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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 January 2020 (02.01.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/002593 A1

(51) International Patent Classification:
A61K 31/44 (2006.01) *A61K 31/4439* (2006.01)
A61K 31/36 (2006.01) *A61K 31/444* (2006.01)
A61K 31/415 (2006.01) *A61K 31/4709* (2006.01)
A61K 31/428 (2006.01) *A61K 31/497* (2006.01)
A61K 31/437 (2006.01) *A61K 45/06* (2006.01)
A61K 31/443 (2006.01) *A61P 33/10* (2006.01)
A61K 31/4436 (2006.01)

(21) International Application Number:
PCT/EP2019/067317

(22) International Filing Date:
28 June 2019 (28.06.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
18180680.3 29 June 2018 (29.06.2018) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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

WO 2020/002593 A1

(54) Title: COMPOUND FOR USE AGAINST HELMINTHIC INFECTION

(57) Abstract: This present application relates to compounds (and salts thereof) that are generally useful as anthelmintic agents. This invention also relates to uses of the compounds and salts to make medicaments, and treatments comprising the administration of the compounds and salts to animals in need of the treatments.

COMPOUND FOR USE AGAINST HELMINTHIC INFECTION

This invention relates to compounds (and salts thereof) that are generally useful as anthelmintic agents. This invention also relates to processes for making the compounds and salts, pharmaceutical compositions and kits comprising the compounds and salts, uses of the compounds and salts to make medicaments, and treatments comprising the administration of the compounds and salts to animals in need of the treatments.

BACKGROUND OF THE INVENTION

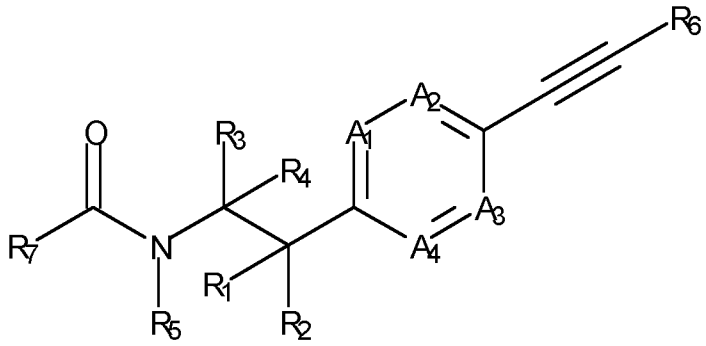
Parasitic diseases in humans and animals cause substantial suffering and economic losses throughout the world. Thus, control of parasitic infections remains an important global endeavor. The causative organisms include endoparasites, such as nematodes, cestodes, and trematodes. These organisms can infect, for example, the stomach, intestinal tract, urinary tract, kidney, bladder, lymphatic system, tissues, liver, lungs, heart, and brain.

There are many known drugs (or "anthelmintic agents") available to treat various endoparasitic infections. These reportedly include, for example, various avermectins (e.g., ivermectin, selamectin, doramectin, abamectin, and eprinomectin); milbemycins (e.g. moxidectin and milbemycin oxime); pro-benzimidazoles (e.g., febantel, netobimin, and thiophanate); a thiazole benzimidazole derivatives (e.g., thiabendazole and cambendazole); carbamate benzimidazole derivatives (e.g., fenbendazole, albendazole (oxide), mebendazole, oxfendazole, parbendazole, oxibendazole, flubendazole, and triclabendazole); imidazothiazoles (e.g., levamisole and tetramisole); tetrahydropyrimidine (e.g. morantel and pyrantel), organophosphates (e.g., trichlorphon, haloxon, dichlorvos, and naphthalophos); salicylanilides (e.g., closantel, oxyclozanide, rafoxanide, and niclosamide); nitrophenolic compounds (e.g., nitroxynil and nitroscanate); benzoenedisulphonamides (e.g., clorsulon); pyrazinaisoquinoline (e.g., praziquantel and epsiprantel); heterocyclic compounds (e.g., piperazine, diethylcarbamazine, dichlorophen, and phenothiazine); arsenicals (e.g., thiacetarsamide, melorsamine, and arsenamide); cyclooctadepsipeptides (e.g., emodepside); amino-acetonitriles (e.g. monepantel) and spiroindoles (e.g. derquantel).

While many endoparasitic infections can be treated with known drugs, evolutionary development of resistance by the parasites can render such drugs obsolete over time. In addition, known drugs may have other deficiencies, such as limited spectrum of activity and the need for repeated treatments. Thus, there still exists a need for new anthelmintic agents to ensure safe, effective, and convenient treatment of a wide range of endoparasitic infections over a long period of time. The following disclosure describes the use of a group of such agents for treatment of endoparasitic infection.

SUMMARY OF THE INVENTION

Briefly, this invention is related to compounds (and salts thereof) that can generally be used as anthelmintic agents. The compounds correspond in structure to Formula I:



(I)

or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

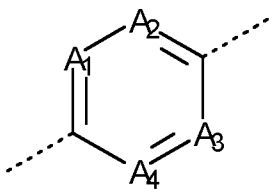
R^1 and R^2 are each independently a hydrogen atom, a halogen atom, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, cyano(C_1-C_4)alkoxy, C_3-C_6 alkenyloxy, C_3-C_6 haloalkenyloxy, C_3-C_6 alkynyloxy, C_3-C_6 haloalkynyloxy, C_1-C_4 alkylthio, C_1-C_4 alkoxyamino, C_1-C_4 alkoxycarbonyl, $-C(=O)NH_2$ or $-C(S)NH_2$;

R^3 and R^4 are each independently a hydrogen atom, C_1-C_4 alkyl, C_1-C4- haloalkyl, C_1-C_4 alkoxymethyl, or C_3-C_6 cycloalkyl or ; R^3 and R^4 together can form C_3-C_6 cycloalkyl,

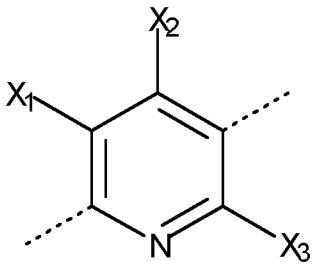
R^5 is a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, (C_1-C_2)alkyl substituted by R^8, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_3-C_4 alkynyl, -OH, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 haloalkylthio, $-C(=O)R^{9,}$ $-C(=O)OR^9$, or C_1-C_4 alkoxycarbonyl;

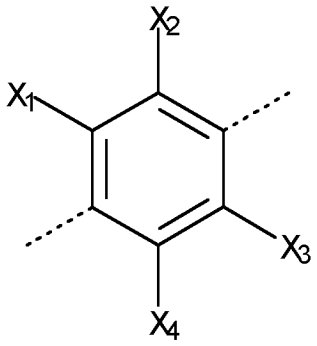
R^6 is aryl or aromatic heterocycle; wherein the aryl and aromatic heterocycle may be optionally substituted;

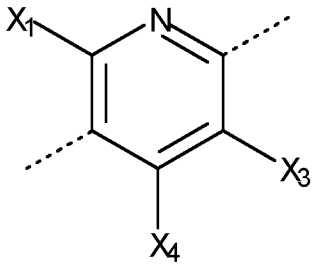
R^7 is aryl or an aromatic heterocycle; wherein the aryl and aromatic heterocycle may be optionally substituted;



is selected from the group consisting of



,


,


(x-1) (x-2) (x-3)

wherein X^1 and X^4 are each independently a hydrogen atom, a halogen atom, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy or C_1-C_4 alkylthio;

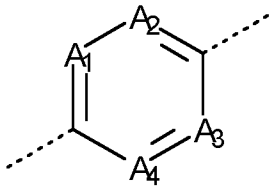
X^2 and X^3 are each independently a hydrogen atom, a halogen atom or methyl;

R^8 is cyano, $-OR^{10}$, C_1-C_4 alkylthio, C_1-C_4 alkoxycarbonyl, $-C(=O)NH_2$ or $-C(S)NH_2$;

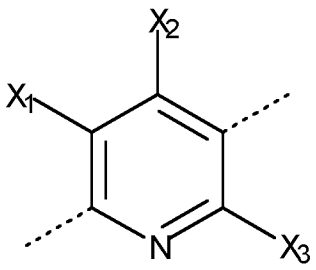
R^9 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, C_3-C_4 cycloalkyl or C_2-C_4 alkenyl, C_2-C_4 haloalkyl;

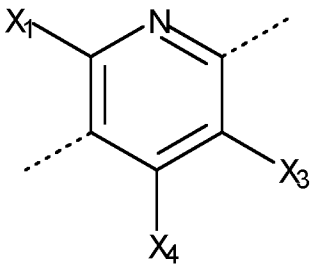
R^{10} is hydrogen, C_1-C_4 alkyl, C_2-C_4 haloalkyl, C_1-C_4 alkylcarbonyl, C_3-C_6 cycloalkylcarbonyl or C_1-C_4 alkoxycarbonyl.

Optionally,



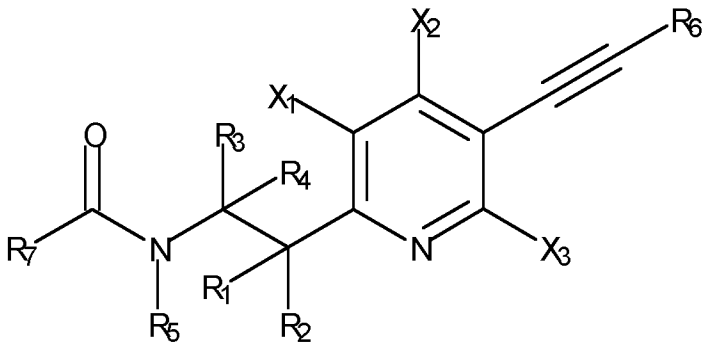
is selected from the group consisting of



, and


. (x-1) (x-3).

The invention is further directed to compounds of formula (II)



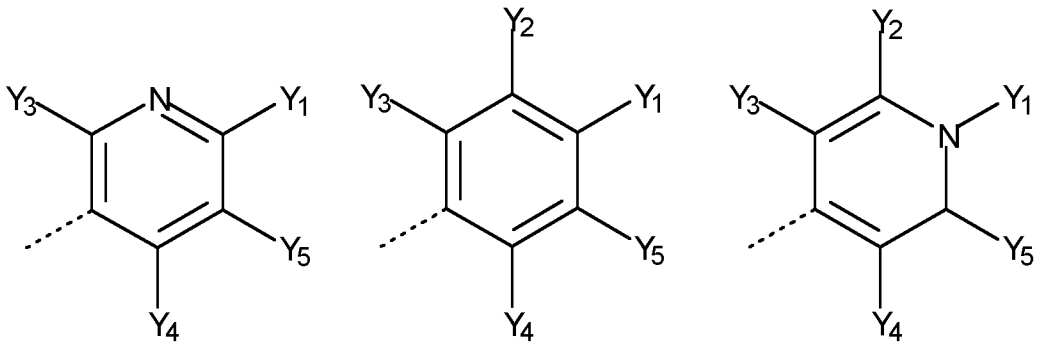
(II)

In certain embodiments of the invention and/or embodiments thereof, X^1 is a halogen atom, preferably a chlorine.

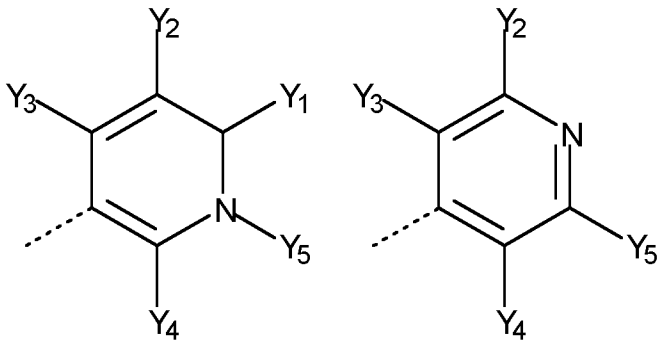
Further in other embodiments of the invention and/or embodiments thereof, X^2 and X^3 are hydrogen.

In some embodiments of the invention and/or embodiments thereof, R^6 is a five- or six-membered aryl or aromatic heterocycle or bicyclic aromatic ringstructures consisting of five or six-membered carbon cycles or heterocycles.

Further R^6 may be selected from the group consisting of;



(y-1) (y-2) (y-3)



(y-4) (y-5)

wherein Y^1, Y^2, Y^3, Y^4, Y^5 are each independently a hydrogen, halogen atom, cyano, nitro, C_1-C_4 alkyl, alkoxy, haloalkoxy, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, trifluoromethylthio, trifluoromethylsulfinyl, trifluoromethylsulfonyl or phenyl, wherein

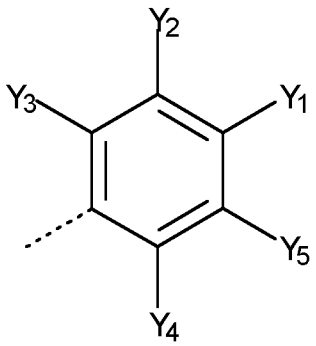
Y^1 and Y^5 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^5 and Y^4 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^1 and Y^2 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^2 and Y^3 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to.

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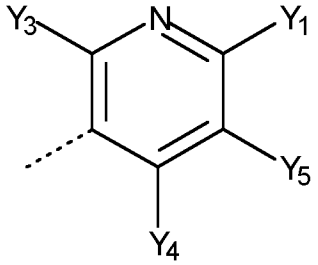
Additionally, Y^1, may be a halogen atom, haloalkoxy, alkoxy, trifluoromethyl, methoxy, difluoromethoxy, or trifluoromethoxy. In some embodiments of the invention and/or embodiments thereof, Y^1, is a halogen atom, trifluoromethyl, preferably a halogen, preferably a fluorine or a chlorine. Most preferably a chlorine. Preferably Y^1 is not hydrogen. In a suitable embodiment, Y^1 is halogen, haloalkoxy or alkoxy. Suitably Y^1 is trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, fluorine or a chlorine. Most preferably a trifluoromethyl, methoxy, or chlorine

Suitably Y^2, Y^3, Y^4, Y^5 are each independently a hydrogen, or a halogen atom. Suitably Y^2 is a hydrogen. Suitably Y^3 is a hydrogen. Suitably Y^4 is a hydrogen. Suitably Y^5 is a hydrogen. Y^2 is preferably a halogen, preferably a fluorine. Suitably Y^3 and Y^4 are both hydrogen.
Suitably, Y^3, Y^5 are each independently a halogen atom. Y^5 is suitably a halogen, preferably a chlorine or a fluorine, most preferably a chlorine. Y^3 is suitably a halogen, preferably a chlorine or a fluorine, most preferably a chlorine.

