a concentration of
such stereoisomer in the analyzed mixture can be determined using common analytical methods, such as chiral HPLC.

[0111] As used herein, and unless otherwise indicated, a composition that is "substantially free" of a compound means that the composition contains less than about 20% by weight, or less than about 15% by weight, or less than about 10% by weight, or less than about 5% by weight, or less than about 3% by weight, or less than about 2% by weight, or less than about 1% by weight of the compound.

[0112] As used herein, the term "substantially free of the (or its) enantiomer" means that a composition contains a significantly greater proportion of a first compound of the invention than a second compound of the invention, wherein the first compound is a non-superimposable mirror image of the second compound. In one embodiment of the invention, the term "substantially free of the enantiomer" means that the composition is made up of at least about 90% by weight of a first compound of the invention, and about 10% by weight or less of a second compound of the invention, wherein the first compound is a non-superimposable mirror image of the second compound. In one embodiment of the invention, the term "substantially free of the (R) enantiomer" means that the composition is made up of at least about 90% by weight of a first compound of the invention which has only one stereocenter and the stereocenter is in an (S) configuration, and about 10% by weight or less of a second compound of the invention, wherein the second compound is the enantiomer of the first compound. In one embodiment of the invention, the term "substantially free of the enantiomer" means that the composition is made up of at least about 95% by weight of a first compound of the invention, and about 5% by weight or less of a second compound of the invention, wherein the first compound is a non-superimposable mirror image of the second compound. In one embodiment of the invention, the term "substantially free of the (R) enantiomer" means that the composition is made up of at least about 95% by weight of a first compound of the invention which has only one stereocenter and the stereocenter is in an (S) configuration, and about 5% by weight or less of a second compound of the invention, wherein the second compound is the enantiomer of the first compound. In one embodiment of the invention, the term "substantially free of the enantiomer" means that the composition is made up of at least about 98% by weight of a first compound of the invention, and about 2% by weight or less of a second compound of
the invention, wherein the first compound is a non-superimposable mirror image of
the second compound. In one embodiment of the invention, the term "substantially free of the (R) enantiomer" means that the composition is made up of at least about 98% by weight of a first compound of the invention which has only one stereocenter and the stereocenter is in an (S) configuration, and about 2% by weight or less of a second compound of the invention, wherein the second compound is the enantiomer of the first compound. In one embodiment of the invention, the term "substantially free of the enantiomer" means that the composition is made up of at least about 99% by weight of a first compound of the invention, and about 1% by weight or less of a second compound of the invention, wherein the first compound is a non-superimposable mirror image of the second compound. In one embodiment of the invention, the term "substantially free of the (R) enantiomer" means that the composition is made up of at least about 99% by weight of a first compound of the invention which has only one stereocenter and the stereocenter is in an (S) configuration, and about 1% by weight or less of a second compound of the invention, wherein the second compound is the enantiomer of the first compound.

In an exemplary embodiment, the invention provides a composition comprising a) first compound described herein; and b) the enantiomer of the first compound, wherein the first compound described herein is present in an enantiomeric excess of at least 80%. In an exemplary embodiment, the enantiomeric excess is at least 92%.

III.c) Combinations comprising additional therapeutic agents

The compounds of the invention may also be used in combination with additional therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound described herein or a pharmaceutically acceptable salt thereof together with at least one additional therapeutic agent. In an exemplary embodiment, the additional therapeutic agent is a compound of the invention. In an exemplary embodiment, the additional therapeutic agent includes a boron atom. In an exemplary embodiment, the additional therapeutic agent does not contain a boron atom.

When a compound of the invention is used in combination with a second therapeutic agent active against the same disease state, the dose of each compound
may differ from that when the compound 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 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.

[0116] In an exemplary embodiment, the additional therapeutic agent is an antiworm agent. In an exemplary embodiment, the additional therapeutic agent is an antihelmintic agent. In an exemplary embodiment, the additional therapeutic agent is selected from the group consisting of abamectin, diethylcarbamazine, mebendazole, niclosamide, suramin, thiabendazole, pyrantel pamoate, levamisole, piperazine, piperazine analogs, praziquantel, thiacetarsamide, triclabendazole, flubendazole, fenbendazole, Ooctadepsipeptides, such asemodepside, amino acetonitrile derivatives (such as monepantel). In an exemplary embodiment, the additional therapeutic agent is albendazole. In an exemplary embodiment, the additional therapeutic agent is ivermectin. In an exemplary embodiment, the additional therapeutic agent is melarsomine. In an exemplary embodiment, the additional therapeutic agent is selected from the group consisting of selamectin, milbemycin, and moxidectin. In an exemplary embodiment, the additional therapeutic agent is selected from the group consisting of tobacco, Moringa oleifera (Moringaceae), black walnut (Juglans nigra), wormwood (Artemisia absinthium), clove (Syzygium aromaticum), tansy tea (Tanacetum vulgare), hagenia (Hagenia abyssinica), garlic (Allium sativum), pineapple (Ananas comosus), kalonji (Nigella sativa) seeds, male fern (Dryopteris filix-mas), plumeria (P. acutifolia or P. rubra), and Peganum harmala.

[0117] The individual components of such combinations may be administered either simultaneously or sequentially in a unit dosage form. The unit dosage form may be a single or multiple unit dosage forms. In an exemplary embodiment, the invention provides a combination in a single unit dosage form. An example of a single unit dosage form is a capsule wherein both the compound of the invention and the additional therapeutic agent are contained within the same capsule. In an exemplary embodiment, the invention provides a combination in a two unit dosage form. An example of a two unit dosage form is a first capsule which contains the compound of the invention and a second capsule which contains the additional therapeutic agent. Thus the term 'single unit' or 'two unit' or 'multiple unit' refers to
the object which the patient ingests, not to the interior components of the object.

Appropriate doses of known therapeutic agents will be readily appreciated by those
skilled in the art.

[0118] The combinations referred to herein may conveniently be presented for use
in the form of a pharmaceutical formulation. Thus, an exemplary embodiment of the
invention is a pharmaceutical formulation comprising a) a compound of the invention;
b) an additional therapeutic agent and c) a pharmaceutically acceptable excipient. In
an exemplary embodiment, the pharmaceutical formulation is a unit dosage form. In
an exemplary embodiment, the pharmaceutical formulation is a two unit dosage
form. In an exemplary embodiment, the pharmaceutical formulation is a two unit
dosage form comprising a first unit dosage form and a second unit dosage form,
wherein the first unit dosage form includes a) a compound of the invention and b) a
first pharmaceutically acceptable excipient; and the second unit dosage form includes
c) an additional therapeutic agent and d) a second pharmaceutically acceptable
excipient.

[0119] It is to be understood that the present invention covers all combinations of
aspects and/or embodiments, as well as suitable, convenient and preferred groups
described herein.

III) Preparation of Boron-Containing Compounds

[0120] Compounds of use in the invention can be prepared using commercially
available starting materials, known intermediates, or by using the synthetic methods
published in references described and incorporated by reference herein, such as U.S.
Pat. Apps. 12/142,692 and U.S. Pat. Pubs. US20060234981, US20070155699 and
US20070293457.

[0121] The following general procedures were used as indicated in generating the
examples and can be applied, using the knowledge of one of skill in the art, to other
appropriate compounds to obtain additional analogues.
1. General Schemes

Scheme 1

\[
\text{SM-Acid (X=F or H)} \xrightarrow{\text{Mel, Cs\textsubscript{2}CO\textsubscript{3}}} \text{Acetone, reflux} \rightarrow \text{C67: R=H; C73: R=MeO; C76: R=Cl}
\]

Scheme 2

\[
\text{J17: } X=F; \text{ J16: } X=H
\]

Scheme 3

\[
\text{C55} \xrightarrow{\text{HS-Ar}} \text{I\textsubscript{2}, EtOH, H\textsubscript{2}O} \rightarrow \text{J4: p-methoxyphenyl; J2: p-chlorophenyl; J1: m-chlorophenyl; J3: m,p-dichlorophenyl; J10: p-nitrophenyl; J11: p-fluorophenyl; J12: 2-naphthalenyl}
\]
IV. *Methods of Inhibiting Worm Growth or of Killing Worms*

[0122] The compounds of the present invention exhibit potency against worms, and therefore have the potential to kill and/or inhibit the growth of such worms. The invention therefore provides a method of killing and/or inhibiting the growth of a worm, comprising: contacting the worm with an effective amount of the compound of the invention, thereby killing and/or inhibiting the growth of the worm.

[0123] In an exemplary embodiment, the worm is a parasitic worm. In an exemplary embodiment, the worm is a helminth. In an exemplary embodiment, the worm is a nematode. In an exemplary embodiment, the nematode is selected from the group consisting of ascarids, filarids, hookworms, pinworms, and whipworms. In an exemplary embodiment, the nematode is a member of *Filarioidea*. In an exemplary embodiment, the nematode is a filarid. In an exemplary embodiment, the nematode is a filarial worm. In an exemplary embodiment, the nematode is a member of the genus *Wuchereria*. In an exemplary embodiment, the nematode is *Wuchereria bancrofti*. In an exemplary embodiment, the nematode is a member of the genus *Brugia*. In an exemplary embodiment, the nematode is *Brugia malayi*. In an exemplary embodiment, the nematode is *Brugia timori*.

[0124] In an exemplary embodiment, the nematode is a member of the genus *Loa*. In an exemplary embodiment, the nematode is *Loa loa*. In an exemplary embodiment, the nematode is a member of the genus *Mansonella*. In an exemplary embodiment, the nematode is selected from the group consisting of *Mansonella streptocerca*, *Mansonella perstans*, and *Monsonella ozzardi*. In an exemplary embodiment, the nematode is a member of the genus *Onchocerca*. In an exemplary embodiment, the nematode is *Onchocerca volvulus*.

[0125] In an exemplary embodiment, the nematode is a pinworm. In an exemplary embodiment, the nematode is *Enterobius vermicularis*. In an exemplary embodiment, the nematode is a member of the genus *Ascaris*. In an exemplary embodiment, the nematode is *Ascaris lumbricoides*. In an exemplary embodiment, the nematode is a member of the genus *Dracunculus*. In an exemplary embodiment, the nematode is *Dracunculus medinensis*. In an exemplary embodiment, the nematode is a member of the genus *Ancylostoma*. In an exemplary embodiment, the nematode is *Ancylostoma duodenale*. In an exemplary embodiment, the nematode is selected from the group
consisting of *Ancylostoma braziliense*, *Ancylostoma tubaeforme*, and *Ancylostoma caninum*. In an exemplary embodiment, the nematode is a member of the genus *Necator*. In an exemplary embodiment, the nematode is *Necator americanus*.