Also compound are contemplated wherein R^6 is

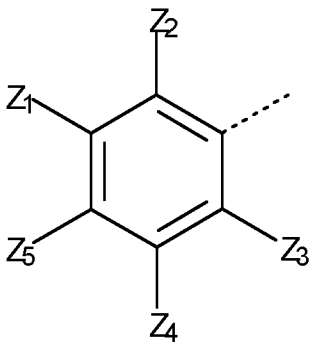


or

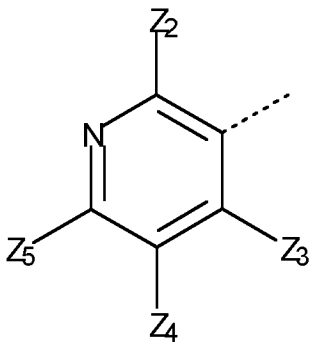


(y-2) (y-1)

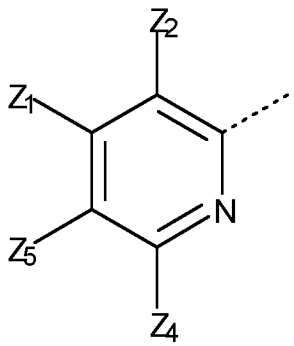
In the compound of the invention R^7 may be selected from the group consisting of;



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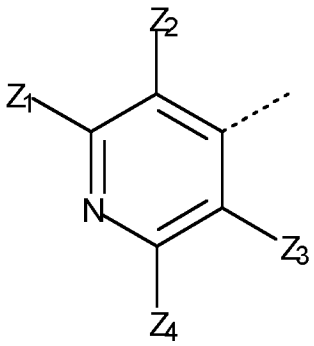


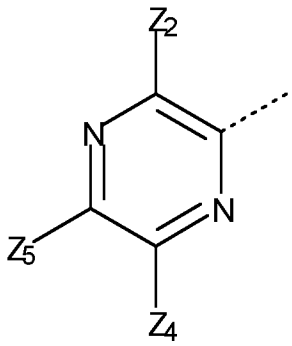
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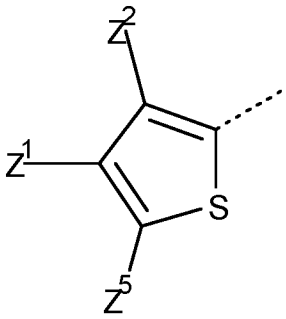


,

(z-1) (z-2) (z-3)







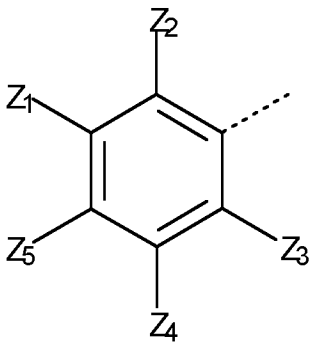
, and

(z-4) (z-5) (z-6)

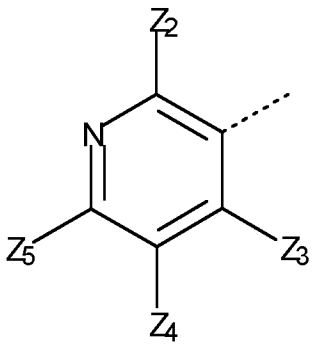
wherein $Z^{2,}$ Z^3 are each independently a hydrogen, halogen atom, nitro, C_1-C_4 alkyl or C_1-C_4 haloalkyl,

Z^1, Z^4, Z^5 are each independently hydrogen, a halogen atom, or C_1-C_4 alkyl.

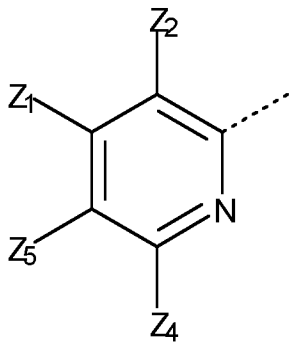
Suitably R^7 is selected from the group consisting of;



,



,



,

(z-1) (z-2) (z-3)

Further, suitably in certain compounds, Z^2 is a halogen atom or C_1-C_4 haloalkyl.

In addition, Z^2 may be chlorine or CF_3.

Moreover Z^1, Z^4, Z^5 may each be hydrogen, preferably at least two of . Z^1, Z^4, Z^5 are hydrogen, preferably all of Z^1, Z^4, Z^5 are hydrogen.

Also compounds are contemplated wherein R^4 is hydrogen and R^3 is hydrogen or CH_3., or wherein R^3 and R^4 together form a cyclopropyl, or a cyclobutyl

In addition, compounds are contemplated wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, C_1-C_4 alkyl, or C_1-C_4 haloalkyl, Suitably, R^1 and R^2 are each independently a hydrogen atom, or a halogen atom preferably R^1 and R^2 are fluorine.

In some embodiments of the invention and/or embodiments thereof, R^5 is a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, alkyloxycarbonyl, preferably -C(=O)OR^9 or hydrogen, preferably methylformate, ethylformate or hydrogen.

The compound of the present invention and/or embodiments thereof may be administered orally, subcutaneously, or topically. Preferably, the compound of the present invention and/or embodiments thereof is administered orally. Preferably, the compound of the present invention and/or embodiments thereof is administered subcutaneously. Preferably, the compound of the present invention and/or embodiments thereof is administered topically.

The compound of the present invention and/or embodiments thereof is useful against an infection with nematode, cestode or trematatode. Preferably the compound of the present invention and/or embodiments thereof is useful against a nematode. Preferably the compound of the present invention and/or embodiments thereof is useful against *Haemonchus contortus* and/or *Trichostrongylus colubriformis*.

The compound of the present invention and/or embodiments thereof is useful in the treatment of non-human animals. The compound of the present invention and/or embodiments thereof may be used for the treatment of an animal selected from the group consisting of ruminant, equine, companion animal, swine, poultry, fish, preferable selected from the group consisting of sheep, bovine, horse. Preferably sheep. Preferably ruminants. Preferably cow.

Suitably, the compound of the present invention and/or embodiments thereof is administered in a composition comprising a pharmaceutically acceptable carrier.

Suitably, the compound of the present invention and/or embodiments thereof is administered in an effective dose between about 0.01 and about 50 mg/ kg bodyweight of the animal.

Suitably, the compound of the present invention and/or embodiments thereof is administered in combination with another pharmaceutical agent. Suitably, the compound is administered in combination with another an antiparasitic agent. Suitably, the compound is administered in combination with another anthelminthic agent.

This invention also is directed, in part, to pharmaceutical compositions. The pharmaceutical compositions comprise at least one compound or salt of this invention, and at least one excipient. This invention also is directed, in part, to methods for treating a disease in an animal, particularly a parasitic infection. The methods comprise administering at least one compound or salt of this invention to the animal.

This invention also is directed, in part, to a use of at least one compound or salt of this invention to prepare a medicament for treating a disease (e.g., a parasitic infection) in an animal.

This invention also is directed, in part, to a kit. The kit comprises at least one compound or salt of this invention. In addition, the kit comprises at least one other component, such as another ingredient (e.g., an excipient or active ingredient), instructions and/or an apparatus for combining the compound or salt with

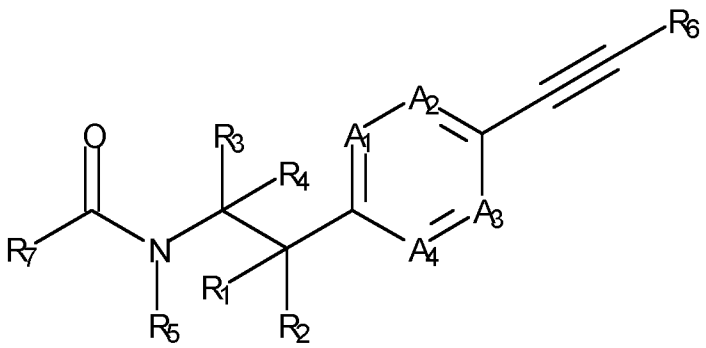
another ingredient, instructions and/or an apparatus for administering the compound or salt, and/or a diagnostic tool.

Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this specification.

DETAILED DESCRIPTION

This detailed description of embodiments of the invention and/or embodiments thereofis intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This detailed description and its specific examples, while indicating preferred embodiments of this invention, are intended for purposes of illustration only. This invention, therefore, is not limited to the preferred embodiments described in this specification, and may be variously modified. The invention is intended to encompass combinations of embodiments, some of which are described herein below, however for conciseness of the description, not all combinations of embodiments are described herein . It should be understood that also combinations of embodiments not explicitly described herein are within the scope of the invention.

Briefly, this invention is related to compounds and salts thereof that can generally be used as anthelmintic agents for treatment against an infection with a helminth. The compounds correspond in structure to Formula I:



(I)

or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

R^1 and R^2 are each independently a hydrogen atom, a halogen atom, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, cyano(C_1-C_4)alkoxy, C_3-C_6 alkenyloxy, C_3-C_6 haloalkenyloxy, C_3-C_6 alkynyloxy, C_3-C_6 haloalkynyloxy, C_1-C_4 alkylthio, C_1-C_4 alkoxyamino, C_1-C_4 alkoxycarbonyl, -C(=O)NH_2 or -C(S)NH_2.

Suitably R^1 is selected from the group consisting of a hydrogen atom, a halogen atom, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, cyano(C_1-C_4)alkoxy, C_3-C_6 alkenyloxy,

C_3-C_6 haloalkenyloxy, C_3-C_6 alkynyloxy, C_3-C_6 haloalkynyloxy, C_1-C_4 alkylthio, C_1-C_4 alkoxyamino, C_1-C_4 alkoxycarbonyl, -C(=O)NH_2 and -C(S)NH_2.

Suitably R^2 is selected from the group consisting of a hydrogen atom, a halogen atom, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, cyano(C_1-C_4)alkoxy, C_3-C_6 alkenyloxy, C_3-C_6 haloalkenyloxy, C_3-C_6 alkynyloxy, C_3-C_6 haloalkynyloxy, C_1-C_4 alkylthio, C_1-C_4 alkoxyamino, C_1-C_4 alkoxycarbonyl, -C(=O)NH_2 and -C(S)NH_2.

Suitably, R^1 and R^2 are each independently selected from the group consisting of a hydrogen atom, a halogen atom, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, cyano(C_1-C_4)alkoxy, C_3-C_6 alkenyloxy, C_3-C_6 haloalkenyloxy, C_3-C_6 alkynyloxy, C_3-C_6 haloalkynyloxy, C_1-C_4 alkoxyamino, C_1-C_4 alkoxycarbonyl, and -C(=O)NH_2.

Suitably, R^1 and R^2 are each independently selected from the group consisting of a hydrogen atom, a halogen atom, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_3-C_6 haloalkenyloxy, C_1-C_4 alkoxycarbonyl, and -C(=O)NH_2.

Suitably, R^1 and R^2 are each independently selected from the group consisting of a hydrogen atom, a halogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxycarbonyl, and -C(=O)NH_2.

In addition, compounds are contemplated wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, C_1-C_4 alkyl, or C_1-C_4 haloalkyl, Suitably, R^1 and R^2 are each independently a hydrogen atom, or a halogen atom. R^1 and R^2 are halogen. R^1 or R^2 may be fluor. Preferably R^1 and R^2 are both fluor.

In certain embodiments of the invention and/or embodiments thereof, R^3 and R^4 are each independently a hydrogen atom, C_1-C_4 alkyl, C_1-C_4- haloalkyl, C_1-C_4 alkoxymethyl, or C_3-C_6 cycloalkyl., or R^3 and R^4 together can form C_3-C_6 cycloalkyl .

Suitably, R^3 and R^4 are each independently a hydrogen atom, C_1-C_4 alkyl, C_1-C4- haloalkyl, C_1-C_4 alkoxymethyl. or ; R^3 and R^4 together can form C_3-C_6 cycloalkyl .

Suitably, R^3 and R^4 are each independently a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, or ; R^3 and R^4 together can form C_3-C_4 cycloalkyl.

Suitably, R^3 and R^4 are each independently a hydrogen atom, C_1-C_4 alkyl, C_1-C_4- haloalkyl or R^3 and R^4 together form cyclopropyl or a cyclobutyl.

Suitably, R^3 and R^4 are each independently a hydrogen atom, or C_1-C_4 alkyl, or R^3 and R^4 together form a cyclopropyl, or a cyclobutyl.

Suitably, R^3 and R^4 are each independently a hydrogen atom, methyl, ethyl, propyl or butyl, or R^3 and R^4 together form a cyclopropyl, or a cyclobutyl..

Suitably, R^3 and R^4 are each independently a hydrogen atom, methyl, ethyl, or propyl, or R^3 and R^4 together form a cyclopropyl..

Suitably, R^3 and R^4 are each independently a hydrogen atom, methyl, or ethyl, or R^3 and R^4 together form a cyclopropyl.

Suitably R^4 is hydrogen atom, methyl, or ethyl. Suitably, R^3 is a hydrogen atom, methyl, or ethyl. Suitably, R^3 is C_1-C_4 alkyl. Suitably, R^3 methyl, ethyl, propyl or butyl. Suitably, R^3 is methyl, or ethyl.

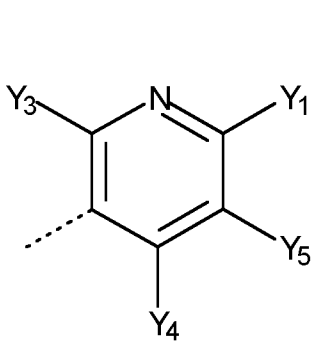
Also compounds are contemplated wherein R^4 is hydrogen. Suitably, R^3 is hydrogen or CH_3.

Also compounds are contemplated wherein R^4 is hydrogen and R^3 is hydrogen or CH_3.

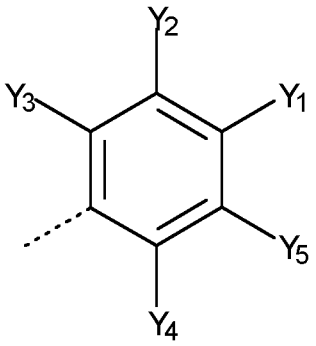
Also compounds are contemplated wherein R^4 is hydrogen and R^3 is hydrogen.
Also compounds are contemplated wherein R^4 is hydrogen and R^3 is CH_3.
Also compounds are contemplated wherein or R^3 and R^4 together form a cyclopropyl.
Also compounds are contemplated wherein or R^3 and R^4 together form a cyclobutyl.

R^5 is a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, (C_1-C_2)alkyl substituted by R^8, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_3-C_4 alkynyl, -OH, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 haloalkylthio, -C(=O)R^9 or C_1-C_4 alkoxycarbonyl. In some embodiments of the invention and/or embodiments thereof, R^5 is a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 alkyloxycarbonyl. Suitably R^5 is a C_1-C_4 alkyl or a C_1-C_4 haloalkyl. Suitably R^5 is a C_1-C_4 alkyl . Suitably R^5 is a C_1-C_4 haloalkyl. Suitably R^5 is methyl, ethyl, propyl or butyl. Suitably, R^5 is hydrogen. Suitably R^5 is C_1-C_4 alkyloxycarbonyl. Suitably R^5 is-C(=O)OR^9. Suitably R^5 is methylformate, or ethylformate.

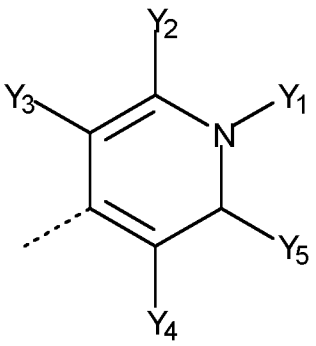
R^6 is aryl or aromatic heterocycle; wherein the aryl and aromatic heterocycle may be optionally substituted.
Further R^6 may be selected from the group consisting of;



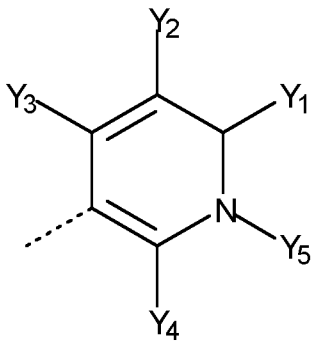
(y-1)



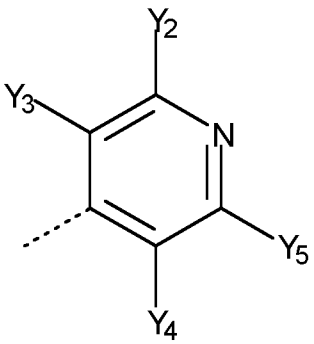
(y-2)



(y-3)



(y-4)



(y-5)

wherein Y^1, Y^2, Y^3, Y^4, Y^5 are each independently a hydrogen, halogen atom, cyano, nitro, C_1-C_4 alkyl, alkoxy, haloalkoxy, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, trifluoromethylthio, trifluoromethylsulfinyl, trifluoromethylsulfonyl or phenyl, wherein Y^1 and Y^5 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^5 and Y^4 may form a ring so that they form a bicyclic ring system together with the

aromatic ring they are attached to, or Y^1 and Y^2 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^2 and Y^3 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to.

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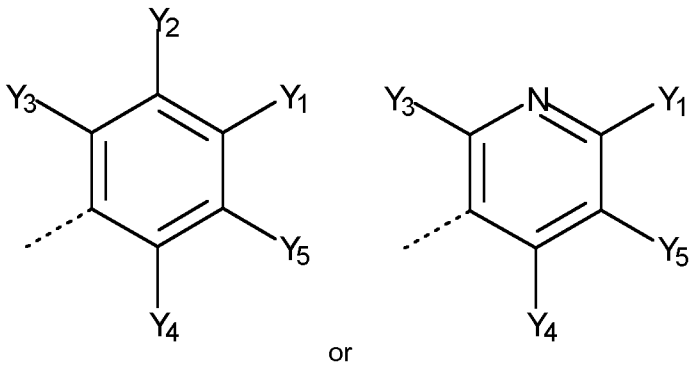
Additionally, Y^1, may be a halogen atom, haloalkoxy,alkoxy, trifluoromethyl, methoxy, difluoromethoxy, or trifluoromethoxy. In some embodiments of the invention and/or embodiments thereof, Y^1, is a halogen atom,or trifluoromethyl, preferably a halogen, preferably a fluorine or a chlorine. Most preferably a chlorine.

Preferably Y^1 is not hydrogen. In a suitable embodiment, Y^1 is halogen, haloalkoxy or alkoxy. Suitably Y^1 is trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, fluorine or a chlorine. Most preferably a trifluoromethyl, methoxy, or chlorine

Suitably Y^2, Y^3, Y^4, Y^5 are each independently a hydrogen, or a halogen atom. Suitably Y^2 is a hydrogen. Suitably Y^3 is a hydrogen. Suitably Y^4 is a hydrogen. Suitably Y^5 is a hydrogen. Y^2 is preferably a halogen, preferably a fluorine. Suitably Y^3 and Y^4 are both hydrogen.

Suitably, Y^3, Y^5 are each independently a halogen atom. Y^5 is suitably a halogen, preferably a chlorine or a fluorine, most preferably a chlorine. Y^3 is suitably a halogen, preferably a chlorine or a fluorine, most preferably a chlorine.

Also compounds are contemplated wherein R^6 is



or

(y-2) (y-1)

In suitable compounds Y^1 and Y^5 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to. In suitable compounds Y^5 and Y^4 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to. In suitable compounds Y^1 and Y^2 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to. In suitable compounds Y^2 and Y^3 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to.

Suitably, Y^1 and Y^5 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to. Suitably Y^1 and Y^2 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to.

The ring formed by Y^1 and Y^5, Y^5 and Y^4, Y^1 and Y^2, or Y^2 and Y^3 may be a heterocycle. The ring formed by Y^1 and Y^5, Y^5 and Y^4 , Y^1 and Y^2, or Y^2 and Y^3 may be aromatic. The ring formed by Y^1 and Y^5, Y^5 and Y^4, Y^1 and Y^2, or Y^2 and Y^3 may be an aromatic heterocycle.

Suitably R^6 is selected from the group consisting of phenyl, cyclopentadienyl, pyrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyranyl, triazinyl, thiopyranyl, oxazinyl, and thiazinyl, dihydropyrolyl, furopyrolyl, thienopyrolyl, benzopyrolyl, benzopyrazolyl, indenyl, indolyl, isoindoly, indolzinyl, indazolyl, benzimidazolyl, azaindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, benzothiadiazolyl, benzothiazolyl, benzisoxazolyl, benzoisothiazolyl, benzoxazolyl, benzodioxolyl, quinolinyl, tetrahydroquinolinyl, dihydroquinolinyl, isoquinolinyl, quinoxalinyl, phtalazinyl, quinazolinyl, quinolizinyl, cinnolinyl, napthpyridinyl, chromenyl, isochromenyl, chromenonyl, chromanyl, benzooxazinyl, quinolinonyl, isoquinolinonyl, .

Suitably R^6 is selected from the group consisting of phenyl, cyclopentadienyl, pyrolyl, pyrazolyl, imidazolyl, triazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyranyl, thiopyranyl, oxazinyl, thiazinyl, dihydropyrolyl, furopyrolyl, thienopyrolyl, benzopyrolyl, benzopyrazolyl, indolzinyl, indazolyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, benzothiadiazolyl, benzothiazolyl, benzisoxazolyl, benzoisothiazolyl, benzoxazolyl, benzodioxolyl, quinolinyl, tetrahydroquinolinyl, dihydroquinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, chromenyl, isochromenyl, chromenonyl, chromanyl, benzooxazinyl, quinolinonyl, isoquinolinonyl.

Suitably R^6 is selected from the group consisting of phenyl, cyclopentadienyl, pyrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, oxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyranyl, thiopyranyl, oxazinyl, thiazinyl, dihydropyrolyl, furopyrolyl, thienopyrolyl, benzopyrolyl, benzopyrazolyl, indolzinyl, indazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, benzodioxolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, quinazolinyl, chromenonyl, chromanyl, benzooxazinyl, quinolinonyl, isoquinolinonyl

Suitably R^6 is selected from the group consisting of phenyl, cyclopentadienyl,pyrazolyl, imidazolyl, furanyl, thiophenyl, pyridinyl, pyrimidinyl, benzopyrazolyl, indolzinyl, indazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzodioxolyl, benzothiazolyl, quinolinyl, quinazolinyl, benzooxazinyl.

Suitably R^6 is selected from the group consisting of phenyl, cyclopentadienyl, pyrazolyl, pyridinyl, benzopyrazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzodioxolyl, benzothiazolyl, quinolinyl,

suitably R^6 is then selected from the group consisting of phenyl, pyrazolyl, indenyl, indolyl, isoindolyl, indozolinyl, benzimidazolyl, azaindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl,

benzothiadiazolyl, benzothiazolyl, benzisoxazolyl, benzoisothiazolyl, benzoxazolyl, benzopyrazolyl, benzodioxolyl, quinolinyl, quinazolinyl,

Suitably R^6 is selected from the group consisting of phenyl, pyrazolyl , benzimidazolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, benzothiadiazolyl, benzothiazolyl, benzisoxazolyl, benzoisothiazolyl, benzoxazolyl, benzopyrazolyl, benzodioxolyl, quinolinyl, quinazolinyl.

Suitably R^6 is selected from the group consisting of phenyl, pyrazolyl , benzimidazolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, benzopyrazolyl,benzodioxolyl, quinolinyl, quinazolinyl,

Suitably R^6 is selected from the group consisting of phenyl, pyrazolyl , benzimidazolyl, benzofuranyl, benzothiophenyl, benzothiazolyl , benzopyrazolyl, benzodioxolyl, quinolinyl, quinazolinyl, benzooxaziny,

Suitably R^6 is selected from the group consisting of phenyl, pyrazolyl benzofuranyl , benzimidazolyl, benzothiophenyl, benzopyrazolyl, benzothiazolyl, benzodioxolyl, quinolinyl, quinazolinyl.

Suitably R^6 is selected from the group consisting of phenyl, pyrazolyl, benzofuranyl, benzothiophenyl, benzopyrazolyl, benzothiazolyl, benzodioxolyl, quinolinyl, quinazolinyl.

Suitably R^6 is selected from the group consisting of phenyl, pyrazolyl, benzopyrazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, benzodioxolyl.

Suitably R^6 is selected from the group consisting of phenyl, pyrazolyl, benzopyrazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, benzodioxolyl.

Suitably R^6 is selected from the group consisting of phenyl, benzothiophenyl, or benzodioxolyl.

R^6 is optionally substituted with substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}-haloalkyl, C_{1-4}-alkyloxy, C_{1-4}-haloalkyloxy, and halogen. R^6 is optionally substituted with substituents selected from the group consisting of halogen, C_{1-4}-haloalkoxy or C_{1-4}-alkoxy and C_{1-4}alkyl. R^6 is optionally substituted with substituents selected from the group consisting of trifluoromethyl, methyl, methoxy, difluoromethoxy, trifluoromethoxy, fluorine or a chlorine. R^6 is optionally substituted with substituents selected from the group consisting of trifluoromethyl, methyl, methoxy, fluorine, or chlorine.

Suitably, R^7 is a six- or five membered aryl or aromatic heterocycle. Suitably R^7 is phenyl or cyclopentadienyl or, a six- or five-membered aromatic heterocycle with at least one heteroatom selected from the group consisting of S, O or N. Suitable the aryl or aromatic heteroclycle of R^7 is selected from the group consisting of phenyl, cyclopentadienyl, pyrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyranyl, triazinyl, thiopyranyl, oxazinyl, and thiazinyl,

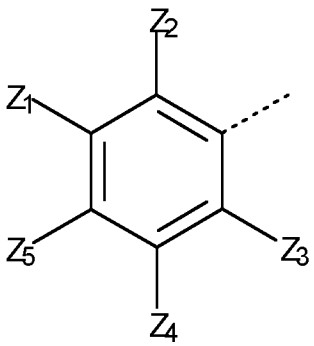
Suitably the aryl or aromatic heteroclycle of R^7 is selected from the group consisting of phenyl, cyclopentadienyl, pyrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyridazinyl,

Suitably the aryl or aromatic heteroclycle of R^7 is selected from the group consisting of phenyl, cyclopentadienyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, and pyrimidinyl,

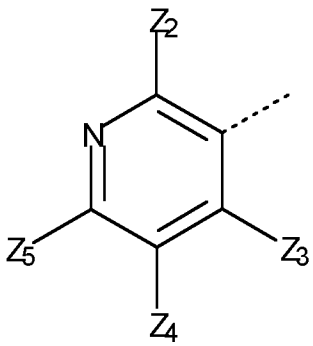
Suitably the aryl or aromatic heterocycle of R^7 is substituted. Suitable substituents of the aryl or aromatic heterocycle of R^7 may be a halogen atom or C_1-C_4 haloalkyl, or C_1-C_4 haloalkyl. Suitably, the substituents of the aryl or aromoatic heterocycle of R^7 is methyl, halogen or halogenated methyl. Suitably, the substituents of the aryl or aromoatic heterocycle of R^7 is fluorine, chlorine, bromine, methyl, monofluormethyl, difluormethyl, trifluormethyl, monochloromethyl, dichloromethyl, trichloromethyl. Suitably, the substituents of the aryl or aromoatic heterocycle of R^7 is fluorine, chlorine, bromine, methyl, and trifluormethyl.

The aryl or aromatic heterocycle of R^7 may be optionally substituted. Optionally R_7 is substituted with a substituent selected from the group consisting of halogen atom, nitro, C_1-C_4 alkyl or C_1-C_4 haloalkyl. Optionally R_7 is substituted with a substituent selected from the group consisting of halogen C_1-C_4 alkyl or C_1-C_4 haloalkyl. Optionally R_7 is substituted with a substituent selected from the group consisting of chlorine, fluorine, methyl, or trifluormethyl.

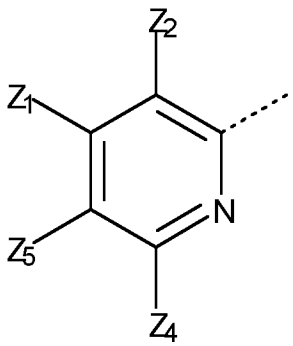
In the compound of the invention R^7 may be selected from the group consisting of;



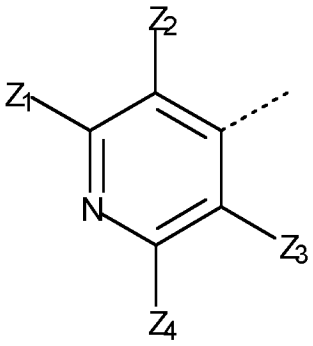
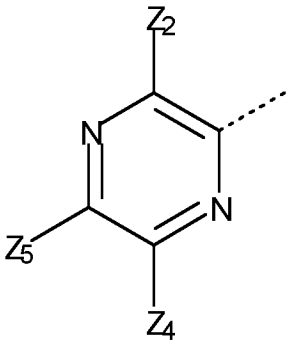
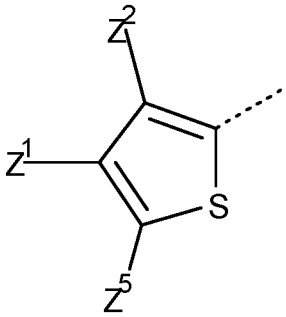
(z-1)



(z-2)



(z-3)

, and

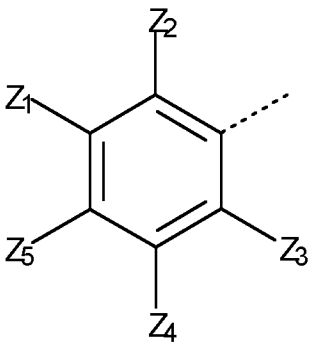
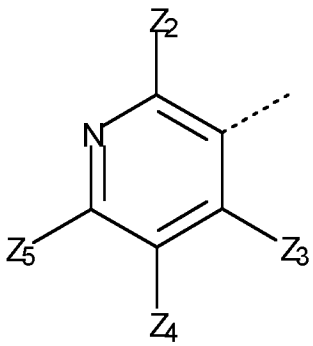
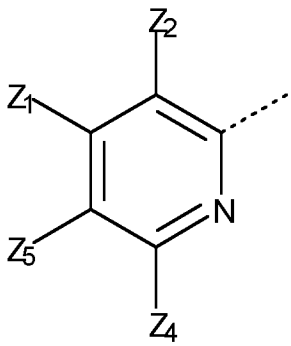
(z-4) (z-5) (z-6)

wherein $Z^{2,}$ Z^3 are each independently a hydrogen, halogen atom, nitro, C_1-C_4 alkyl or C_1-C_4 haloalkyl,

Z^1, Z^4, Z^5 are each independently hydrogen, a halogen atom, or C_1-C_4 alkyl.