[0126] In an exemplary embodiment, the nematode is a member of the genus *Trichuris*. In an exemplary embodiment, the nematode is selected from the group consisting of *Trichuris trichiura*, *Trichuris vulpis*, *Trichuris campanula*, *Trichuris suis*, and *Trichuris muris*. In an exemplary embodiment, the nematode is a member of the genus *Strongyloides*. In an exemplary embodiment, the nematode is selected from the group consisting of *Strongyloides stercoralis*, *Strongyloides canis*, *Strongyloides fuelleborni*, *Strongyloides cebus*, and *Strongyloides kellyi*. In an exemplary embodiment, the nematode is a member of the genus *Nematodirus*. In an exemplary embodiment, the nematode is a member of the genus *Moniezia*.

[0127] In an exemplary embodiment, the nematode is a member of the genus *Oesophagostomum*. In an exemplary embodiment, the nematode is *Oesophagostomum bifurcum*. In an exemplary embodiment, the nematode is *Oesophagostomum aculeatum*. In an exemplary embodiment, the nematode is *Oesophagostomum brumpti*. In an exemplary embodiment, the nematode is *Oesophagostomum stephanostomum*. In an exemplary embodiment, the nematode is *Oesophagostomum stephanostomum var thomasi*. In an exemplary embodiment, the nematode is a member of the genus *Cooperia*. In an exemplary embodiment, the nematode is *Cooperia ostertagi* or *Cooperia oncophora*. In an exemplary embodiment, the nematode is a member of the genus *Haemonchus*. In an exemplary embodiment, the nematode is a member of the genus *Ostertagia*. In an exemplary embodiment, the nematode is *Ostertagia ostertagi*. In an exemplary embodiment, the nematode is a member of the genus *Trichostrongylus*. In an exemplary embodiment, the nematode is *Trichostrongylus axei*.

[0128] In an exemplary embodiment, the nematode is a heartworm. In an exemplary embodiment, the nematode is a member of the genus *Dirofilaria*. In an exemplary embodiment, the nematode is *Dirofilaria immitis*. In an exemplary embodiment, the nematode is *Dirofilaria tenuis* or *Dirofilaria repens*.

[0129] In an exemplary embodiment, the worm is a trematode. In an exemplary embodiment, the trematode is a blood fluke or bilharzia. In an exemplary
embodiment, the trematode is a member of the genus Schistosoma. In an exemplary embodiment, the trematode is selected from the group consisting of Schistosoma incognitum, Schistosoma ovuncatum, and Schistosoma sinensium. In an exemplary embodiment, the trematode is a member of the group Schistosoma indicum. In an exemplary embodiment, the trematode is a member of the group Schistosoma japonicum. In an exemplary embodiment, the trematode is selected from the group consisting of Schistosoma indicum, Schistosoma nasale, and Schistosoma spindale. In an exemplary embodiment, the trematode is a member of the group Schistosoma japonicum. In an exemplary embodiment, the trematode is selected from the group consisting of Schistosoma japonicum, Schistosoma malayensis, and Schistosoma mekongi. In an exemplary embodiment, the trematode is a member of the group Schistosoma haematobium. In an exemplary embodiment, the trematode is selected from the group consisting of Schistosoma bovis, Schistosoma curassoni, Schistosoma guineensis, Schistosoma haematobium, Schistosoma intercalatum, Schistosoma leiperi, Schistosoma margrebowiei, and Schistosoma mattheei. In an exemplary embodiment, the trematode is a member of the group Schistosoma mansoni. In an exemplary embodiment, the trematode is selected from the group consisting of Schistosoma edwardienne, Schistosoma hippotami, Schistosoma mansoni, and Schistosoma rodhaini. In an exemplary embodiment, the trematode is Schistosoma mansoni. In an exemplary embodiment, the trematode is Schistosoma intercalatum. In an exemplary embodiment, the trematode is Schistosoma japonicum. In an exemplary embodiment, the trematode is Schistosoma mekongi. In an exemplary embodiment, the trematode is Schistosoma bovis. In an exemplary embodiment, the trematode is Schistosoma mattheei. In an exemplary embodiment, the trematode is Schistosoma margrebowiei. In an exemplary embodiment, the trematode is Schistosoma curassoni. In an exemplary embodiment, the trematode is Schistosoma rodhaini.

[0130] In an exemplary embodiment, the compounds of the invention exhibit potency against bacteria which are associated with worms. In an exemplary embodiment, the compounds of the invention exhibit potency against bacteria which live inside of worms. In an exemplary embodiment, the invention provides a method of killing and/or inhibiting the growth of a bacteria which is associated with a worm, comprising: contacting the bacteria with an effective amount of the compound of the invention, thereby killing and/or inhibiting the growth of the bacteria. In an
exemplary embodiment, the bacteria is of the *Wolbachia* genus. In an exemplary embodiment, the bacteria is *Wolbachia pipientis*.

V. **Methods of Treating and/or Preventing Disease**

[0131] In another aspect, the invention provides a method of treating and/or preventing a disease. The method includes administering to the animal a therapeutically effective amount of the compound of the invention, sufficient to treat and/or prevent the disease. In an exemplary embodiment, the compound of the invention can be used in human or veterinary medical therapy, particularly in the treatment or prophylaxis of worm-associated disease. In an exemplary embodiment, the compound of the invention can be used in human or veterinary medical therapy, particularly in the treatment or prophylaxis of helminth-associated disease. In an exemplary embodiment, the disease is associated with a worm described herein. In an exemplary embodiment, the disease is associated with a nematode. In an exemplary embodiment, the disease is associated with a nematode described herein. In an exemplary embodiment, the nematode is *Wuchereria bancrofti*. In an exemplary embodiment, the nematode is *Brugia malayi*. In an exemplary embodiment, the nematode is *Brugia timori*. In an exemplary embodiment, the nematode is *Dirofilaria immitis*. In an exemplary embodiment, the disease is associated with a trematode. In an exemplary embodiment, the disease is associated with a trematode described herein. In an exemplary embodiment, the disease is a member selected from enterobiasis, oxyuriasis, ascariasis, dracunculiasis, filariasis, onchocerciasis, schistosomiasis, and trichuriasis. In an exemplary embodiment, the disease is lymphatic filariasis. In an exemplary embodiment, the disease is subcutaneous filariasis. In an exemplary embodiment, the disease is serious cavity filariasis. In an exemplary embodiment, the disease is elephantiasis. In an exemplary embodiment, the disease is elephantiasis tropica. In an exemplary embodiment, the disease is onchocerciasis. In an exemplary embodiment, the compound is described herein, or a salt, prodrug, hydrate or solvate thereof, or a combination thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt, hydrate or solvate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a prodrug thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt thereof. In another exemplary embodiment, the compound of the invention is a compound described herein, or a
pharmaceutically acceptable salt thereof. In another exemplary embodiment, the compound is described by a formula listed herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound is part of a pharmaceutical formulation described herein. In another exemplary embodiment, the contacting occurs under conditions which permit entry of the compound into the worm. Such conditions are known to one skilled in the art and specific conditions are set forth in the Examples appended hereto.

[0132] In another exemplary embodiment, the animal is a member selected from human, cattle, deer, reindeer, goat, honey bee, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, camel, yak, elephant, ostrich, otter, chicken, duck, goose, guinea fowl, pigeon, swan, and turkey. In another exemplary embodiment, the animal is a human. In another exemplary embodiment, the animal is a mouse. In another exemplary embodiment, the animal is a member selected from goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.

[0133] In an exemplary embodiment, the disease is treated through oral administration of the compound of the invention. In an exemplary embodiment, the disease is treated through intravenous administration of the compound of the invention. In an exemplary embodiment, the disease is treated through topical administration of the compound of the invention. In an exemplary embodiment, the disease is treated through intraperitoneal administration of the compound of the invention. In an exemplary embodiment, the compound is administered in a topically effective amount. In an exemplary embodiment, the compound is administered in a cosmetically effective amount. In an exemplary embodiment, the pharmaceutical formulation is administered in an orally effective amount.

VI. Pharmaceutical Formulations

[0134] In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound of the invention. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a compound according to a formula described herein. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a compound described herein, or a salt, prodrug, hydrate or solvate thereof, or a combination thereof. In another aspect, the
pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a compound described herein, or a salt, hydrate or solvate thereof, or a combination thereof. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a compound described herein, or a salt, hydrate or solvate thereof. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a salt of a compound described herein. In an exemplary embodiment, the salt is a pharmaceutically acceptable salt. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a prodrug of a compound described herein. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a compound described herein. In an exemplary embodiment, the pharmaceutical formulation is a unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a single unit dosage form.

[0135] The pharmaceutical formulations of the invention can take a variety of forms adapted to the chosen route of administration. Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutical formulations incorporating the compounds described herein. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, propylene glycol, mineral oil, vegetable oil and dimethylsulfoxide (DMSO).

[0136] The pharmaceutical formulation of the invention may be administered orally, topically, intraperitoneally, parenterally, by inhalation or spray or rectally in unit dosage forms containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It is further understood that the best method of administration may be a combination of methods. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. In an exemplary embodiment, the pharmaceutical formulation is administered orally. In an exemplary embodiment, the pharmaceutical formulation is administered intravenously. In an exemplary embodiment, the pharmaceutical formulation is administered in a topically effective dose. In an
exemplary embodiment, the pharmaceutical formulation is administered in a
cosmetically effective dose. In an exemplary embodiment, the pharmaceutical
formulation is administered in an orally effective dose.

[0137] The pharmaceutical formulations containing compounds of the invention
are preferably in a form suitable for oral use, for example, as tablets, troches,
lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion,
hard or soft capsules, or syrups or elixirs.

[0138] Compositions intended for oral use may be prepared according to any
method known in the art for the manufacture of pharmaceutical formulations, and
such compositions may contain one or more agents selected from the group consisting
of sweetening agents, flavoring agents, coloring agents and preserving agents in order
to provide pharmaceutically elegant and palatable preparations. Tablets may contain
the active ingredient in admixture with non-toxic pharmaceutically acceptable
excipients that 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. For example, a time delay material such as
glycercylnonostearate or glycercyl distearate may be employed.

[0139] Formulations for oral use may also be presented as hard gelatin capsules
wherein the active ingredient is mixed with an inert solid diluent, for example,
calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein
the active ingredient is mixed with water or an oil medium, for example peanut oil,
liquid paraffin or olive oil.