In suitably compounds R^7 is (z-1), (z-2), or (z-3). Suitably, R^7 is (z-1) or (z-2). Most suitably, R^7 is (z-1).

Suitably R^7 is selected from the group consisting of;

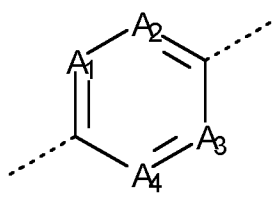
, , ,

(z-1) (z-2) (z-3)

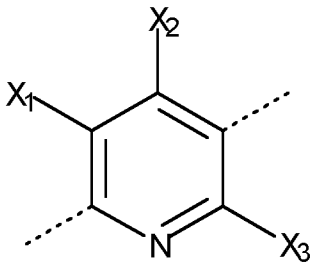
Further, suitably in certain compounds, Z^2 is a halogen atom or C_1-C_4 haloalkyl.

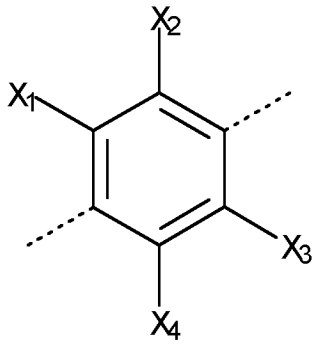
In addition, Z^2 may be chlorine or CF_3.

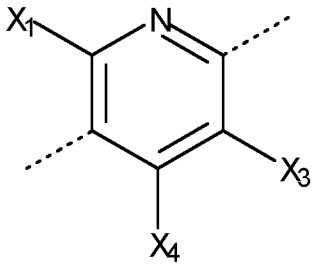
Moreover Z^1, Z^4, Z^5 may each be hydrogen, preferably at least two of . Z^1, Z^4, Z^5 are hydrogen, preferably all of Z^1, Z^4, Z^5 are hydrogen.



is selected from the group consisting of


(x-1)

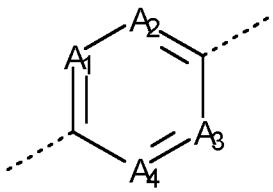

(x-2)


(x-3)

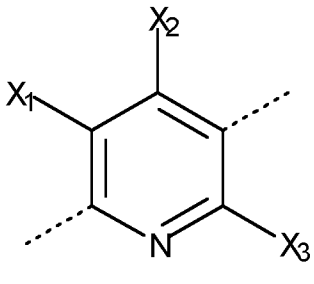
wherein X^1 and X^4 are each independently a hydrogen atom, a halogen atom, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy or C_1-C_4 alkylthio,

X^2 and X^3 are each independently a hydrogen atom, a halogen atom or methyl;

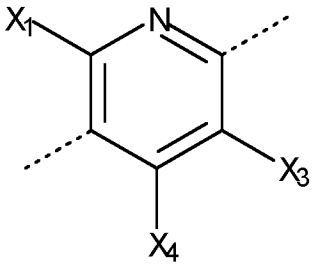
Optionally,



is selected from the group consisting of

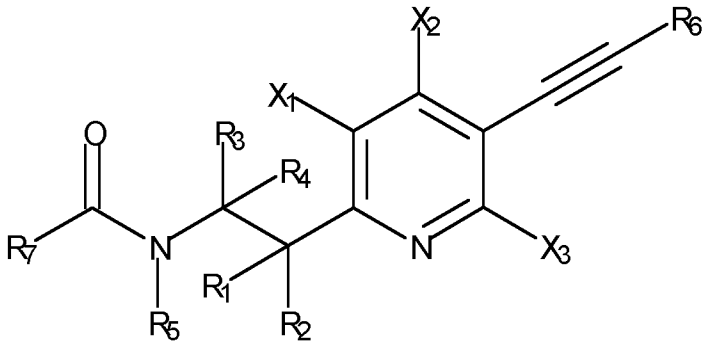

(x-1)

, and


(x-3)

.

The invention is further directed to compounds of formula (II)


(II)

In certain embodiments of the invention and/or embodiments thereof, X^1 is a halogen atom, preferably a chlorine.

Further in other embodiments of the invention and/or embodiments thereof, X^2 and X^3 are hydrogen.

Optionally, X^1 and X^4 are each independently a hydrogen atom, a halogen atom, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy or C_1-C_4 alkylthio,
Optionally, X^1 and X^4 are each independently a hydrogen atom, a halogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy.
Optionally, X^1 and X^4 are each independently a hydrogen atom, a chlorine, C_1-C_4 alkyl, or C_1-C_4 haloalkyl.
Optionally, X^1 is not hydrogen. Optionally X^1 is chlorine, methyl, triflluormethyl, methoxy, trifluormethyloxy
Optionally, X^4 is hydrogen. Optionally X^4 is hydrogen, chlorine, methyl, triflluormethyl, methoxy, trifluormethyloxy,

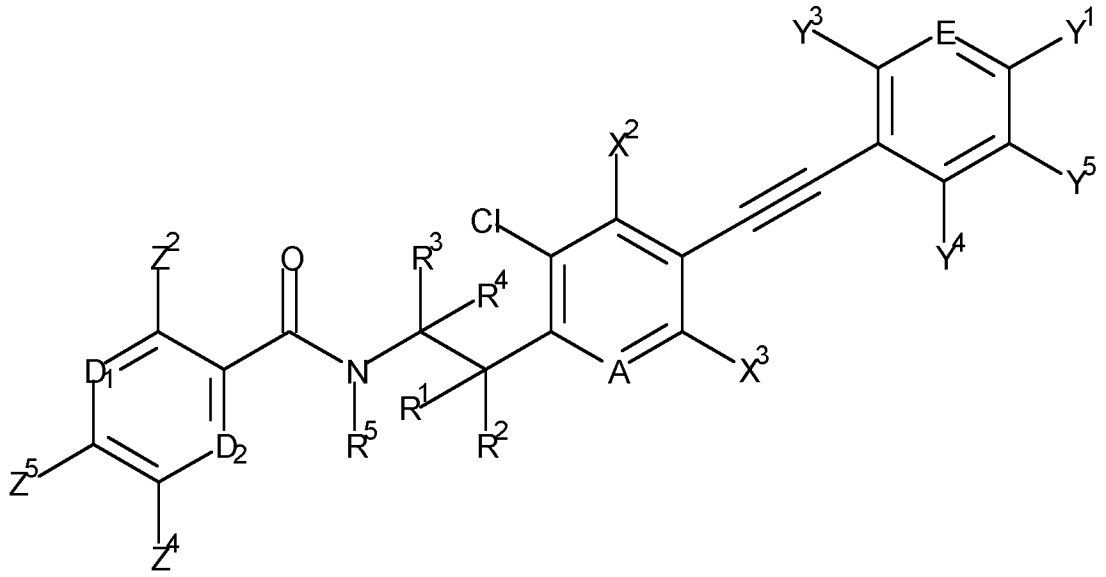
X^2 and X^3 are each independently a hydrogen atom, a halogen atom or methyl. Optionally X^2 and X^3 are each independently a hydrogen, a chlorine or a methyl.

R^8 may be selected from the group consisting of cyano, $-OR^{10}$, C_1-C_4 alkylthio, C_1-C_4 alkoxycarbonyl, $-C(=O)NH_2$ or $-C(S)NH_2$. Suitably R^8 may be selected from the group consisting of cyano, $-OR^{10}$, C_1-C_4 alkoxycarbonyl, $-C(=O)NH_2$ or $-C(S)NH_2$. R^8 may be selected from the group consisting of cyano, $-OR^{10}$, C_1-C_4 alkoxycarbonyl, or $-C(=O)NH_2$. R^8 may be selected from the group consisting of cyano, $-OR^{10}$, or $-C(=O)NH_2$. R^8 may be selected from the group consisting of cyano,or $-OR^{10}$.

In certain embodiments of the invention and/or embodiments thereof, R^9 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, C_3-C_4 cycloalkyl or C_2-C_4 alkenyl. Suitably, R^9 is C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, or C_3-C_4 cycloalkyl. Suitably R^9 is C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, or C_2-C_4 alkenyl. Suitably R^9 is C_1-C_4 alkyl, or C_1-C_4 alkoxymethyl. Suitably R^9 is C_1-C_4 alkyl. Suitably R^9 is methyl, ethyl, propyl or butyl. Suitably R^9 is hydrogen.

R^{10} is hydrogen, C_1-C_4 alkyl, C_2-C_4 haloalkyl, C_1-C_4 alkylcarbonyl, C_3-C_6 cycloalkylcarbonyl or C_1-C_4 alkoxycarbonyl. In some embodiments of the invention and/or embodiments thereof R^{10} is hydrogen, C_1-C_4 alkyl, or C_2-C_4 haloalkyl, Suitably R^{10} is C_1-C_4 alkyl, or C_2-C_4 haloalkyl, Optionally R^{10} is hydrogen, or C_1-C_4 alkyl, Optionally R^{10} is hydrogen, Optionally R^{10} is C_1-C_4 alkyl,

In a suitable embodiment of the invention and/or embodiments thereof the compoundis according to formula (III)

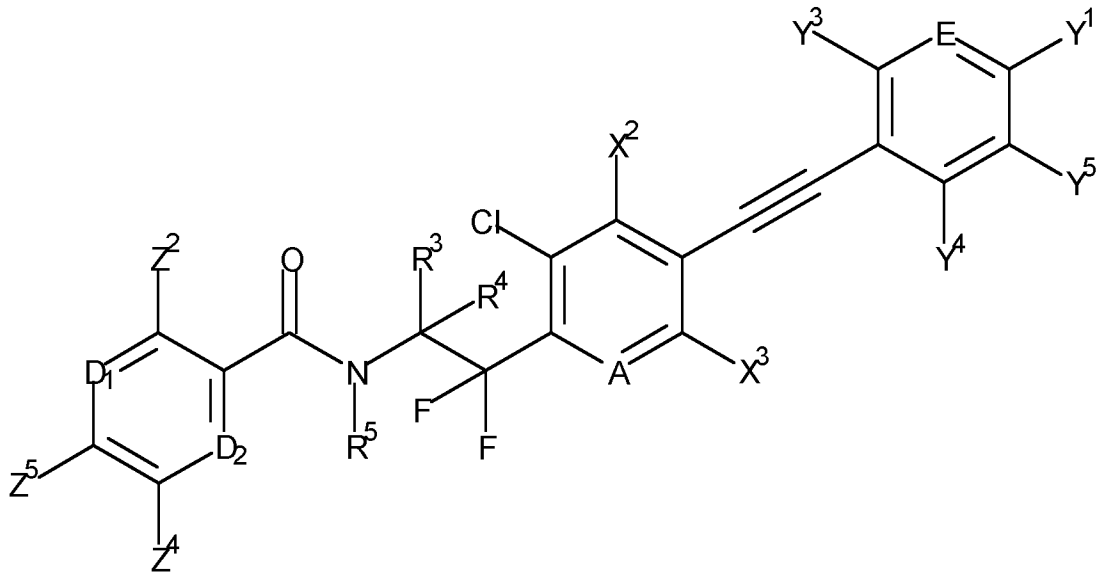


(III)

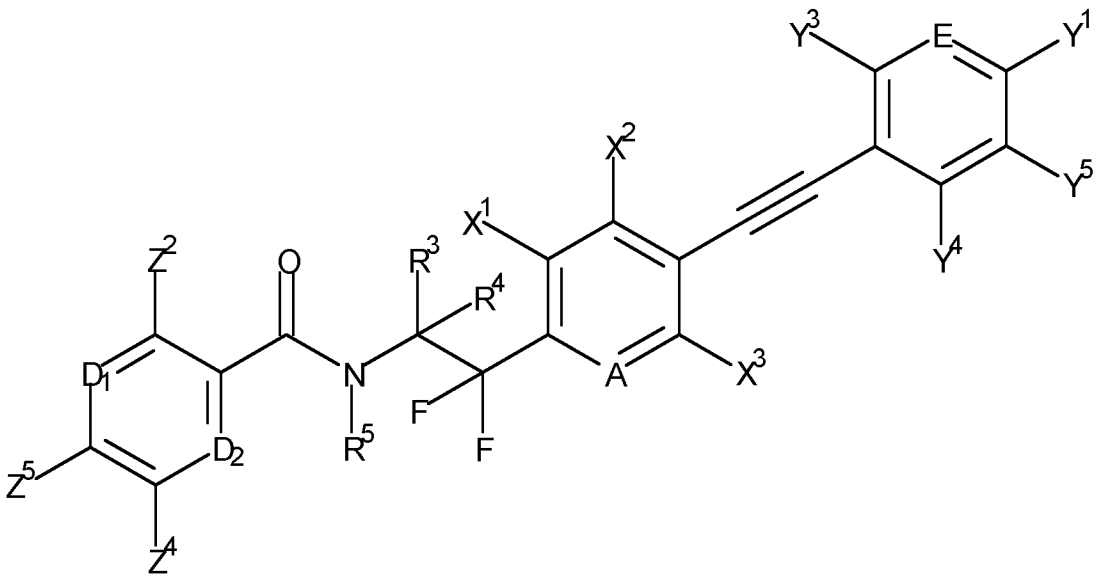
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^1, R^2, R^3, R^4, R^5, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (IV) or (V)



(IV)

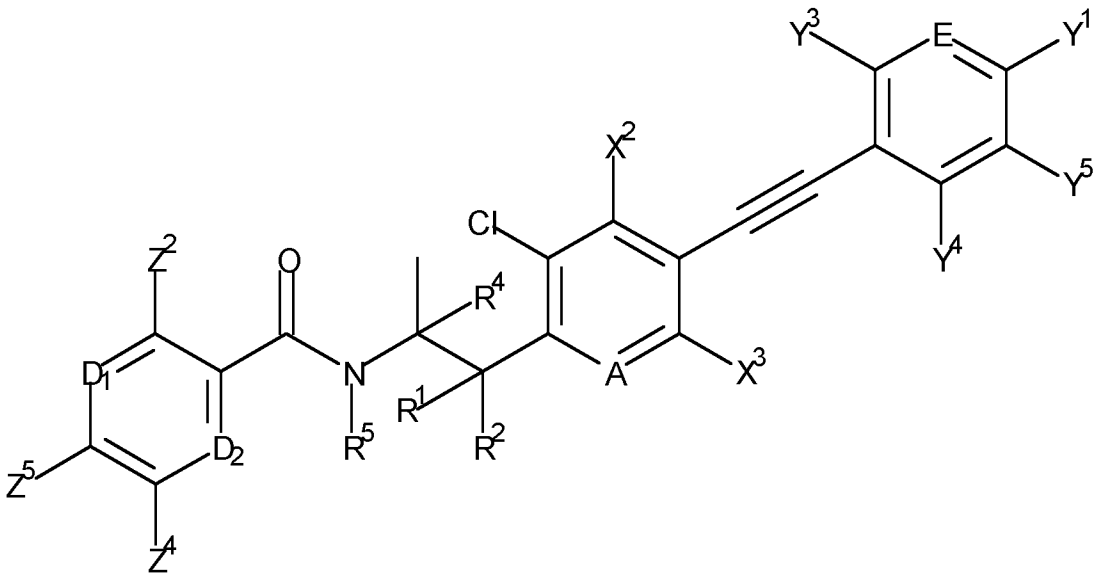


(V)

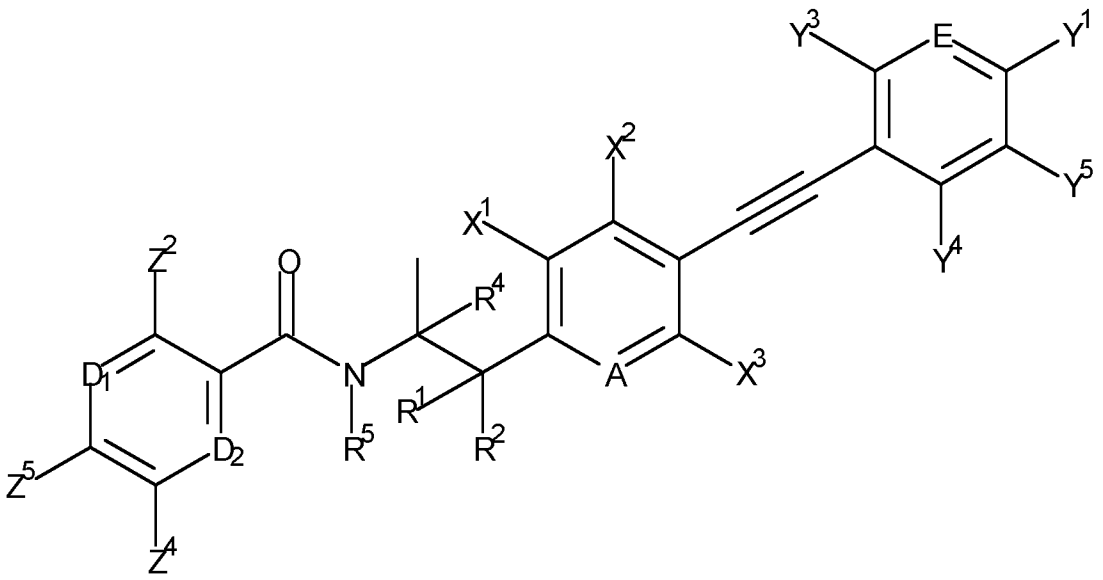
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (VI) or (VII)



(VI)

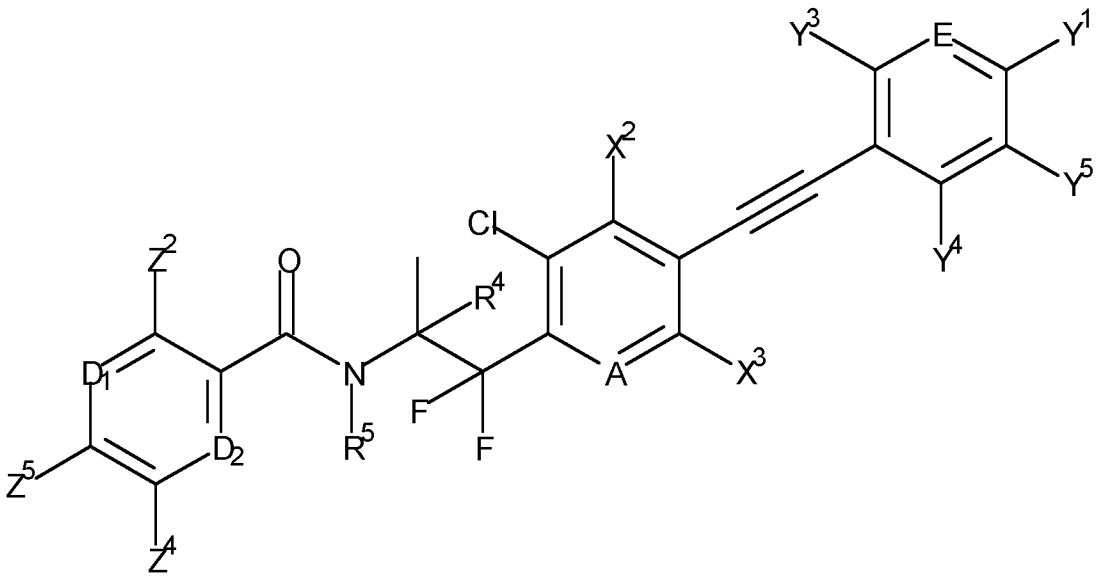


(VII)

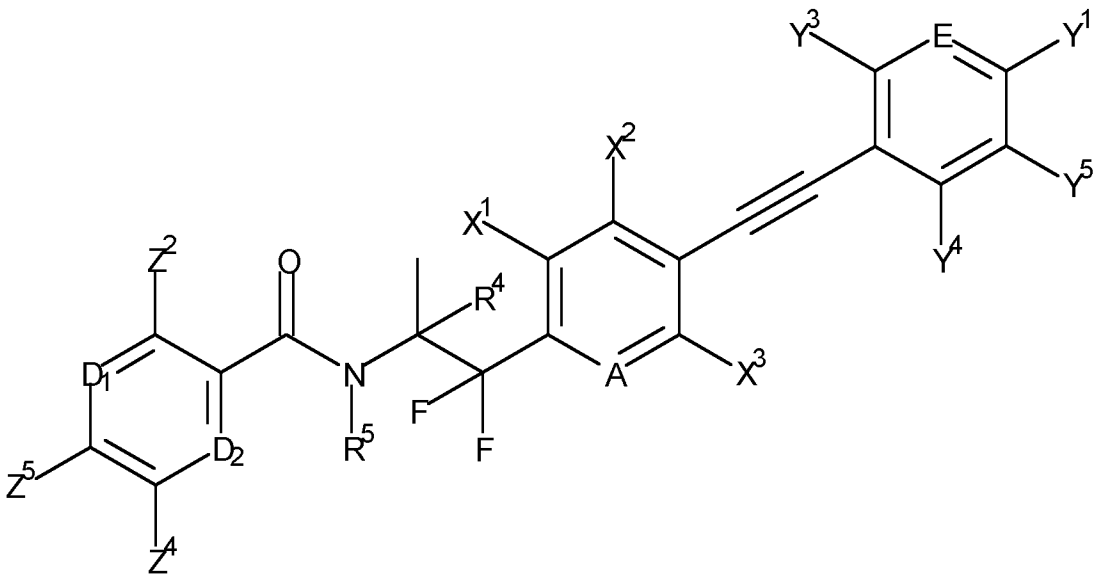
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^1, R^2, R^4, R^5, X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (VIII) or (IX)



(VIII)

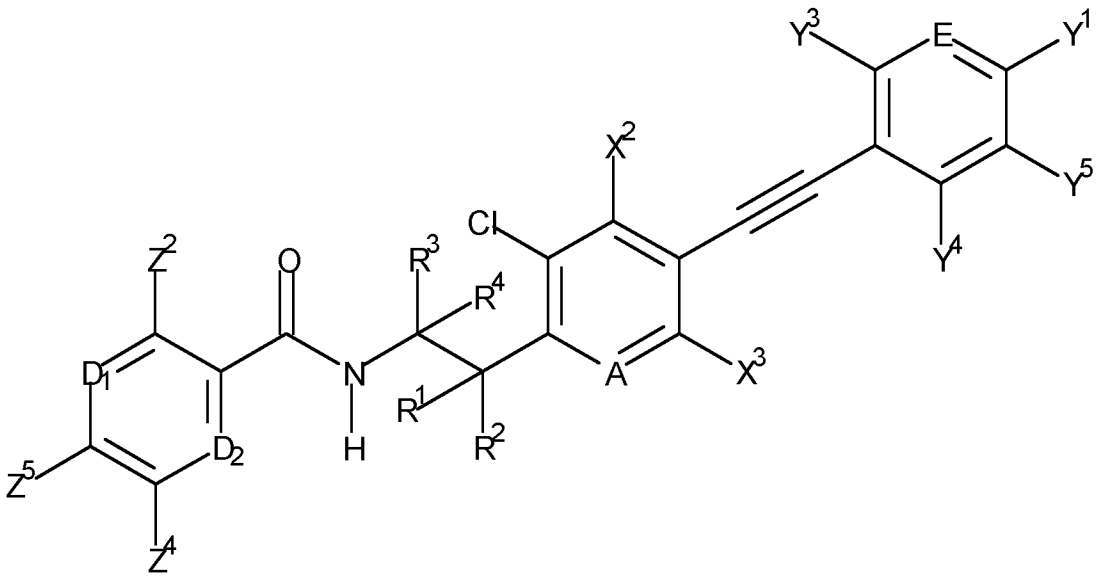


(IX)

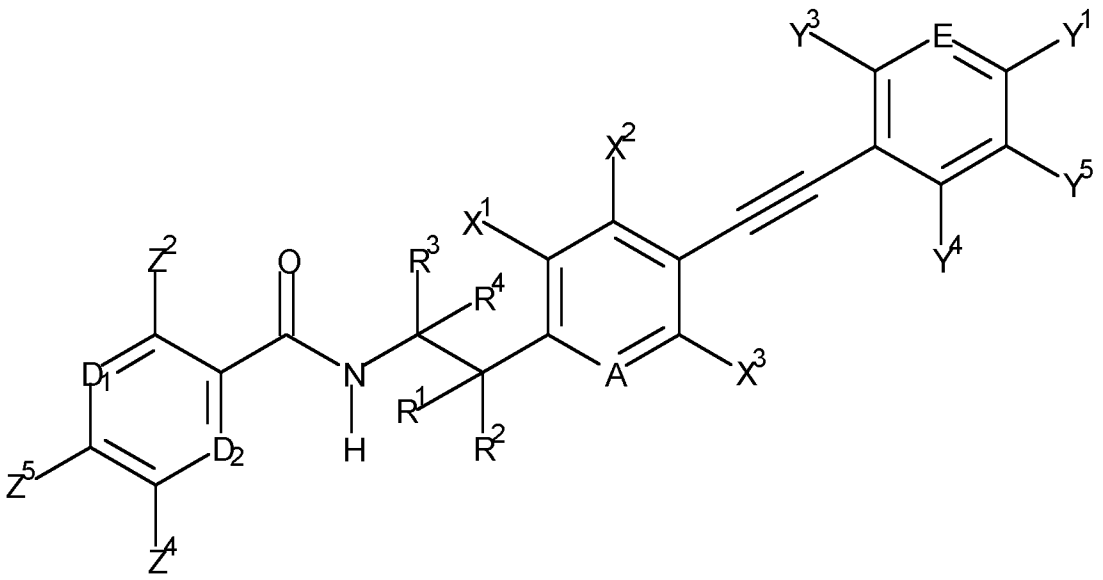
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^4, R^5, X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (X) or (XI)



(X)

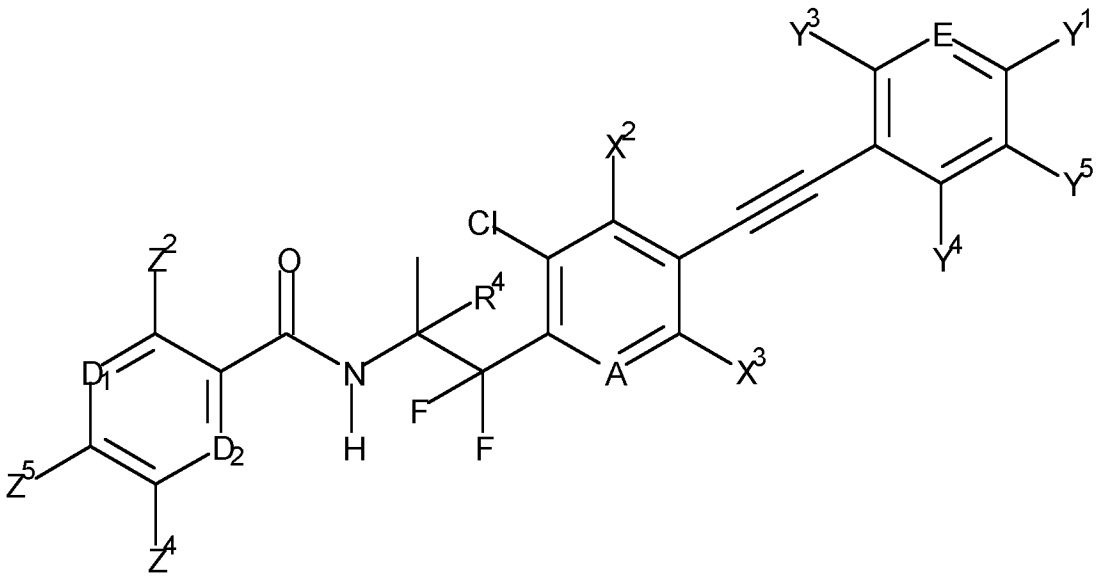


(XI)

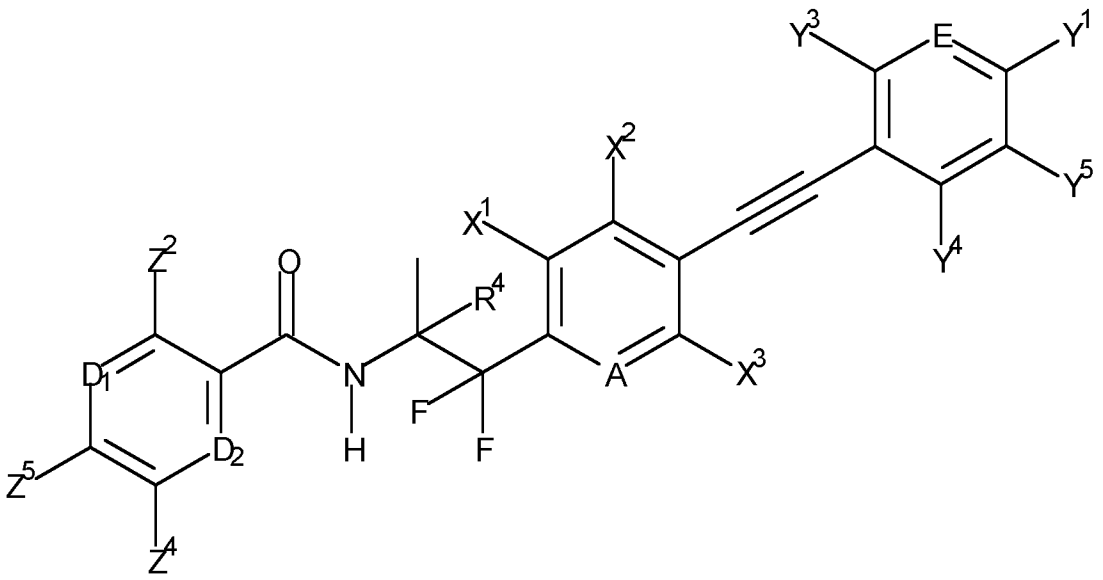
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5, X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XII) or (XIII)



(XII)