[0140] Aqueous suspensions contain the active materials in admixture with
excipients suitable for the manufacture of aqueous suspensions. Such excipients are
suspending agents, for example sodium carboxymethylcellulose, methylcellulose,
hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum
tragacanth and gum acacia; and dispersing or wetting agents, which may be a
naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylenoxycetanol, 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, such as sucrose or saccharin.

[0141] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a 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 those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0142] 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, flavoring and coloring agents, may also be present.

[0143] Pharmaceutical formulations of the invention may also be in the form of oil-in-water emulsions and 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 gums, for example gum acacia or gum tragacanth; naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol; anhydrides, for example sorbitan monooleate; and condensation products of
the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0144] 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, and flavoring and coloring agents. The pharmaceutical formulations may be in the form of a sterile injectable aqueous or oleaginous 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-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. 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.

[0145] The composition of the invention may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0146] Alternatively, the compositions can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0147] For administration to non-human animals, the composition containing the therapeutic compound may be added to the animal's feed or drinking water. Also, it will be convenient to formulate animal feed and drinking water products so that the animal takes in an appropriate quantity of the compound in its diet. It will further be convenient to present the compound in a composition as a premix for addition to the
feed or drinking water. The composition can also be added as a food or drink supplement for humans.

[0148] Dosage levels of the order of from about 5 mg to about 250 mg per kilogram of body weight per day and more preferably from about 25 mg to about 150 mg per kilogram of body weight per day, are useful in the treatment of the above-indicated conditions. The amount of active ingredient that may be combined with the carrier materials to produce a unit dosage form will vary depending upon the condition being treated and the particular mode of administration. Unit dosage forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

[0149] Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[0150] In an exemplary embodiment, the unit dosage form contains from about 1 mg to about 800 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 1 mg to about 500 mg of an active ingredient. In an exemplary embodiment, the unit dosage form contains from about 100 mg to about 800 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 200 mg to about 500 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 500 mg to about 800 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 1 mg to about 100 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 10 mg to about 100 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 50 mg to about 100 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 25 mg to about 75 mg of a compound of the invention.
invention. In an exemplary embodiment, the unit dosage form contains from about 40 mg to about 60 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 75 mg to about 200 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 1 mg to about 5 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 10 mg to about 25 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 50 mg to about 350 mg of a compound of the invention. In an exemplary embodiment, the unit dosage form contains from about 200 mg to about 400 mg of a compound of the invention.

[0151] In an exemplary embodiment, the daily dosage contains from about 1 mg to about 800 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 1 mg to about 500 mg of an active ingredient. In an exemplary embodiment, the daily dosage contains from about 100 mg to about 800 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 200 mg to about 500 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 500 mg to about 800 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 1 mg to about 100 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 10 mg to about 100 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 50 mg to about 100 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 75 mg to about 200 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 1 mg to about 5 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 10 mg to about 25 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 50 mg to about 350 mg of a compound of the invention. In an exemplary embodiment, the daily dosage contains from about 200 mg to about 400 mg of a compound of the invention.

[0152] Preferred compounds of the invention will have desirable pharmacological properties that include, but are not limited to, oral bioavailability, low toxicity, low serum protein binding and desirable in vitro and in vivo half-lives. Penetration of the
blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

[0153] Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of laboratory animals that receive the compound intravenously.

[0154] Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcova, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

[0155] Compound half-life is inversely proportional to the frequency of dosage of a compound. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

[0156] The amount of the composition required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician.

VI. a) Testing

[0157] Preferred compounds for use in the pharmaceutical formulations described herein will have certain pharmacological properties. Such properties include, but are not limited to, low toxicity, low serum protein binding and desirable in vitro and in vivo half-lives. Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcova et al. (1996, J. Chromat. B677: 1-27). Compound half-life is inversely proportional to the frequency of dosage of a compound. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).
Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD50 and ED50. Compounds that exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the unit dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See, e.g.* Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1, p. 1).

**VI. b) Administration**

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays, as disclosed herein. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC50 (effective dose for 50% increase) as determined in cell culture, *i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of worm growth. Such information can be used to more accurately determine useful doses in humans.

In general, the compounds prepared by the methods, and from the intermediates, described herein will be administered in a therapeutically or cosmetically effective amount by any of the accepted modes of administration for agents that serve similar utilities. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination, the severity of the particular disease undergoing therapy and the judgment of the prescribing physician. The drug can be administered from once or twice a day, or up to 3 or 4 times a day.
Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety that are sufficient to maintain helminth growth inhibitory effects. Usual patient dosages for systemic administration range from 0.1 to 1000 mg/day, preferably 1-500 mg/day, more preferably 10-200 mg/day, even more preferably 100-200 mg/day. Stated in terms of patient body surface areas, usual dosages range from 50-91 mg/m²/day.

The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt%) basis, from about 0.01-10 wt% of the drug based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 0.1-3.0 wt%, more preferably, about 1.0 wt%.

Exemplary embodiments are summarized herein below.

In an exemplary embodiment, the invention provides a structure which is:

wherein X is N or CH; R⁵ is H or halogen and R¹ or R² is selected from the group consisting of alkoxy, optionally substituted with a substituted or unsubstituted phenyl; alkoxy, optionally substituted with a substituted or unsubstituted heteroaryl; alkylamino, optionally substituted with a substituted or unsubstituted phenyl; alkylamino, optionally substituted with a substituted or unsubstituted heteroaryl; -NHC(O)R¹₂, wherein R¹₂ is unsubstituted alkyl; or a hydrate, solvate or salt thereof.

In an exemplary embodiment, the invention provides a structure according to the following formula:
wherein $R^5$ is H or halogen and $R^1$ is alkoxy, substituted with a substituted or unsubstituted phenyl, or a hydrate, solvate or salt thereof.

[0166] In an exemplary embodiment, according to the above paragraph, $R^5$ is F.

[0167] In an exemplary embodiment, according to any of the above paragraphs, $R^1$ is benzoxy.

[0168] In an exemplary embodiment, the invention provides a combination comprising the compound according to any of the above paragraphs, together with at least one other therapeutically active agent.

[0169] In an exemplary embodiment, the invention provides a pharmaceutical formulation comprising: a) the compound according to any of the above paragraphs, or a salt thereof; and b) a pharmaceutically acceptable excipient.

[0170] In an exemplary embodiment, according to any of the above paragraphs, the pharmaceutical formulation is a unit dosage form.

[0171] In an exemplary embodiment, according to any of the above paragraphs, the salt of the compound according to any of the above paragraphs is a pharmaceutically acceptable salt.

[0172] In an exemplary embodiment, the invention provides a method of killing and/or inhibiting the growth of a helminth, comprising: contacting the helminth with an effective amount of the compound of the invention, thereby killing and/or inhibiting the growth of the helminth.

[0173] In an exemplary embodiment, according to any of the above paragraphs, the helminth is a nematode or a trematode.

[0174] In an exemplary embodiment, according to any of the above paragraphs, the helminth is a nematode, and the nematode is selected from the group consisting of *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*.

[0175] In an exemplary embodiment, according to any of the above paragraphs, the compound has a structure described herein.

[0176] In an exemplary embodiment, the invention provides a method of treating and/or preventing a disease in an animal, comprising: administering to the animal a
therapeutically effective amount of the compound of the invention, thereby treating and/or preventing the disease.

[0177] In an exemplary embodiment, according to any of the above paragraphs, the compound has a structure described herein.

[0178] In an exemplary embodiment, according to any of the above paragraphs, the disease is lymphatic filariasis.

[0179] In an exemplary embodiment, according to any of the above paragraphs, the animal is a human.

[0180] In an exemplary embodiment, according to any of the above paragraphs, the invention is a use of a compound of the invention or a combination of the invention in the manufacture of a medicament for the treatment and/or prophylaxis of worm infection.

[0181] The invention is further illustrated by the Examples that follow. The Examples are not intended to define or limit the scope of the invention.

**EXAMPLES**

[0182] 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.

[0183] 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 Buchi Rotary Evaporator.
Analytical HPLC was performed using a Supelco discovery C\textsubscript{18} 15 cm x 4.6 mm / 5 µm column coupled with an Agilent 1050 series VWD UV detector at 210 nm. Conditions: Solvent A: H\textsubscript{2}O/1% acetonitrile/0.1% HC\textsubscript{2}H\textsubscript{3}; Solvent B: methanol.

Proton magnetic resonance (1H NMR) spectra were recorded on a Varian INOVA NMR spectrometer [400 MHz (1H) or 500 MHz (1H)]. 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 H NMR. Interproton coupling constants are reported in Hertz (Hz).

LCMS spectra were obtained using a ThermoFinnigan AQA MS ESI instrument utilizing a Phenomenex Aqua 5 micron C\textsubscript{18} 125 A 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.

Silica gel chromatography was carried out on either a Teledyne ISCO CombiFlash Companion or Companion Rf 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 CH\textsubscript{2}C\textsubscript{2} 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 C\textsubscript{18} column, Dyonex Chromleon operating system coupled with a Varian Prostar 320 UV-vis detector (254 nm) and a Sedex55 ELS detector. Conditions: Solvent A: H\textsubscript{2}O/1% acetonitrile/0.1% HC\textsubscript{2}H\textsubscript{3}; Solvent B:
MeOH. 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.

[0189] 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.

[0190] All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of N₂.

[0191] Compounds are named using the AutoNom 2000 add-on for MDL ISIS™ Draw 2.5 SP2 or their catalogue name if commercially available.

[0192] Starting materials used were either available from commercial sources or prepared according to literature procedures and had experimental data in accordance with those reported. 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol (C50), for example, can be synthesized according to the methods described in U.S. Pat. Pubs. US20060234981 and US20070155699.

EXAMPLE 1

C55. 6-(indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole
2-(2-bromo-4-fluorophenyl)-1,3-dioxolane (70)

[0193] To a solution of compound 24 (2.43g, 12mmol) in toluene (50mL) were added ethylene glycol (7.44g, 120mmol, 10.0eq) and p-toluenesulfonic acid monohydrate (0.23g, 1.2mmol, 0.1eq). After it was heated to reflux and stirred overnight, the mixture was washed with saturated NaHCO₃, water, and brine, and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound 70 (2.07g, 8.4mmol, 70.0%
yield. H NMR (400 MHz, CDCl$_3$): $\delta$ 7.58 (dd, J = 8.8 & 6.4 Hz, 1H), 7.30 (dd, J = 8 & 2.8 Hz, 1H), 7.05 (m, 1H), 6.03 (s, 1H), 4.12 (m, 2H) and 4.02 (m, 2H) ppm.