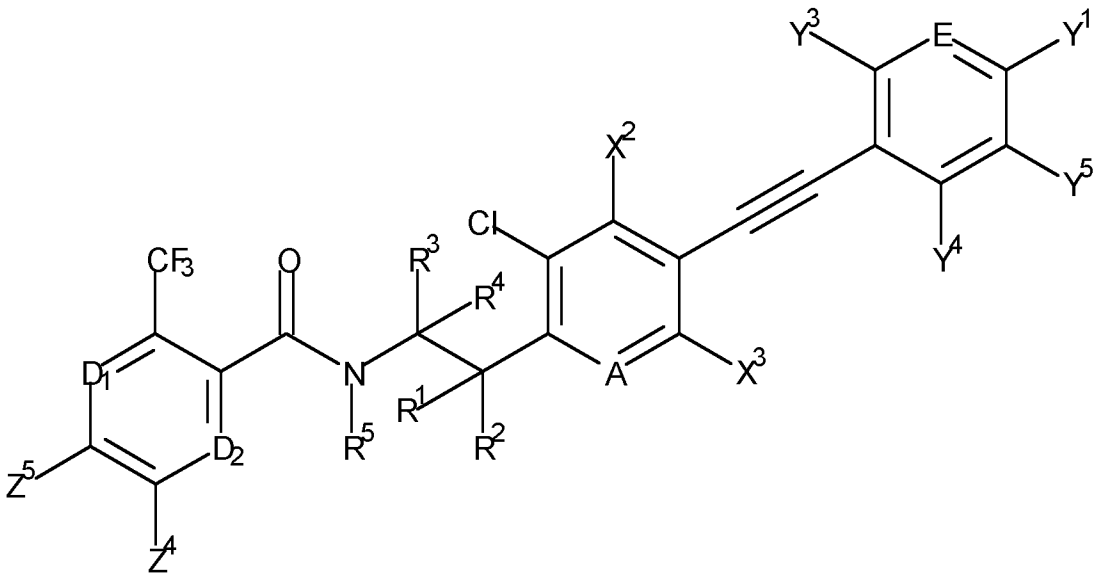


(XIII)

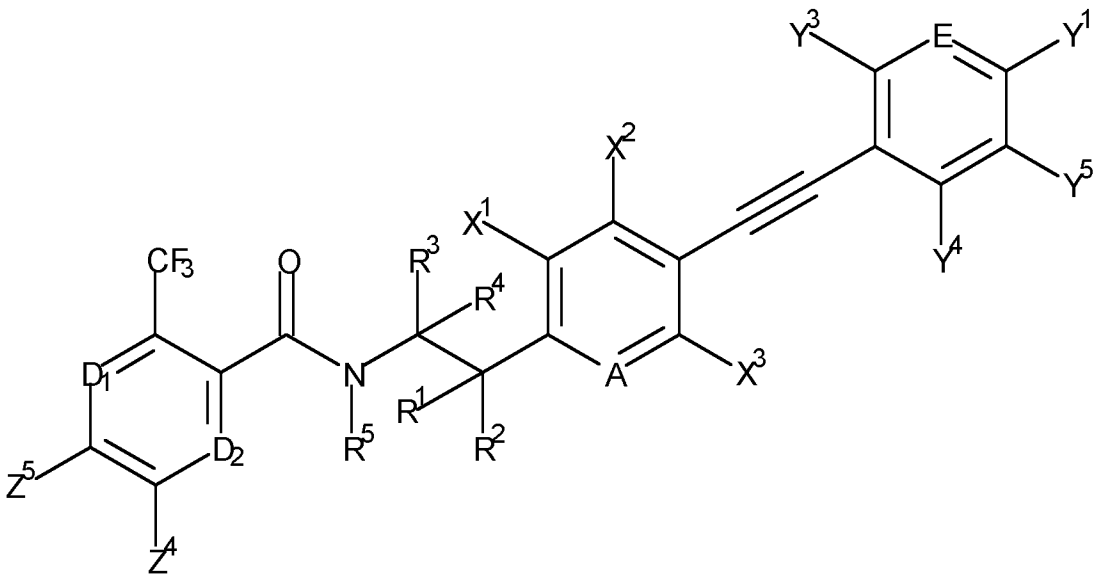
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^4, X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XIV) or (XV)



(XIV)

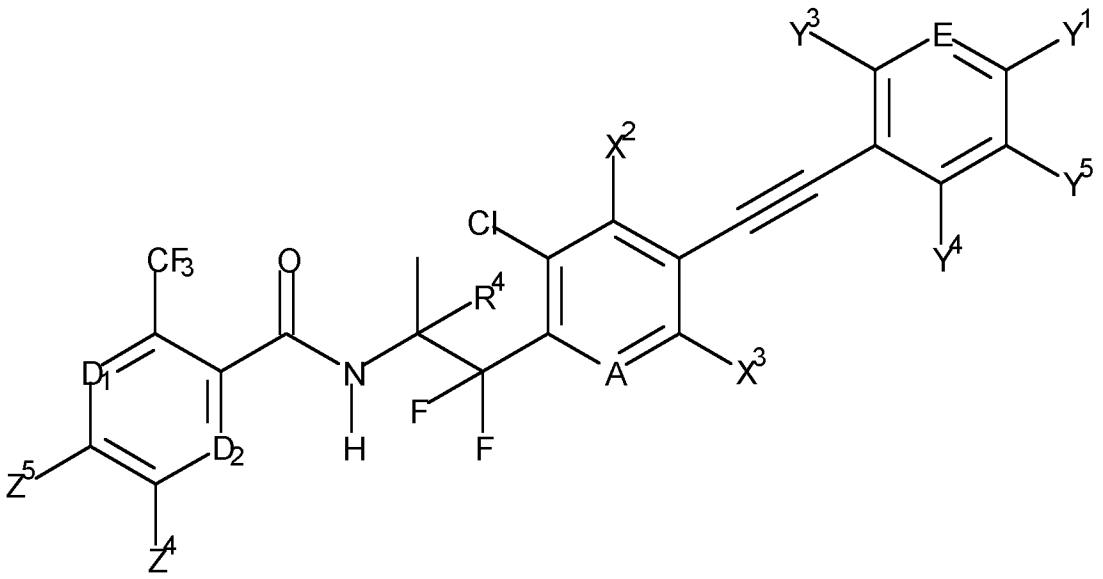


(XV)

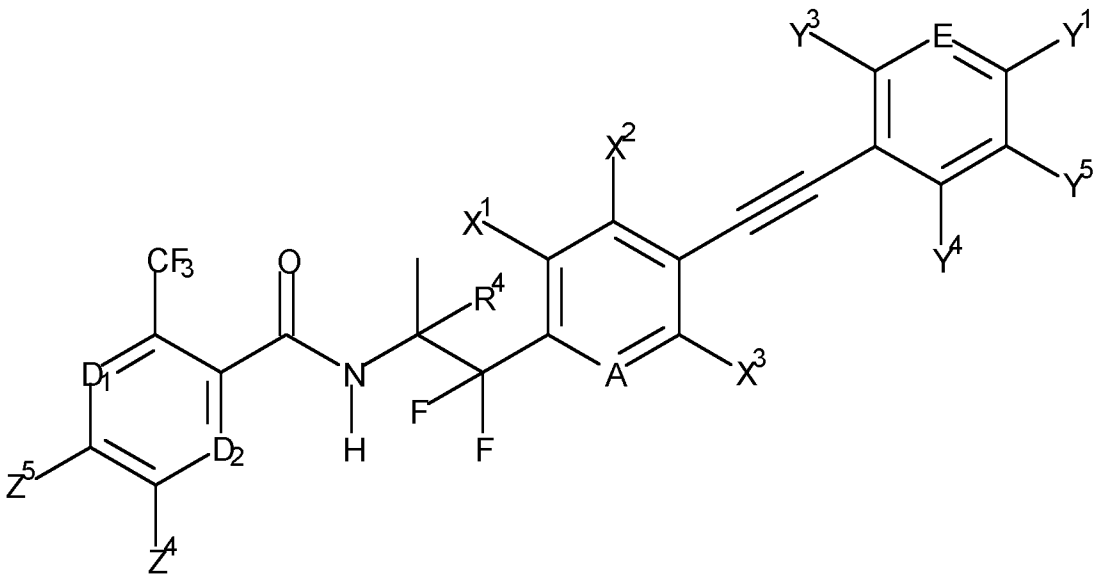
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5, X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1,Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XVI) or (XVII)



(XVI)

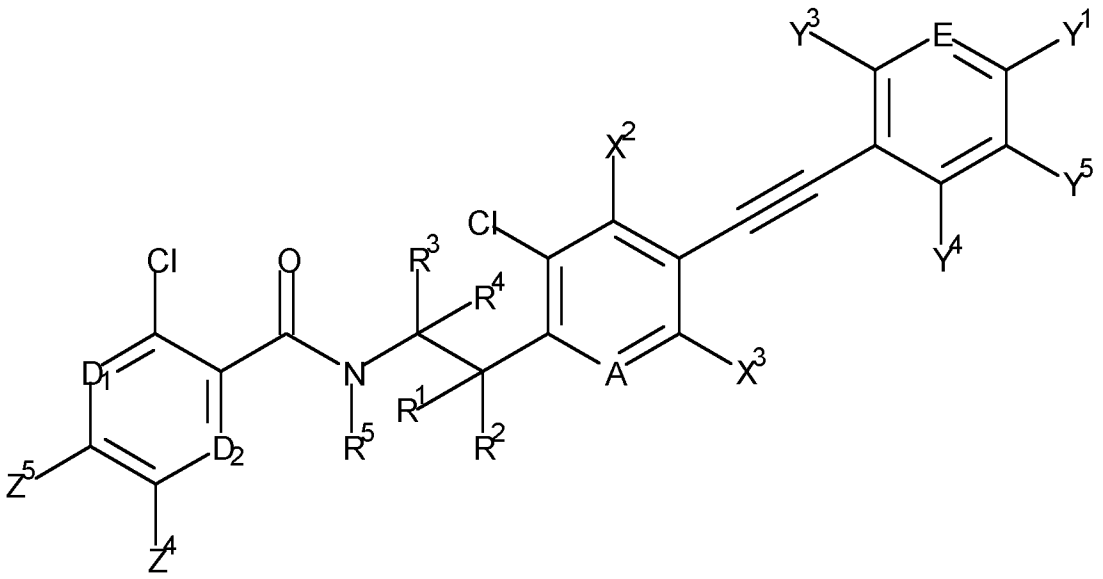


(XVII)

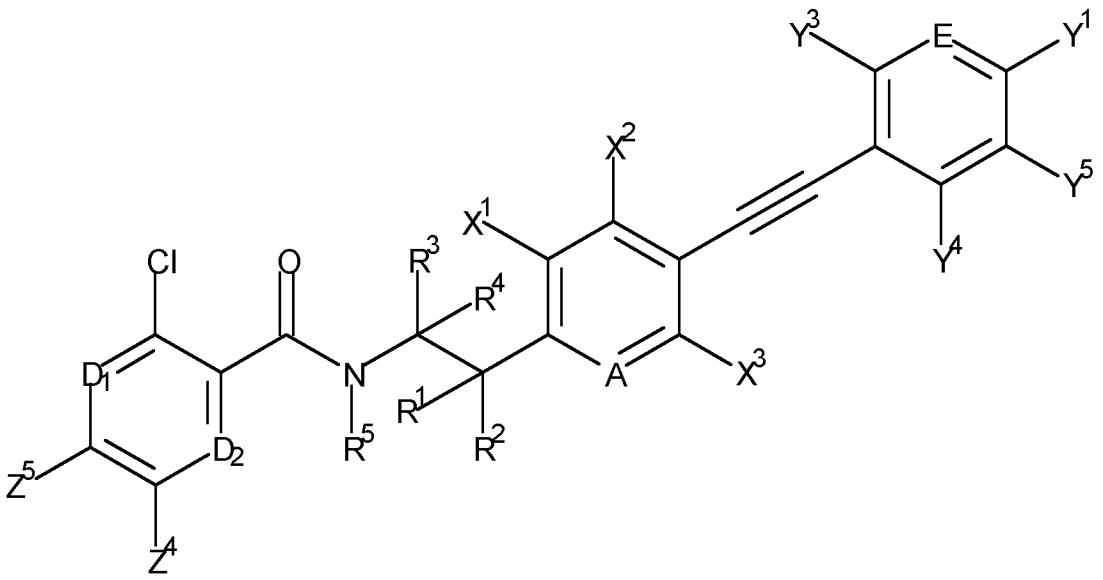
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^4,X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XVIII) or (XIX)



(XVIII)

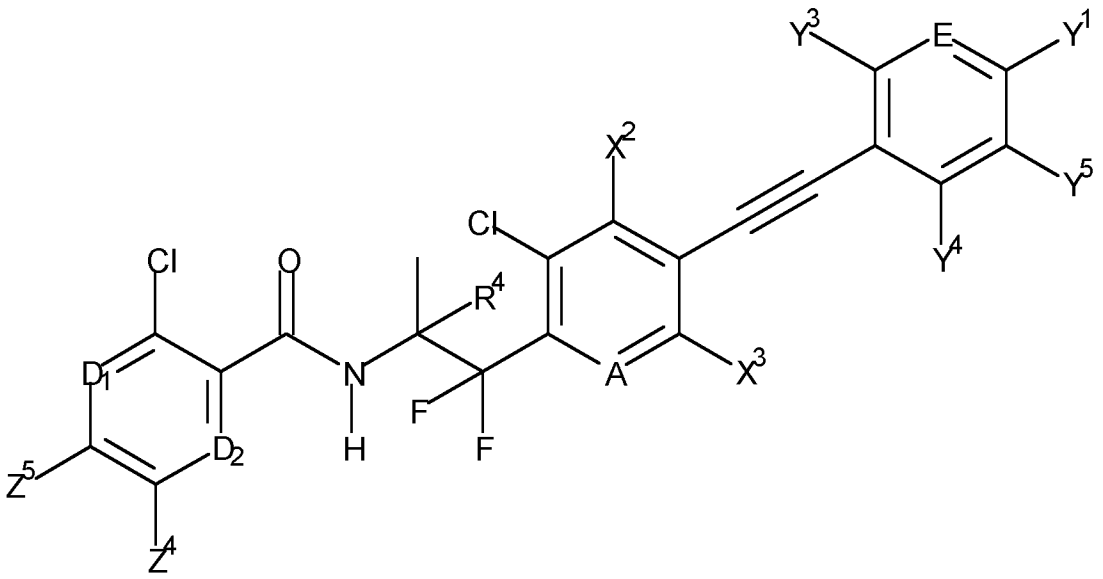


(XIX)

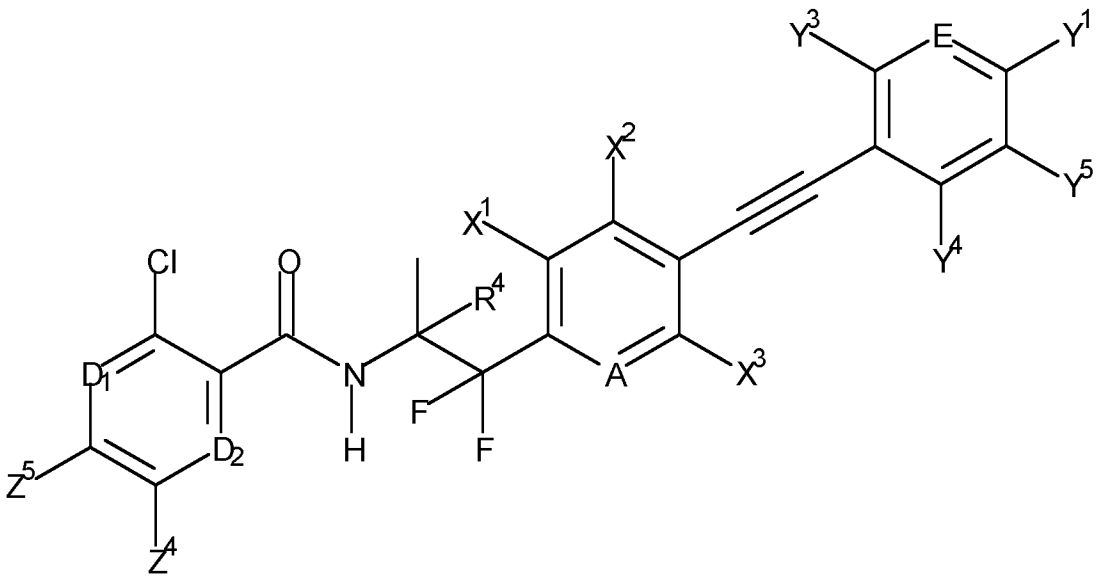
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XX) or (XXI)



(XX)

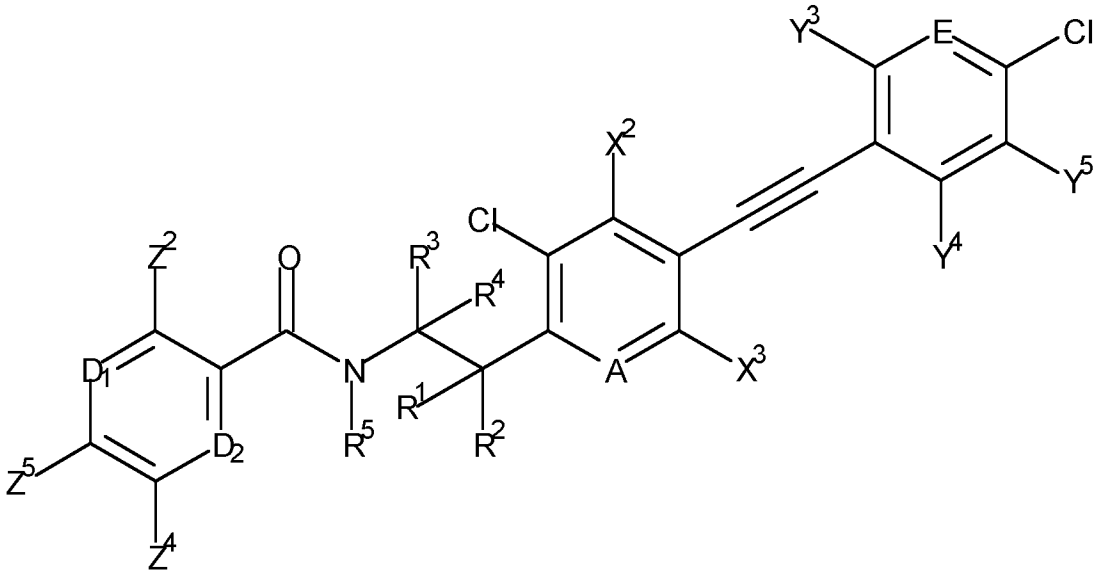


(XXI)

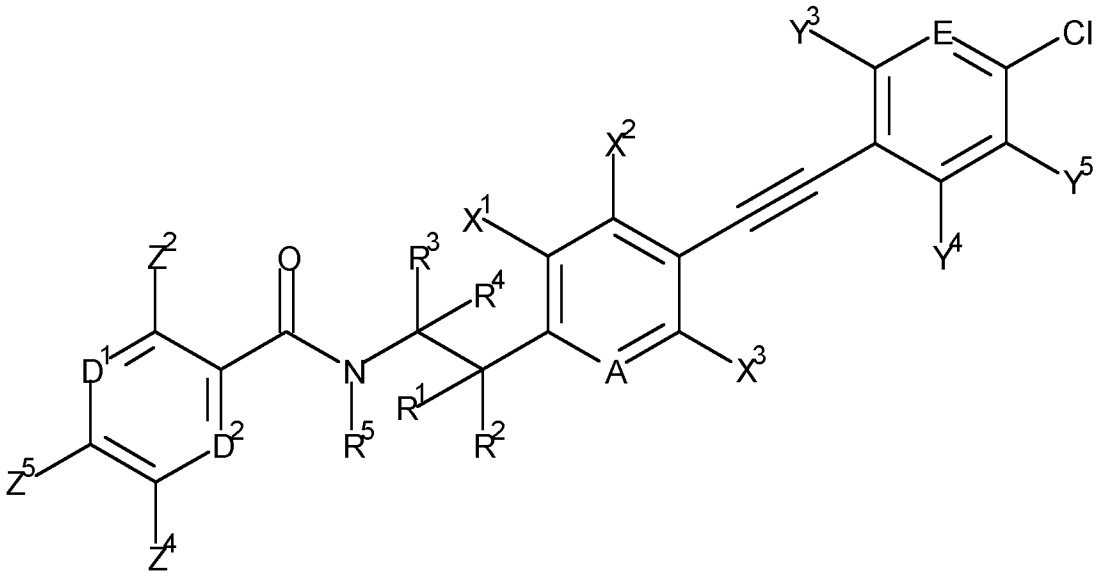
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^4,X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXII) or (XXIII)



(XXII)

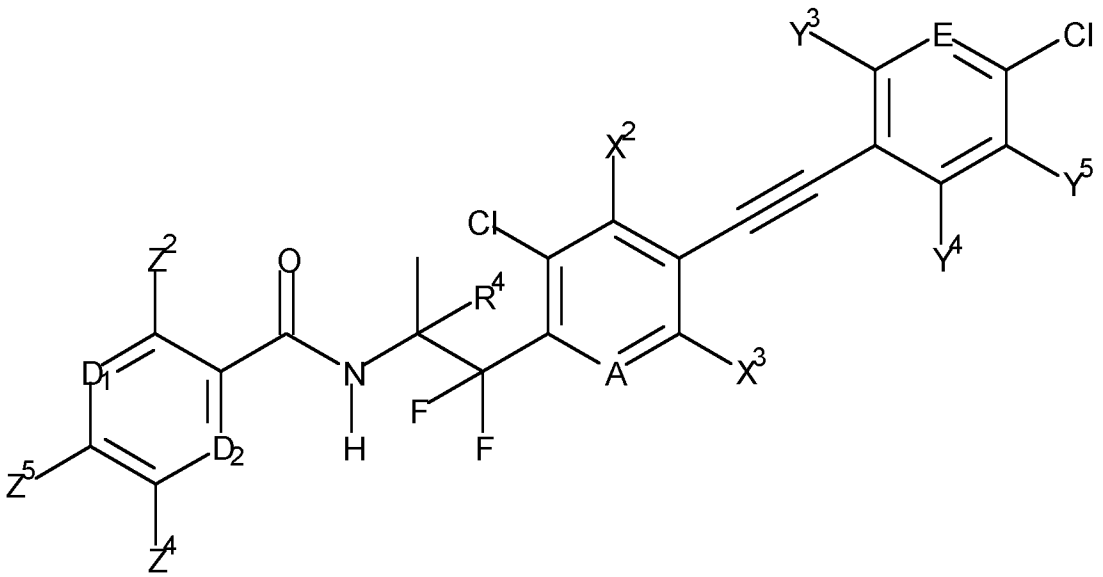


(XXIII)

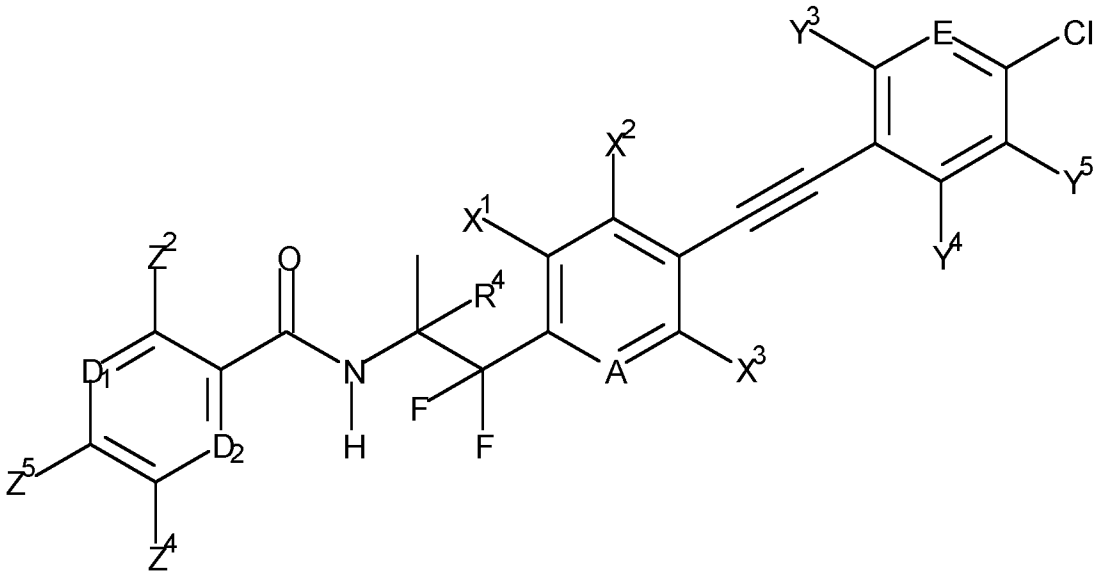
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXIV) or (XXV)



(XXIV)

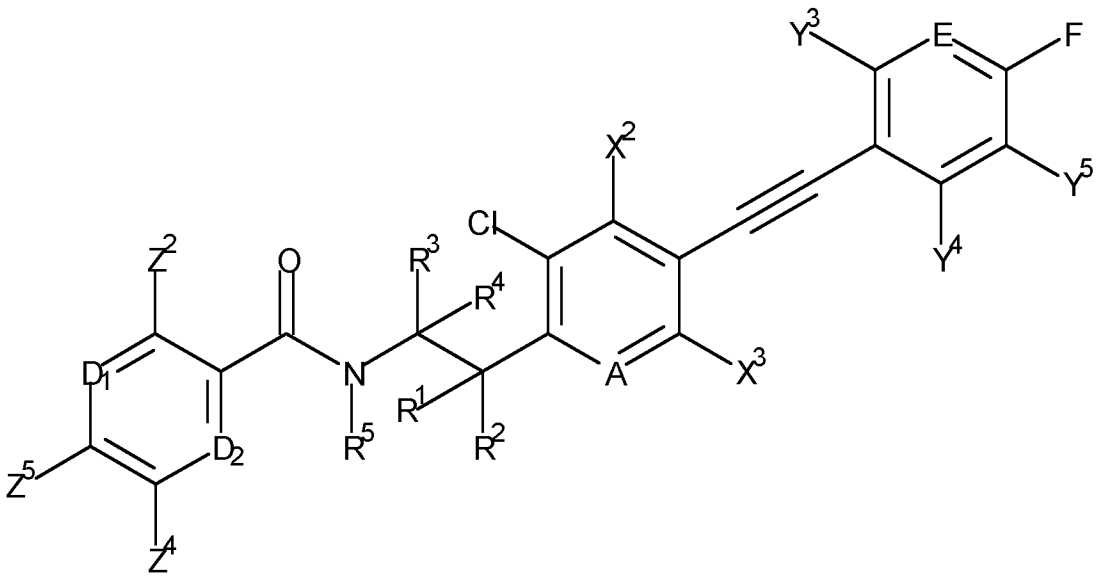


(XXV)

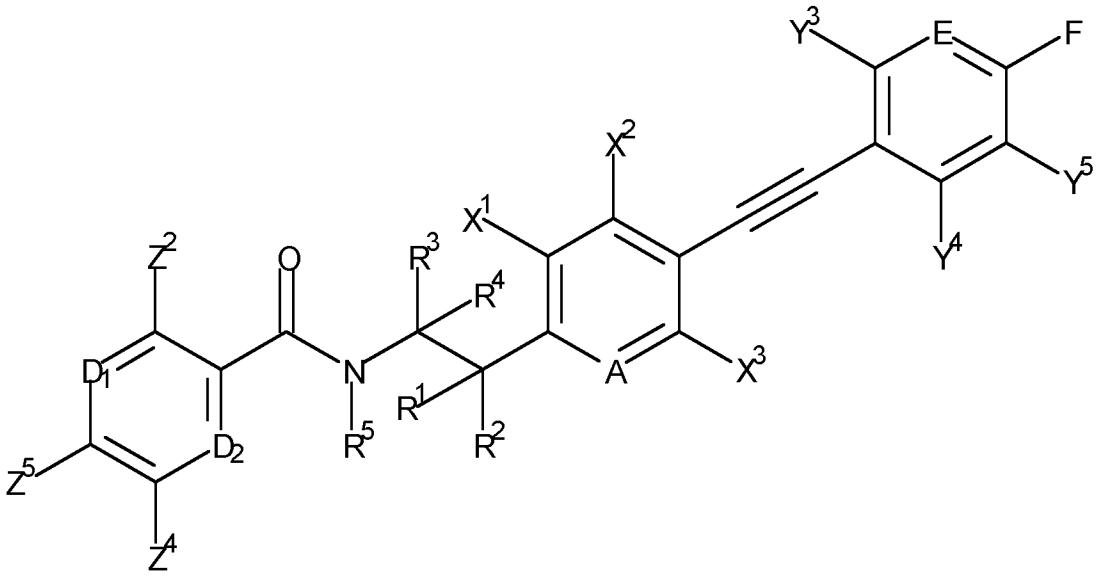
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^4, ,X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXVI) or (XXVII)



(XXVI)

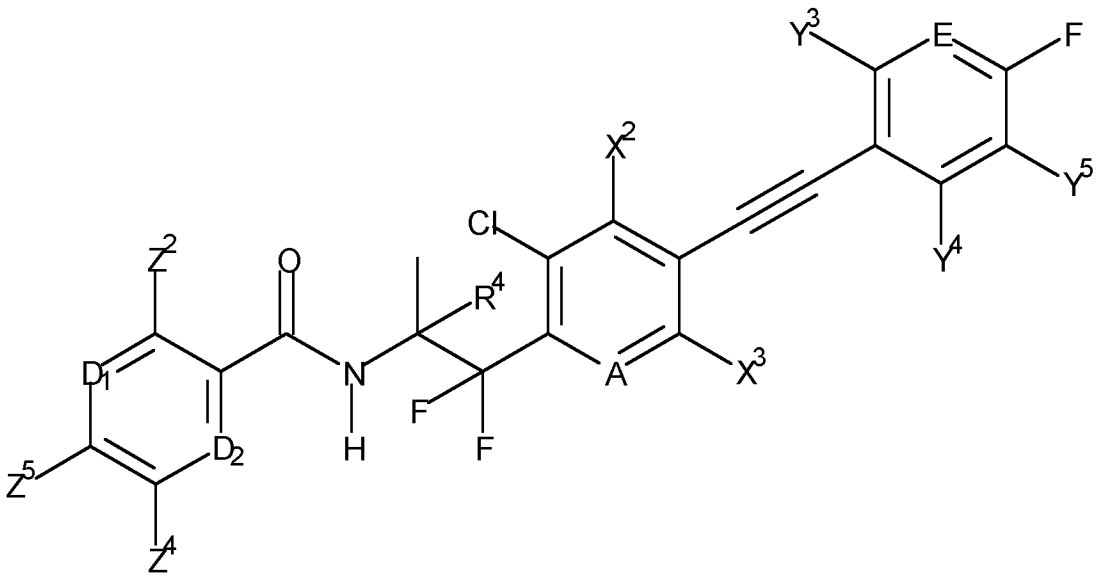


(XXVII)