2-f2-bromo-4-(indol-l-yl)phenyl]-1,3-dioxolane (71)

![Chemical Structure]

[0194] To a solution of Compound 70 (200mg, 0.809mmol) in DMF (5mL) were added Cs$_2$CO$_3$ (395mg, 1.213mmol, 1.5eq) and indole (98.4mg, 0.809mmol, leq). The mixture was heated to reflux and stirred for 2 hours. The mixture was poured into water (20mL), extracted with ether and dried over anhydrous Na$_2$SO$_4$. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound 71 (120mg, 0.35mmol, 43.3% yield). H NMR (400MHz, CDCl$_3$): $\delta$ 7.75 (m, 2H), 7.70 (m, 1H), 7.60 (dd, J = 8.2 & 0.4 Hz, 1H), 7.50 (m, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.2 (m, 2H), 6.7 (dd, J = 2 & 0.8 Hz, 1H), 6.14 (s, 1H), 4.20 (m, 2H) and 4.10 (m, 2H) ppm.

2-bromo-4-(indol-l-yl) benzyl alcohol (72)

![Chemical Structure]

[0195] To a solution of compound 71 (2.47g, 7.2mmol) in THF (20mL) was added 1M HCl (lOmL) dropwise and stirred for 3 hours. After it was neutralized with saturated NaHCO$_3$, the mixture was extracted with ethyl acetate and dried with anhydrous Na$_2$SO$_4$. After evaporation the residue was re-dissolved in MeOH (30mL). To this solution NaBH$_4$ (0.4g, 10.8mmol, 1.5eq) was added and stirred for 1 hour. The mixture was quenched with water (lOmL), evaporated, extracted with ethyl acetate, and dried over anhydrous Na$_2$SO$_4$. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound 72 (2.01g, 6.67mmol, 92.6% yield). H NMR (400MHz, CDCl$_3$): $\delta$ 7.73 (d, J = 2 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 4.4 Hz, 1H), 7.55 (d, J = 4 Hz, 1H), 7.50 (dd, J = 8.4 & 2 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.26 (m, 1H), 7.21 (m, 1H), 6.70 (d, J = 3.2 Hz, 1H) and 4.8 (s, 2H) ppm.
To a solution of compound 72 (400mg, 1.32mmol) in anhydrous THF (80mL) at -78°C under nitrogen was added dropwise 1.6M n-BuLi in THF (1.82mL, 2.90mmol, 2.2eq). After 15 minutes, B(iPrO)₃ (0.76mL, 2.90mmol, 2.2eq) was added dropwise at -78°C. The mixture was allowed to warm to room temperature gradually and stirred overnight. After addition of 2M HCl (10mL), the mixture was stirred for 2 hours and evaporated. The residue was dissolved in ethyl acetate, washed with water, and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound 73 (249mg, 1.00mmol, 75.7% yield). H NMR (400 MHz, DMSO-d₆): δ 9.34 (s, 1H), 7.89 (d, J = 2 Hz, 1H), 7.65 (m, 3H), 7.60 (d, J = 12.4 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H), 7.10 (dd, J = 7.6 & 4 Hz, 1H), 6.69 (d, J = 2.8 Hz, 1H) and 5.06 (s, 2H) ppm. Mp 145-147°C.

C66. 6-(3-(phenylthio)-1H-indol-1-yl)benzo[f]l,2]oxaborol-1(3H)-ol

This compound was originally disclosed as C66 in U.S. Pat. App. No. 11/505,591.

C67. 3-(1-(1-hydroxy-1,3-dihydrobenzo[f]l,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile

This compound was originally disclosed as C67 in U.S. Pat. App. No. 11/505,591.
C68.  6-(5-methoxy-lH-indol-l-yl)benzofcJfl,21oxaborol-l(3H)-ol

[0199] This compound was originally disclosed as C68 in U.S. Pat. App. No. 11/505,591. This compound was synthesized by starting with 2-bromo-4-fluorobenzoic acid and using similar methods as described for the preparation of J15.

C72.  6-(5-methoxy-3-(phenylthio)-lH-indol-l-yl)benzofcJfl,2

[0200] This compound was originally disclosed as C72 in U.S. Pat. App. No. 11/505,591.

C73.  3-(l-(l-hydroxy-l,3-dihydrobenzofcJfl,2Joxaborol-6-yl)-5-methoxy-lH-indol-3-thio)propanenitrile

[0201] This compound was originally disclosed as C73 in U.S. Pat. App. No. 11/505,591.

C75.  6-(5-chloro-lH-indol-l-yl)benzofcJfl,21oxaborol-l(3H)-ol

[0202] This compound was originally disclosed as C75 in U.S. Pat. App. No. 11/505,591. This compound was synthesized by starting with 2-bromo-4-fluorobenzoic acid and using similar methods as described for the preparation of J15.
C76. 3-(5-Chloro-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile

[0203] This compound was originally disclosed as C76 in U.S. Pat. App. No. 11/505,591.

C80. 6-(5-Chloro-3-(phenylthio)-1H-indol-1-yl)benzof[c][1,2]oxaborol-1(3H)-ol

[0204] This compound was originally disclosed as C80 in U.S. Pat. App. No. 11/505,591.

Jl. 6-f3-(3-Chloro-phenylsulfenyl)indol-1-yl)-1,3-dihydro-l-hydroxy-2,1-benzoxaborole (74)

[0205] To a mixture of 6-(1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol (100mg, 0.40mmol) and 3-chlorobenzenethiol (63.8mg, 0.44mmol, 1.1eq) in EtOH (8mL) and water (1mL) was added dropwise a solution of I₂ (112mg, 0.44mmol, 1.1eq) in EtOH (1mL). After it was refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water, and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (78.4mg, 0.24mmol, 60.0% yield). H NMR (400 MHz, DMSO-de): δ 9.34 (s, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 7.76 (dd, J = 8.2 & 1.6 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.50 (d, J = 6 Hz, 1H), 6.69 (m, 6H) and 5.09 (s, 2H) ppm. Mp 104-105°C.
J2. 6-f3-(4-Chloro-phenylsulfenyl)indol-l-ylJ-l,3-dihydro-l-hydroxy-2,1-benzoxaborole (75)

To a mixture of 6-(lH-indol-l-yl)benzo[c][1,2]oxaborol-l(3H)-ol (100mg, 0.40mmol) and 4-chlorobenzenethiol (63.8mg, 0.44mmol, 1.1eq) in EtOH (8mL) and water (1mL) was added dropwise a solution of I2 (112mg, 0.44mmol, 1.1eq) in EtOH (1mL). After it was refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water, and dried over anhydrous Na2SO4. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (105.7mg, 0.27mmol, 67.5% yield). 1H NMR (400 MHz, DMSO-de): δ 9.34 (s, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.62 (dd, J = 11.2 & 2.8 Hz, 1H), 7.55 (d, J = 11.2 Hz, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.30 (m, 3H), 7.12 (m, 3H) and 5.09 (s, 2H) ppm. Mp 100-102°C.

J3. 6-f3-(3, 4-Dichlorophenylsulfenyl)indol-l-ylJ-l,3-dihydro-l-hydroxy-2,1-benzoxaborole (76)

To a mixture of 6-(lH-indol-l-yl)benzo[c][1,2]oxaborol-l(3H)-ol (200mg, 0.80mmol) and 3,4-dichlorobenzenethiol (157mg, 0.88mmol, 1.1eq) in EtOH (16mL) and water (2mL), was added dropwise a solution of I2 (224mg, 0.88mmol, 1.1eq) in EtOH (2mL). After it was refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water, and dried over anhydrous Na2SO4. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (213mg, 0.50mmol, 62.5% yield). 1H NMR (400 MHz, DMSO-de): δ 9.34 (s, 1H), 8.19 (s, 1H), 7.96 (d, J = 2 Hz, 1H), 7.76 (dd, J = 8.2 & 2.4 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.49 (dd, J = 8.5 & 0.8 Hz, 2H), 7.36 (d, J = 1.6 Hz, 1H), 7.30 (m, 1H), 7.23 (m, 1H), 7.05 (dd, J = 8.4 & 2 Hz, 1H) and 5.09 (s, 2H) ppm. Mp 104-105°C.
J4.  

6-[3-(4-Methoxyphenylsulfenyl)indol-1-yl]-1,3-dihydro-1-hydroxy-2,1-
benzoxaborole

[0208]  To a mixture of 6-(1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol (100mg, 0.40mmol) and 4-methoxybenzenethiol (56mg, 0.44mmol, 1.1 eq) in EtOH (8mL) and water (1mL) was added dropwise a solution of I₂ (112mg, 0.44mmol, 1.1 eq) in EtOH (1mL). After it was refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (118mg, 0.305mmol, 76.2% yield).  

H NMR (400 MHz, DMSO-d₆): δ 9.34 (s, 1H), 8.06 (s, 1H), 7.93 (d, J = 2 Hz, 1H), 7.73 (dd, J = 8 & 2.8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.50 (dd, J = 7.6 & 1.6 Hz, 2H), 7.2 (m, 4H), 6.84 (dd, J = 6.6 & 2.4 Hz, 1H), 5.08 (s, 2H) and 3.67 (s, 3H) ppm. Mp 99-100°C.

J5.  

6-[3-(4-Methoxyphenylsulfinyl)indol-1-yl]-1,3-dihydro-1-hydroxy-2,1-
benzoxaborole

[0209]  To a solution of 6-[3-(4-Methoxyphenylsulfenyl)indol-1-yl]-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (100mg, 0.258mmol) in acetic acid (8mL) at 0°C was added dropwise 45µL H₂O₂ in AcOH (0.13mL). The mixture was stirred for 2 hours at room temperature. After evaporated, the mixture was dissolved in ethyl acetate, washed with saturated NaHCO₃, water, and brine, and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give compound 78 (65mg, 0.161mmol, 62.4% yield).  

H NMR (400 MHz, DMSO-d₆): δ 9.37 (s, 1H), 8.36 (s, 1H), 7.93 (s, 1H), 7.73 (d, J = 12 Hz, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 7.6 Hz, 2H), 7.2 (m, 1H), 7.09 (d, J = 7.6 Hz, 3H), 5.09 (s, 2H) and 3.77 (s, 3H) ppm. Mp 119-120°C.
J6. **6-f3-(4-Methoxyphenylsulfonyl)indol-l-yl-l,3-dihydro-l-hydroxy-2,l-benzoxaborole**

[0210] To a solution of 6-[3-(4-methoxyphenylsulfenyl)indol-1-yl]-1,3-dihydro-l-hydroxy-2,l-benzoxaborole (80 mg, 0.129 mmol) in acetic acid (5 mL) at 0°C was added dropwise 4.0 M H₂O₂ in acetic acid (0.2 mL). The mixture was stirred for 2 hours at 75°C. After evaporation the mixture was dissolved in ethyl acetate, washed with saturated NaHCO₃, water, and brine, and dried over anhydrous Na₂SO₄. The residue after evaporation was purified by column chromatography over silica gel to give the title compound (61 mg, 0.072 mmol, 56.3% yield). H NMR (300 MHz, DMSO-d₆): δ 10.31 (s, 1H), 8.38 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.99 (dd, J = 10 & 5.1 Hz, 1H), 7.86 (m, 1H), 7.56 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.33 (m, 2H), 7.10 (d, J = 8.7 Hz, 1H), 7.09 (m, 3H), 5.10 (s, 2H) and 3.80 (s, 3H) ppm. Mp 177-179°C.

J8. **6-f3-(4-Hydroxyphenylsulfanyl)indol-l-yl-l,3-dihydro-l-hydroxy-2,l-benzoxaborole**

[0211] H NMR (400 MHz, DMSO-d₆): δ 9.44 (s, 1H), 9.36 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.74 (d, J = 7.2, 1H), 7.64 (d, J = 8 Hz, 1H), 7.54 (m, 2H), 7.25 (m, 2H), 7.15 (d, J = 8 Hz, 2H), 6.68 (d, J = 8 Hz, 2H) and 5.10 (s, 2H) ppm. Mp 221-224°C.

J8. **6-f3-(4-Aminophenylsulfanyl)indol-l-yl-l,3-dihydro-l-hydroxy-2,l-benzoxaborole**

[0212] To a mixture of 6-(IH-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol (200 mg, 0.80 mmol) and 4-aminobenzenethiol (110.6 mg, 0.88 mmol) in EtOH (15 mL) and
water (1 mL) was added dropwise a solution of I\textsubscript{2} (224 mg, 0.88 mmol) in EtOH (2 mL). After refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (146 mg, 48.9% yield). H\textsuperscript{1} NMR (400 MHz, DMSO-d\textsubscript{6}): δ 9.34 (s, 1H), 7.92 (s, 1H), 7.91 (s, 1H), 7.71 (d, J = 2 Hz, 1H), 7.62 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.15 (m, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 5.16 (s, 2H) and 5.07 (s, 2H) ppm; Mp: 142-145 °C.

**J9. 6-f3-(2-Hydroxyphenylsulfanyl)indol-l-yl]-l,3-dihydro-l-hydroxy-2,l-benzoxaborole**

[0213] To a mixture of 6-(lH-indol-l-yl)benzo[c][1,2]oxaborol-l(3H)-ol (200 mg, 0.80 mmol) and 2-hydroxybenzenethiol (111.5 mg, 0.88 mmol) in EtOH (15 mL) and water (1 mL) was added dropwise a solution of I\textsubscript{2} (224 mg, 0.88 mmol) in EtOH (2 mL). After refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (160 mg, 53.4% yield). H\textsuperscript{1} NMR (300 MHz, DMSO-d\textsubscript{6}): δ 9.97 (s, 1H), 9.36 (s, 1H), 8.05 (s, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.26 (m, 2H), 6.89 (m, 2H), 6.59 (d, J = 4.2 Hz, 2H) and 5.10 (s, 2H) ppm; Mp: 133-136 °C.

**J10. 6-f3-(4-Nitrophenylsulfanyl)indol-l-yl]-l,3-dihydro-l-hydroxy-2,l-benzoxaborole**

[0214] To a mixture of 6-(lH-indol-l-yl)benzo[c][1,2]oxaborol-l(3H)-ol (200 mg, 0.80 mmol) and 4-nitrobenzenethiol (136.9 mg, 0.88 mmol) in EtOH (15 mL) and water (1 mL) was added dropwise a solution of I\textsubscript{2} (224 mg, 0.88 mmol) in EtOH (2 mL). After refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (146 mg, 48.9% yield). H\textsuperscript{1} NMR (400 MHz, DMSO-d\textsubscript{6}): δ 9.34 (s, 1H), 7.92 (s, 1H), 7.91 (s, 1H), 7.71 (d, J = 2 Hz, 1H), 7.62 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.15 (m, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 5.16 (s, 2H) and 5.07 (s, 2H) ppm; Mp: 142-145 °C.
mL). After refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (75 mg, 23.3% yield). 1H NMR (300 MHz, DMSO-d₆): δ 9.38 (s, 1H), 8.26 (s, 1H), 8.10 (d, J = 1.5 Hz, 2H), 8.00 (d, J = 1.8 Hz, 1H), 7.80 (dd, J = 8.1 & 2.1 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.63(d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.20 (m, 4H) and 5.12 (s, 2H) ppm; Mp: 115-118 °C.

**JII. 6-f3-(4-Fluorophenylsulfanyl)indol-l-yl-l,3-dihydro-l-hydroxy-2,1-benzoxaborole**

![Structure](image)

[0215] To a mixture of 6-(1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol (200 mg, 0.80 mmol) and 4-fluorobenzenethiol (113 mg, 0.88 mmol) in EtOH (15 mL) and water (1 mL) was added dropwise a solution of I₂ (224 mg, 0.88 mmol) in EtOH (2 mL). After refluxed for 2 hours, the mixture was poured into ice-water, extracted with ethyl acetate, washed with water and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (80 mg, 26.5% yield). 1H NMR (300 MHz, DMSO-d₆): δ 9.34 (s, 1H), 8.17 (s, 1H), 7.96 (d, J = 1.5 Hz, 1H), 7.75 (dd, J = 8.1 & 1.2 Hz, 1H), 7.64 (d, J = 6.3 Hz, 1H), 7.57(d, J = 6.3 Hz, 1H), 7.49 (d, J = 6.0 Hz, 1H), 7.20 (m, 6H) and 5.10 (s, 2H) ppm; Mp: 91-95 °C.

**J12. 6-f3-(2-Naphthylsulfanyl)indol-l-yl-l,3-dihydro-l-hydroxy-2,1-benzoxaborole**

![Structure](image)

[0216] To a mixture of 6-(1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol (200 mg, 0.80 mmol) and naphthalene-2-thiol (141.4 mg, 0.88 mmol) in EtOH (15 mL) and water (1 mL) was added dropwise a solution of I₂ (224 mg, 0.88 mmol) in EtOH (2 mL). After refluxed for 2 hours, the mixture was poured into ice-water, extracted with
ethyl acetate, washed with water and dried over anhydrous Na₂SO₄. The residue after rotary evaporation was purified by column chromatography over silica gel to give the title compound (77 mg, 25.6% yield). H NMR (400 MHz, DMSO-d₆): δ 9.34 (s, 1H), 8.21 (s, 1H), 8.01 (d, J = 2 Hz, 1H), 7.75 (m, 3H), 7.68 (m, 3H), 7.59 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.20 (m, 5H) and 5.10 (s, 2H) ppm; Mp: 139-142 °C.

J13. 5-Fluoro-6-((methoxy)indol-1-yl)-1,3-dihydro-1-hydroxy-2H-benzoxaborole

[0217] The title compound was synthesized by using similar methods as described for the preparation of J15.

J14. 6-(Benzyloxy)indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

[0218] The title compound was synthesized by starting with 2-bromo-4-fluorobenzoic acid and using similar methods as described for the preparation of J15.

J15. 6-(5-(benzyloxy)-1H-indol-1-yl)-5-fluorobenzof[c]fl,2H oxaborol-1(3H)-ol

Methyl 2-bromo-4,5-difluorobenzoate

[0219] To a solution of 2-bromo-4,5-difluorobenzoic acid (23.7g, 10mmol) in acetone (150 mL) were added Cs₂CO₃ (48.8g, 15mmol) and CH₃I (10mL, 15mmol). The mixture was stirred and refluxed for 1 hour then cooled to room temperature. The suspension was diluted with 300 mL petroleum ether. The solid was removed by filtration and washed with petroleum ether. The filtrate was concentrated to give clear oil product. (Yield: 25g, 99.6%). ¹H NMR (500 MHz, DMSO-d₆) δ 8.00 (t, 1H), 7.92 (t, 1H) and 3.88 (s, 3H) ppm.

Methyl 4-(5-(benzyloxy)-1H-indol-1-yl)-2-bromo-5-fluorobenzoate

[0220] A mixture of 5-benzyloxy indole (11.2g, 0.05 mmol), methyl 2-bromo-4,5-difluoro-benzoate (12.6g, 0.05 mol) and Cs₂CO₃ (24.4g, 0.075 mol) in DMF (150 mL) was stirred at 100 °C under N₂ atmosphere overnight. The mixture was cooled to room temperature and then filtrated. The filtrate was poured into 150 mL water. A gradual formation of a cream-colored precipitate was observed. Filtration gave the
desired intermediate product as a cream-colored solid which is pure enough for further reaction (Yield: 17g, 74.8%). $^1$HNMR (500 MHz, DMSO-$d_6$) $\delta$: 8.02 (d, J=7 Hz, IH), 7.98 (d, J=1 Hz, IH), 7.60 (s, IH), 7.48 (d, J=7.5 Hz, 2H), 7.39 (t, J=7.5 Hz, 2H), 7.32 (t, J=7 Hz, IH), 7.26 (d, J=8.5 Hz, 2H), 6.96 (d, J=8.5 Hz, IH), 6.68 (s, IH), 5.14 (s, 2H) and 3.91 (s, 3H) ppm.

(4-(5-(Benzyloxy)-1H-indol-1-yl)-2-bromo-5-fluorophenyl)methanol

[0221] A mixture of methyl 4-(5-(benzyloxy)-1H-indol-1-yl)-2-bromo-5-fluorobenzoate (22.5g, 49.5 mmol), NaBH$_4$ (3.75g, 99.1 mmol) and LiCl.H$_2$O (5.98g, 99.1 mmol) in 100 mL THF and 50 mL EtOH was stirred at room temperature overnight. The mixture was quenched with dilute HCl (0.5M, 150 mL) and concentrated under reduced pressure to removed solvents, then, white precipitate appeared. The precipitate was collected and washed with petroleum ether to give a pale yellow solid which is pure enough to do next reaction (Yield: 21g, 95.2%). MS: m/z=427 (M+1, ESI+); $^1$HNMR (500 MHz, DMSO-$d_6$) $\delta$: 7.83 (d, J=6.5 Hz, IH), 7.58 (d, J=1.5 Hz, IH), 7.53 (s, IH), 7.48 (d, J=7 Hz, 2H), 7.39 (t, J=7.5 Hz, 2H), 7.32 (t, J=7 Hz, IH), 7.24 (d, J=2 Hz, IH), 7.15 (d, J=8.5 Hz, IH), 7.69 (dd, J=8.5 Hz, J=1.5 Hz, IH), 6.63 (d, J=2.5 Hz, IH), 5.74 (t, J=5 Hz, IH), 5.13 (s, 2H) and 4.57 (d, J=5.5 Hz, 2H) ppm.

6-f5-fbenzyloxy)-1H-indol-1-yl)-5-fluorobenzo[c] _/1,2]oxaborol-1(3H)-ol

[0222] To a mixture of (4-(5-(benzyloxy)-1H-indol-1-yl)-2-bromo-5-fluorophenyl)methanol (15.5g, 36.4 mmol) in 500 mL dry toluene was added (i-PrO)$_3$B (12.6 mL, 54.6 mmol) at N$_2$ atmosphere. The mixture was heated and distilled out 450 mL toluene. The mixture was cooled to room temperature and dissolved into 500 mL dry THF, then the mixture was cooled to -78 °C and n-BuLi (2.5M, 21.8 mL, in hexane) was added dropwise at N$_2$ atmosphere. The mixture was stirred at -78 °C for 2 hours and slowly warmed into room temperature and continuously stirred over night. The reaction was quenched with saturated NH$_4$Cl aqueous solution (300 mL) and extracted with ethyl acetate three times. The combined organic layer was concentrated and the residue was purified by silica gel chromatography (eluted with DCM) to give pure product as a cream solid (Yield: 11.5g, 84.6%). MS: m/z=374 (M+1, ESI+); $^1$HNMR (500 MHz, DMSO-$d_6$) $\delta$: 9.38 (s, IH), 7.88 (d, J=9.5 Hz, IH), 7.60 (d, J=13.5 Hz, IH), 7.52 (d, J=2 Hz, IH), 7.48 (d, J=9 Hz, 2H), 7.39 (t, J=9 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 6.96 (d, J=8.5 Hz, IH), 6.68 (s, IH), 5.14 (s, 2H) and 3.91 (s, 3H) ppm.
2H), 7.33 (t, J=9 Hz, IH), 7.26 (d, J=3 Hz, IH), 7.13 (d, J=1 1 Hz, IH). 6.92 (dd, J=1 1 Hz, J=3 Hz, IH), 6.63 (d, J=3.5Hz, IH), 5.14 (s, 2H) and 5.08 (s, 2H) ppm.

J16. \( l-(l\text{-hydroxy-l,3-dihydrobenzofcJfl,2oxaborol-6-yl})\text{-IH-indol-5-ol} \)

[0223] The title compound was synthesized by using similar methods as described for the preparation of J17.

J17. \( l-(5\text{-fluoro-l-hydroxy-l,3-dihydrobenzofcJfl,2oxabowl-6-yl})\text{-IH-indol-5-ol} \)

[0224] A mixture of 6-(5-(benzyloxy)-IH-indol-1-yl)-5-fluorobenzo[c][1,2] oxaborol-l(3H)-ol (1.0g, 2.68mmol) and 10% Pd/C (0.1g) in EtOH (100mL) was sealed with a rubber septa stopper and connected to a H2 balloon. It was stirred for 4 h at room temperature, filtered and evaporated to give a residue that was mixed with hexane and sonicated to provide the desired title compound as a yellow solid (0.75g, 2.66 mmol, yield 99.2%). M.p. >230 °C; IH NMR (DMSO-d6, 300 MHz): \( \delta = 9.36 \) (s, IH), 8.90 (s, IH), 7.85 (d, J=7.8 Hz, IH), 7.56 (d, J=10.5 Hz, IH), 7.43-7.42 (m, IH), 7.00 (d, J=7.5 Hz, IH), 6.94 (d, J=2.1 Hz, IH), 6.67 (dd, J = 9.0 & 2.4 Hz, IH), 6.52 (d, J=3.3 Hz, IH) and 5.05 (s, 2H) ppm; HPLC: 95.2% at 220 nm and 93.8% at 254 nm; MS: m/z = 282 (M-1, ESI-).

J18. \( 6-(5\text{-Chloro-IH-indol-1-yl})\text{-5-fluorobenzofcJfl,2oxaborol-l(3H)-ol} \)

[0225] The title compound can be synthesized using similar methods as described for the preparation of J15.

J19. \( 5\text{-Fluoro-6-(lH-indol-1-yl)benzofcJfl,2oxaborol-l(3H)-ol} \)

[0226] The title compound can be synthesized using similar methods as described for the preparation of J15.
5-Fluoro-6-(isoyroDoxy)indol-1-yl,1,S-dihydro-l-hydroxy-2,l-benzoxaborole

[0227] The title compound can be synthesized according to the following scheme:

5-Fluoro-6-(benzyloxy)benzimidazol-1-yl,1,3-dihydro-l-hydroxy-2,l-benzoxaborole

[0228] The title compound can be synthesized according to the following scheme:

1-(5-Fluoro-l-hydroxy-l,3-dihydrobenzoicilil,21oxaborol-6-yl)-N-phenethyl-lH-imidazole-4-carboxamide

[0229] The title compound can be synthesized according to the following scheme:
1-(5-Fluoro-1-hydroxy-1,3-dihydrobenzoil-2[oxaborol-6-yl]-N4sopentyl-1H-imidazole-4-carboxamide

[0230] The title compound can be synthesized by using similar methods as described in the Example above with 3-methylbutan-1-amine to replace 2-phenylethanamine.

5-Fluoro-645-(pyridin-2-loyx)indol4-yl]-1,3-dihydro44tydroxy-2,14enzoxaborole

[0231] The title compound can be synthesized according to the following scheme:

5-Fluoro-645-(pyridin-3-loyx)indol_1-yll_1,3-dihydro44tydroxy-2,14enzoxaborole

[0232] The title compound can be synthesized according to the following scheme:
5-Fluoro-6-(pyridin-4-yloxy)indol-1-yl)-4,3-dihydro-4-hydroxy-2,1-benzoxaborole

[0233] The title compound can be synthesized according to the following scheme:

\[
\text{HO-} \begin{array}{c} \text{F} \\ \text{N} \end{array} \text{B} \begin{array}{c} \text{F} \\ \text{OH} \end{array} + \begin{array}{c} \text{HCl} \\ \text{N} \end{array} \text{Cl} \xrightarrow{\text{NaH/DMF}} \begin{array}{c} \text{F} \\ \text{N} \end{array} \text{B} \begin{array}{c} \text{F} \\ \text{OH} \end{array}
\]

5-(1-(5-Fluoro-1-hydroxy-1,3-dihydrobenzo[c]cinnolin-2-yl)-1H-indol-5-yl)benzatnide

[0234] The title compound can be synthesized according to the following scheme:

\[\text{Ph} \begin{array}{c} \text{H} \\ \text{N} \end{array} \text{N} \begin{array}{c} \text{F} \\ \text{OH} \end{array} \xrightarrow{\text{H}_2/\text{Pd/C, MeOH}} \begin{array}{c} \text{H}_2 \text{N} \\ \text{N} \end{array} \text{N} \begin{array}{c} \text{F} \\ \text{OH} \end{array} \xrightarrow{\text{Et}_3\text{N, DCM}} \begin{array}{c} \text{Ph} \\ \text{N} \end{array} \text{N} \begin{array}{c} \text{F} \\ \text{OH} \end{array}\]

5-Fluoro-6-(benzylamino)indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

[0235] The title compound can be synthesized according to the following scheme:

\[\text{Ph} \begin{array}{c} \text{NH} \\ \text{N} \end{array} \text{N} \begin{array}{c} \text{F} \\ \text{OH} \end{array} \xrightarrow{\text{C}_2\text{H}_2\text{CO}, \text{DMF}} \begin{array}{c} \text{F} \\ \text{Br} \end{array} \text{N} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{F} \\ \text{OH} \end{array} \xrightarrow{\text{Fe/HCl}} \begin{array}{c} \text{F} \\ \text{Br} \end{array} \text{N} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{F} \\ \text{OH} \end{array} \xrightarrow{\text{PhCHO, NaBH}_4} \begin{array}{c} \text{Ph} \\ \text{N} \end{array} \text{N} \begin{array}{c} \text{F} \\ \text{OH} \end{array}\]

5-Fluoro-6-(aminomethylbenzoxo)indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

[0236] The title compound can be synthesized according to the following scheme:
wherein $R^{21}$ and $R^{22}$ are independently selected unsubstituted alkyl.

**N-(1-(5-Fluoro-1-hydroxy-1,3-dihydrobenzo[1,2]oxaborol-6-yl)-1H-indol-5-yl)benzenesulfonamide**

[0237] The title compound can be synthesized according to the following scheme:

5-Fluoro-6-f5-(imidazol-2-ylmethoxy)indol-1-yl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

[0238] The title compound can be synthesized according to the following scheme:

5-Fluoro-6-f5-(thiazol-2-ylmethoxy)indol-1-yl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

[0239] The title compound can be synthesized according to the following scheme:
**5-Fluoro-6-(pyrimidin-6-ylmethoxy)indol-1-yl)-4,3-dihydro-4-hydroxy-2,1-benzoxaborole**

[0240] The title compound can be synthesized according to the following scheme:

![Chemical Structure](image)

**5-Fluoro-6-(pyridin-3-yloxy)indol-4-yl)-4,3-dihydro-4-hydroxy-2,1-benzoxaborole**

[0241] To a solution of l-(5-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-5-ol (400 mg, 1.413 mmol, 1 eq) in DMF (7 mL) was added NaH (283 mg, 60%, 5 eq) at 0°C and the mixture was stirred for 30 min. 3-(Chloromethyl)pyridine hydrochloride (278 mg, 1.696 mmol, 1.2 eq) was added and the reaction was stirred at 50°C for 3 h. The reaction was quenched with water and adjusted pH to 7-8 with IN HCl. The solid precipitated was filtered, washed with ether to give 250 mg of the title compound in 47% yield. 

\[
\begin{align*}
\text{H NMR} & : \delta 9.33 (s, 1H), 8.69 (s, 1H), 8.54 (m, 1H), 7.88 (t, 1H), 7.57 (d, 1H), 7.51 (d, 1H), 7.42 (m, 1H), 7.28 (s, 1H), 7.12 (d, 1H, J=8 Hz), 6.93 (d, 1H), 6.91 (d, 1H), 6.63 (s, 1H), 5.20 (s, 2H), 5.07 (s, 2H) ppm.
\end{align*}
\]

**5-Fluoro-6-f5-(benzyloxy)benzifnidazol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole**

Preparation of ethyl 2-bromo-5-fluoro-4-(4-methoxy-2-nitrophenylamino) benzoate

[0242] To a solution of 4-methoxy-2-nitroaniline (6 g, 22.6 mmol, 1 eq) and ethyl 2-bromo-4,5-difluorobenzoate (3.8 g, 22.6 mmol, 1 eq) in dry DMF (225 mL) was added Cs₂CO₃ (12.7 g, 33.9 mmol, 1.5 eq) under N₂ protection. The mixture was heated to 100°C for 4h. TLC analysis showed there was no starting material remained. The mixture was mixed with 300mL water. The mixture was extracted with EA (2 x 100 mL) and the organic layer separated was washed with 0.5N HCl, water, brine and dried over anhydrous Na₂SO₄. The mixture was filtered and the
filtrate was concentrated. The solid was purified by recrystallization with EA/PE to give 6 g of product (yield 65%).

Preparation of methyl 2-bromo-5-fluoro-4-(5-hydroxy-lH-benzo[d]imidazol-1-yl) benzoate

To a solution of ethyl 2-bromo-5-fluoro-4-(4-methoxy-2-nitrophenylamino)benzoate (6 g, 14.5 mmol, 1 eq) in HCOOH (70 mL) was added Fe (4 g, 72.6 mmol, 5 eq). The mixture was refluxed for 5 h. TLC showed there was no starting material remained. The mixture was filtered and filtrate was adjusted to pH~7 with 10% NaOH. The aqueous phase was extracted with EA for three times.

The organic layer was washed with saturated aqueous NaHCO₃, brine and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated to give 5 g of the product. The yield was 88%.

Preparation of methyl 4-(5-(benzyloxy)-lH-benzo[d]imidazol-1-yl)-2-bromo-5-fluorobenzoate

To a solution of ethyl 2-bromo-5-fluoro-4-(5-methoxy-lH-benzo[d]imidazol-1-yl)benzoate (5 g, 12.7 mmol) in toluene (60 mL) was added AICI₃ (4.2 g, 31.8 mmol, 2.5 eq) under N₂ protection, the mixture was refluxed overnight. TLC showed no starting material was remained. The solvent was removed. Cone. H₂SO₄ (1 mL, 3 eq) and MeOH (60 mL) were added. The reaction mixture was heated to reflux overnight. The mixture was concentrated and water (30 mL) was added. The aqueous was extracted with EA for three times and the organic layer was washed with water, brine and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated. The crude product was purified by silica gel to provide 2.1 g of the desired product. The yield was 48%. 1H NMR (500Hz, DMSO-de): δ 9.26 (s, 1H), 8.37 (s, 1H), 8.14 (d, 1H, J=6.95 Hz), 7.96 (d, 1H, J=10.5 Hz), 7.22 (d, 1H, J=6.35 Hz), 7.06 (s, 1H), 6.81 (d, 1H, J=6.55 Hz), 3.9 (s, 3H) ppm.

Preparation of (4-(5-(benzyloxy)-lH-benzo[d]imidazol-1-yl)-2-bromo-5-fluorophenyl) methanol

To a suspension of methyl 2-bromo-5-fluoro-4-(5-hydroxy-1H-benzo[d]imidazol-1-yl)benzoate (1 g, 2.74 mmol, 1 eq) and K₂CO₃ (570 mg, 4.11 mmol, 1.5 eq) in acetone (13 mL) was added benzyl bromide (0.33 mL, 1.2 eq) and the mixture was refluxed overnight. Water (10 mL) was added and the mixture was extracted with DCM twice and the organic layer was washed with water, brine and
dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel to afford 400 mg of the desired product (yield 35%).

Preparation of 4-(5-(benzylxy)-1H-benzo[d]imidazol-1-yl)-2-bromo-5-fluorophenyl methanol

[0246] To a solution of methyl 4-(5-(benzylxy)-1H-benzo[d]imidazol-1-yl)-2-bromo-5-fluorobenzoate (220 mg, 0.6 mmol, leq) in dry EtOH (10 mL) was added NaBH₄ (46 mg, 1.2 eq) in portions at 0°C. The mixture was warmed to rt and stirred overnight. TLC showed no starting material was remained. The reaction was quenched with acetic acid. The residue was concentrated and dissolved in EA. The organic layer was washed with water, brine and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated to generate 220 mg of the desired product (yield 80%).

Preparation of 4-(5-(benzylxy)-1H-benzo[d]imidazol-1-yl)-2-bromo-5-fluorobenzyl acetate

[0247] To a solution of (4-(5-(benzylxy)-1H-benzo[d]imidazol-1-yl)-2-bromo-5-fluorophenyl)methanol (220 mg, 0.516 mmol, 1.0 eq) in dry DCM (15 mL) was added Et₃N (105 mg, 1.2 eq) followed by addition of acetic anhydride (105 mg, 1.1 eq). The reaction was stirred for 2 h. TLC showed no starting material. The mixture was concentrated and dissolved in EA. The organic layer was washed with water, IN HC1, saturated aqueous NaHCO₃, brine and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated to afford 225 mg of the product (yield 100%).

Preparation of 4-(5-(benzylxy)-1H-benzo[d]imidazol-1-yl)-5-fluoro-2-(4, 4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzyl acetate

To a solution of 4-(5-(benzylxy)-1H-benzo[d]imidazol-1-yl)-2-bromo-5-fluorobenzyl acetate (250 mg, 0.533 mmol, leq) and bis(pinacolato)diboron (203 mg, 0.79 mmol, 1.5 eq) in 1,4-dioxane (3 mL) was added KOAc (209 mg, 2.13 mmol, 4 eq), followed by addition Pd(dppf)Cl₂CH₂Cl₂ (44 mg, 10%). The mixture was stirred at 108°C overnight. HPLC showed no starting material was remained. The reaction was filtered through a short silica gel column and 285 mg crude product was obtained. It was used directly without further purification.
Preparation of 6-(5-(benzyloxy)-1H-benzo[d]imidazol-1-yl)-5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol

[0248] To a solution of 4-(5-(benzyloxy)-1H-benzo[d]imidazol-1-yl)-5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)benzyl acetate, obtained from the previous step, in MeOH (2 mL) was added NaOH (58 mg, 2.5 eq). The mixture was stirred for 2 h. TLC showed no starting material was remained. The solvent was removed and THF (3 mL) was added. The residue was adjusted to pH=2 with 6N HCl. The mixture was stirred for 1 h and the solvent was removed. The mixture was extracted with EA twice. The organic layer was washed with brine and dried over anhydrous Na$_2$SO$_4$. The mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel to give 110 mg of the title compound (yield 54%).

$^1$H NMR (500Hz, DMSO-d$_6$): δ 9.39 (s, 1H), 8.41 (s, 1H), 7.93 (d, 1H), 7.63 (t, 1H), 7.48 (d, 2H), 7.39 (m, 3H), 7.32 (m, 1H), 7.24 (m, 1H), 7.02 (t, 1H), 5.18 (s, 2H), 5.09 (s, 2H) ppm.

5-fluoro-6-(5-(piperidin-4-ylmethoxy)-1H-indol-1-yl)benzof[c][1,2]oxaborol-1(3H)-ol hydrochloride

[0249] To a solution of 1-(5-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-5-ol (758 mg, 2.678 mmol, 1 eq) in DMF (14 mL) was added NaH (429 mg, 60%, 4 eq) at 0°C and the mixture was stirred for 30 min. tert-butyl 4-((methylsulfonyloxy) methyl) piperidine-1-carboxylate (1.68 g, 5.365 mmol, 2.0 eq) was added and the reaction was stirred at 50°C for 3 h. The reaction was quenched with water and adjusted pH=6 with 1N HCl. The residue was extracted with EA and the organic layer was washed with NaHCO$_3$, brine and dried over anhydrous Na$_2$SO$_4$.

The mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel to give 300 mg of tert-butyl 4-((1-(5-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-5-ylmethoxy) methyl)piperidine-1-carboxylate. To a solution of tert-butyl 4-((1-(5-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-5-ylmethoxy) methyl) piperidine-1-carboxylate (300 mg) in MeOH (2 mL) was added HCl/MeOH and the mixture was stirred for 2h. TLC showed no starting material was remained. The reaction was concentrated and the solid was washed with MeOH/ether to give the title compound (150 mg). $^1$H NMR (500Hz, DMSO-d$_6$): δ 9.33 (s, 1H), 8.74 (s, 1H), 8.33 (s, 1H).
7.88 (d, 1H, J = 8 Hz), 7.57 (d, 1H), 7.51 (d, 1H), 7.18 (d, 1H), 7.09 (d, 1H), 6.83 (m, 1H), 6.62 (d, 1H), 5.07 (s, 1H), 3.89 (d, 2H), 3.29 (m, 2H), 2.87 (m, 2H), 2.08 (m, 2H), 1.93 (m, 2H), 1.52 (m, 1H) ppm.

**N-(l-(5-fluoro-l-hydroxy-l,3-dihydrobenzofl,2)oxaborol-6-yl)-lH-indol-5-yldibenztamide**

![Chemical structure](image)

**Preparation of ethyl 2-bromo-5-fluoro-4-(5-nitro-lH-indol-l-yl) benzoate**

[0250] To a solution of 5-nitro-lH-indole (2 g, 6.17 mmol, 1 eq) and ethyl 2-bromo-4,5-difluorobenzoate (3.27 g, 6.17 mmol, 1 eq) in dry DMF (40 mL) was added 

\[ CS_2CO_3 \] (6.0 g, 9.25 mmol, 1.5 eq) under N\_2 protection. The mixture was heated to 100°C for 4 h. TLC showed no starting material was remained. The mixture was poured into 400 mL water. The residue was extracted with EA (2 x 100 mL) and the organic layer was washed with 0.5N HCl, water, brine and dried over anhydrous Na\_2SO\_4. The mixture was filtered and the filtrate was concentrated. The solid was purified by recrystallization from EA/PE to give 3.6 g of the product (yield 74%).

**Preparation of ethyl 4-(5-amino-lH-indol-l-yl)-2-bromo-5-fluorobenzoate**

[0251] To a suspension of ethyl 2-bromo-5-fluoro-4-(5-nitro-lH-indol-l-yl)benzoate (1 g, 2.457 mmol, 1 eq), NH\_4Cl (0.79 g, 14.742 mmol, 6 eq), Fe (0.83 g, 14.742 mmol, 6 eq) in EtOH (16 mL) and water (8 mL) was added 0.089 mL cone. HCl. The mixture was refluxed for 20 min. TLC showed no starting material was remained. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in EA, washed with water, NaHCO\_3, brine and dried over anhydrous Na\_2SO\_4. The mixture was filtered and the filtrate was concentrated to afford 926 mg of product (yield 100%).

**Preparation of ethyl 4-(5-benzamido-lH-indol-l-yl)-2-bromo-5-fluorobenzoate**

[0252] To a solution of ethyl 4-(5-amino-lH-indol-l-yl)-2-bromo-5-fluorobenzoate (900 mg, 2.387 mmol, 1 eq) in dry DCM (20 mL) was added Et\_3N (0.664 mL, 2 eq) followed by addition of benzoyl chloride (0.306 mL, 1.1 eq). The reaction was stirred for 2 h. TLC showed no starting material. The mixture was concentrated and dissolved in EA. the organic layer was washed with water, IN HCl, saturated aqueous...
NaHCO₃, brine and dried over anhydrous Na₂S₀₄. The mixture was filtered and the filtrate was concentrated to provide 1.14 g of the product (yield 100%).

Preparation of N-(l-(5-bromo-2-fluoro-4-(hydroxymethyl)phenyl)-IH-indol-5-yl)benzamide

To a solution of ethyl 4-(5-benzamido-lH-indol-l-yl)-2-bromo-5-fluorobenzoate (2.3 g, 4.7 mmol, 1 eq) in dry EtOH (18 mL) and THF (6 mL) was added NaBH₄ (0.45 g, 1.95 mmol, 2.5 eq) in portions at 0°C. The mixture was warmed to rt and stirred overnight. TLC showed no starting material was remained. The reaction was quenched with acetic acid. The residue was concentrated and dissolved in EA. The organic layer was washed with water, brine and dried over anhydrous Na₂S₀₄. The mixture was filtered and the filtrate was concentrated to afford 1.86 g of the product (yield 88.6%).

Preparation of 4-(5-benzamido-lH-indol-l-yl)-2-bromo-5-fluorobenzyl acetate

To a solution of N-(l-(5-bromo-2-fluoro-4-(hydroxymethyl)phenyl)-IH-indol-5-yl)benzamide (1.86 g, 4.234 mmol, 1 eq) in dry DCM (20 mL) was added Et₃N (1.76 mL, 3 eq) followed by addition of acetic anhydride (0.8 mL, 2 eq). The reaction was stirred for 2 h. TLC showed no starting material. The mixture was concentrated and dissolved in EA. The organic layer was washed with water, IN HCl, saturated aqueous NaHCO₃, brine and dried over anhydrous Na₂S₀₄. The mixture was filtered and the filtrate was concentrated to yield 1.89 g of the product (yield 94.5%). H NMR (300Hz, DMSO-d₆): δ 10.21 (s, 1H), 8.13 (s, 1H), 7.96 (m, 3H), 7.70 (s, 1H), 7.54 (m, 5H), 7.22 (d, 1H, J=6.4 Hz), 6.73 (d, 1H, J=3.2 Hz), 5.17 (s, 1H), 2.15 (s, 3H) ppm.

Preparation of 4-(5-benzamido-lH-indol-l-yl)-5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate

To a solution of 4-(5-benzamido-lH-indol-l-yl)-2-bromo-5-fluorobenzyl acetate (900 mg, 1.89 mmol, 1 eq), bis(pinacolato) diboron (720 mg, 0.84 mmol, 1.5 eq) in 1,4-dioxane (10 mL) was added KOAc (742 mg, 7.56 mmol, 4 eq), followed by addition Pd(dppf)₂Cl₂.CH₂Cl₂ (154 mg). Under nitrogen atmosphere, the mixture was stirred at 108°C overnight. HPLC analysis indicated no starting material was remained. The reaction was filtered through a short silica gel column and 1.2 g of the crude product was obtained.
Preparation of N-(1-(5-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-IH-indol-5-yl)benzamide

[0256] To a solution of 4-(5-benzamido-lH-indol-l-yl)-5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate, obtained from the previous step, in MeOH (5 mL) and THF (5 mL) was added NaOH (200 mg, 2.2 eq). The mixture was stirred for 2 h. TLC shown no starting material was remained. The solvent was removed and THF (20 mL) was added. The residue was adjusted to pH=2 with 6N HCl. The mixture was stirred for 1 h and the solvent was removed. The mixture was extracted with EA twice. The organic layer was washed with brine and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel column to give 250 mg of the title compound (yield 28.5%). ¹H NMR (300Hz, DMSO-d₆); δ 10.20 (s, 1H), 9.37 (s, 1H), 8.14 (s, 1H), 7.92 (m, 3H), 7.55 (m, 6H), 7.18 (d, 1H), 6.72 (d, 1H), 5.09 (s, 2H) ppm.

EXAMPLE 2

Activity against Brugia malayi

[0257] Compounds were tested initially at 100 µM concentrations for their ability to kill adult female B. malayi in vitro using the methods published previously by Dhananjayan et al, J. Med. Chem. 2005, 48: 2822-2830. Compounds that demonstrated rapid killing at 100 µM were retested at sequential 10 fold lower concentrations. Two adult female B. malayi worms were cultured in RPMI 1640 containing HEPES and L-glutamine. Worm motility and morphology were visually assessed every day for 21 days and observations recorded. Negative control parasites, cultured in the absence of compounds (0.1% DMSO only), remained alive and actively motile for 21 days in this assay. Dead worms were identified by cessation of motility and elongated morphology. For each compound, the rate of in vitro killing was compared to the rate at which worms are killed by a known anti-filarial compound, albendazole at 100 µM. The concentration of albendazole and exposure times for parasites in the presence of albendazole were specifically chosen in order to achieve a killing rate of ~20 days, so that new drugs with shorter killing times could be identified.
<table>
<thead>
<tr>
<th>Structure</th>
<th>cLogP</th>
<th>Days to death at 10 mM</th>
<th>Days to death at 1 mM</th>
<th>Days to death at 0.01 mM</th>
<th>Days to death at 1 pM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-(5-benzyloxy)-1H-indol-1-yl)-5-fluorobenzof[c][1,2]oxaborol-1(3H)-ol</td>
<td>5.64</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>6-(5-chloro-1H-indol-1-yl)benzof[c][1,2]oxaborol-1(3H)-ol</td>
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<td>8</td>
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<td>NT</td>
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<tr>
<td>6-(5-methoxy-1H-indol-1-yl)benzof[c][1,2]oxaborol-1(3H)-ol</td>
<td>3.69</td>
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<td>8</td>
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</tr>
<tr>
<td>6-indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole</td>
<td>3.63</td>
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<td>15</td>
<td>NT</td>
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<tr>
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<td>1</td>
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<td>12</td>
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<tr>
<td>6-(3-phenylthio)-1H-indol-1-yl)benzof[c][1,2]oxaborol-1(3H)-ol</td>
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<td>1</td>
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<td>5-Fluoro-6-(5-(methoxy)indol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole</td>
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<td>3.4</td>
<td>7 (at 100 mM)</td>
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<td>3.2</td>
<td>7 (at 100 mM)</td>
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<td>3-(5-Chloro-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile</td>
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<td>3-(1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile</td>
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No killing
**EXAMPLE 3**

*Additional activity against worms*


[0262] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.
WHAT IS CLAIMED IS:

1. A compound having a structure which is:

   
   
   
   

   
   
   
   

   
   
   
   

   
   
   
   

   wherein

   1. X is N or CH;
   2. R^5 is H or halogen and
   3. R^1 or R^2 is selected from the group consisting of

   - alkoxy, optionally substituted with a substituted or unsubstituted phenyl;
   - alkoxy, optionally substituted with a substituted or unsubstituted heteroaryl;
   - alkylamino, optionally substituted with a substituted or unsubstituted phenyl;
   - alkylamino, optionally substituted with a substituted or unsubstituted heteroaryl;
   - -NHC(O)R^1, wherein R^1 is unsubstituted phenyl or unsubstituted heteroaryl;
   - -NHS(O)R^1, wherein R^1 is unsubstituted phenyl or unsubstituted heteroaryl;
   - -NHC(O)R^2, wherein R^2 is unsubstituted alkyl;
   - -C(O)NHR^2, wherein R^2 is unsubstituted alkyl;

   or a hydrate, solvate or salt thereof.

2. The compound of claim 1, wherein R^5 is fluorine.

3. The compound of a previous claim, wherein R^1 is benzoxy.

4. A combination comprising the compound of a preceding claim, together with at least one other therapeutically active agent.

5. A pharmaceutical formulation comprising:

   a) the compound of a preceding claim, or a salt thereof; and
   b) a pharmaceutically acceptable excipient.
6. The pharmaceutical formulation of claim 5, wherein the pharmaceutical formulation is a unit dosage form.

7. The pharmaceutical formulation of claim 5, wherein the salt of said compound of a preceding claim is a pharmaceutically acceptable salt.

8. A method of killing and/or inhibiting the growth of a helminth, comprising: contacting the helminth with an effective amount of the compound of the invention, thereby killing and/or inhibiting the growth of the helminth.

9. The method of claim 8, wherein the compound is according to claim 1.

10. The method of claim 8, wherein the helminth is nematode or trematode.

11. The method of claim 8, wherein the helminth is a nematode, and the nematode is selected from the group consisting of Wuchereria bancrofti, Brugia malayi, and Brugia timori.

12. A method of treating and/or preventing a disease in an animal, comprising: administering to the animal a therapeutically effective amount of the compound of the invention, thereby treating and/or preventing the disease.

13. The method of claim 12, wherein the compound is according to claim 1.

14. The method of claim 12, wherein the disease is lymphatic filariasis.

15. The method of claim 12, wherein the animal is a human.

16. A use of a compound of the invention or a combination of the invention in the manufacture of a medicament for the treatment and/or prophylaxis of helminth infection.
A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F5/02 A61K31/69
ADD. A61P33/10

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07F

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 practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search
11 January 2011

Date of mailing of the international search report
26/01/2011

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

Authorized officer
Herz, Claus
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