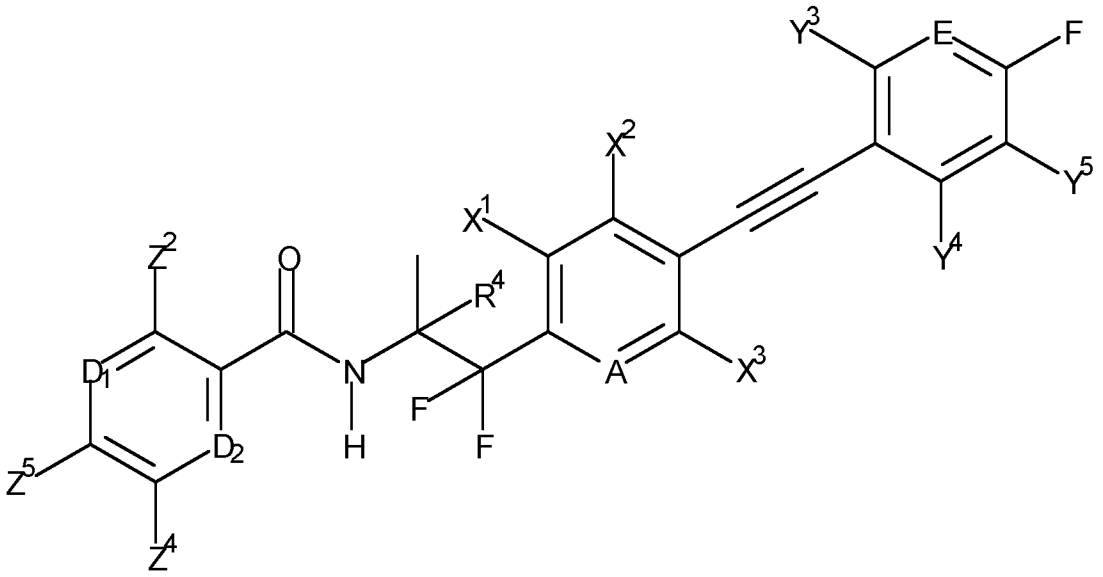
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXVIII) or (XXIX)



(XXVIII)

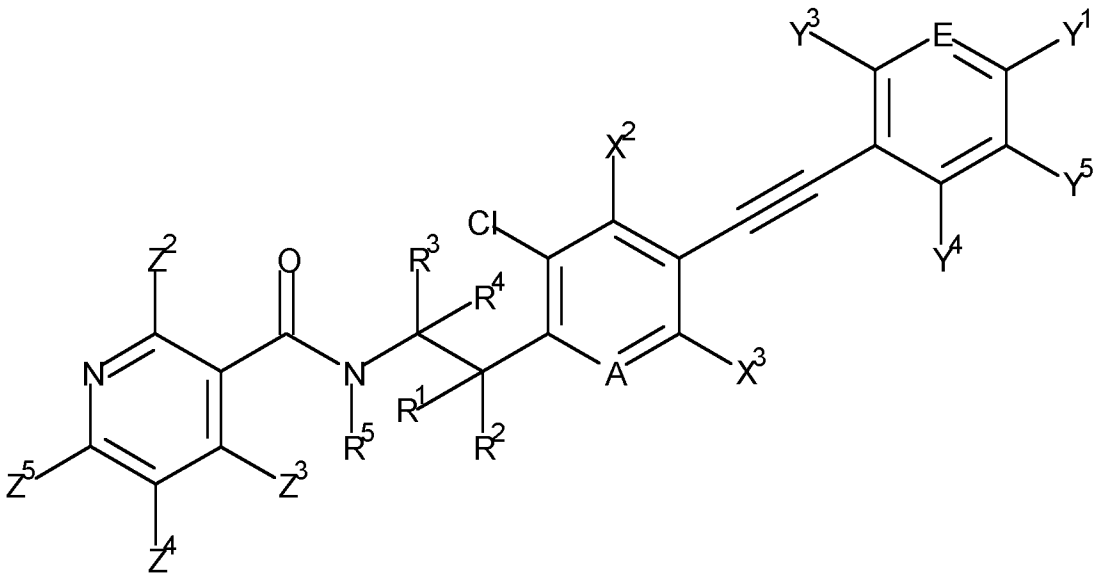


(XXIX)

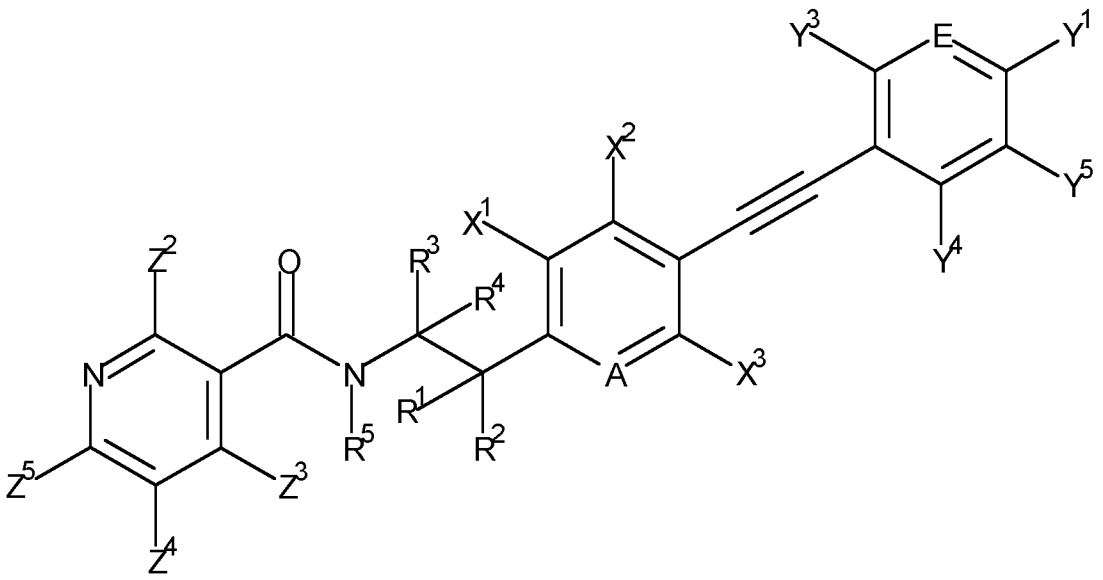
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is C-Y^2 or N; and wherein R^4, ,X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXXI) or (XXXII)



(XXX)

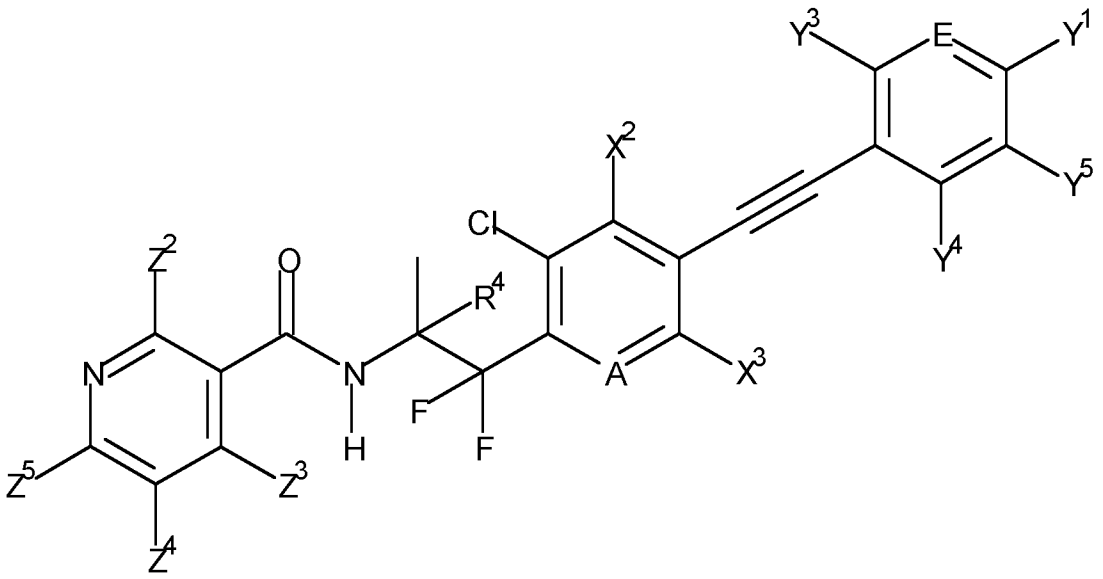


(XXXI)

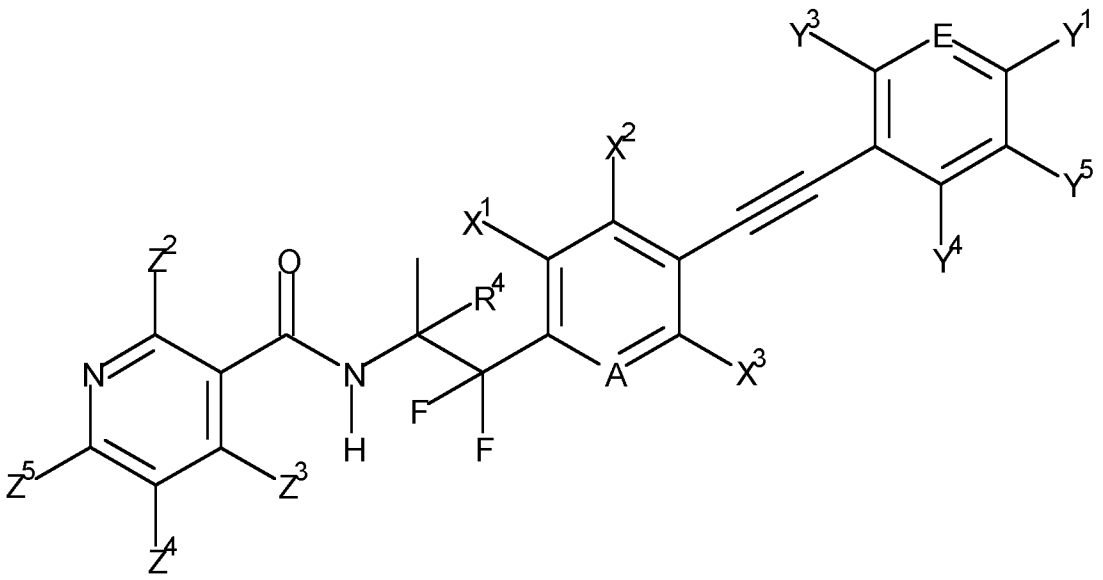
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXXII) or (XXXIII)



(XXXII)

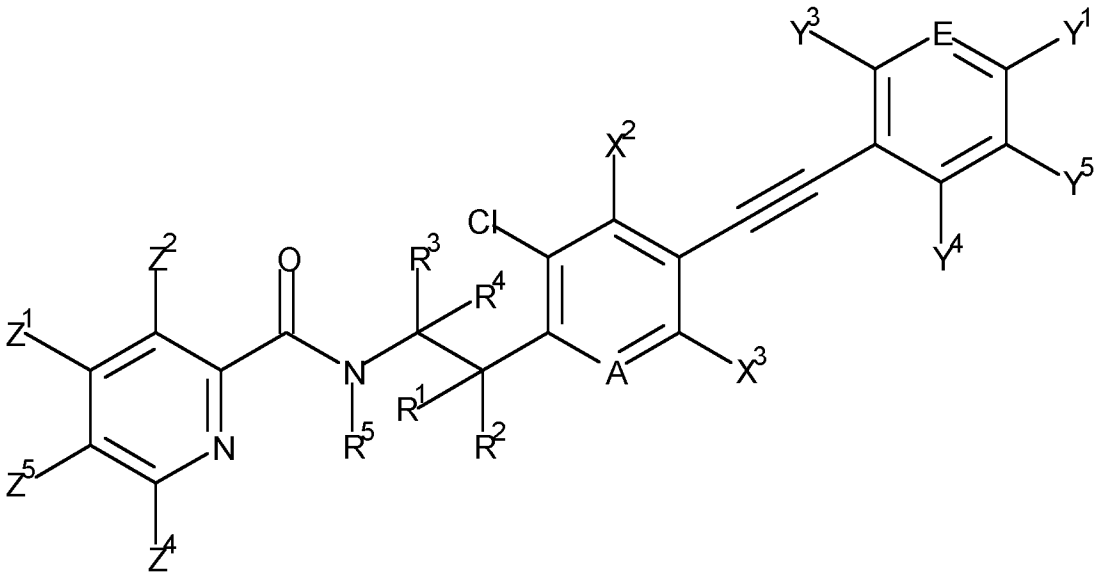


(XXXIII)

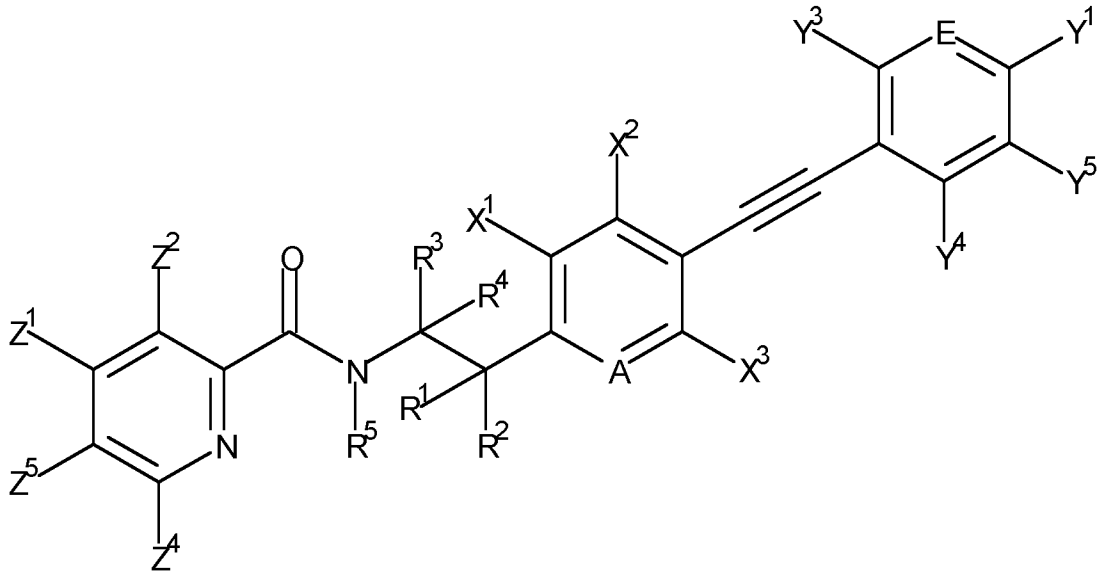
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is C-Y^2 or N; and wherein R^4, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXXIV) or (XXXV)



(XXXIV)

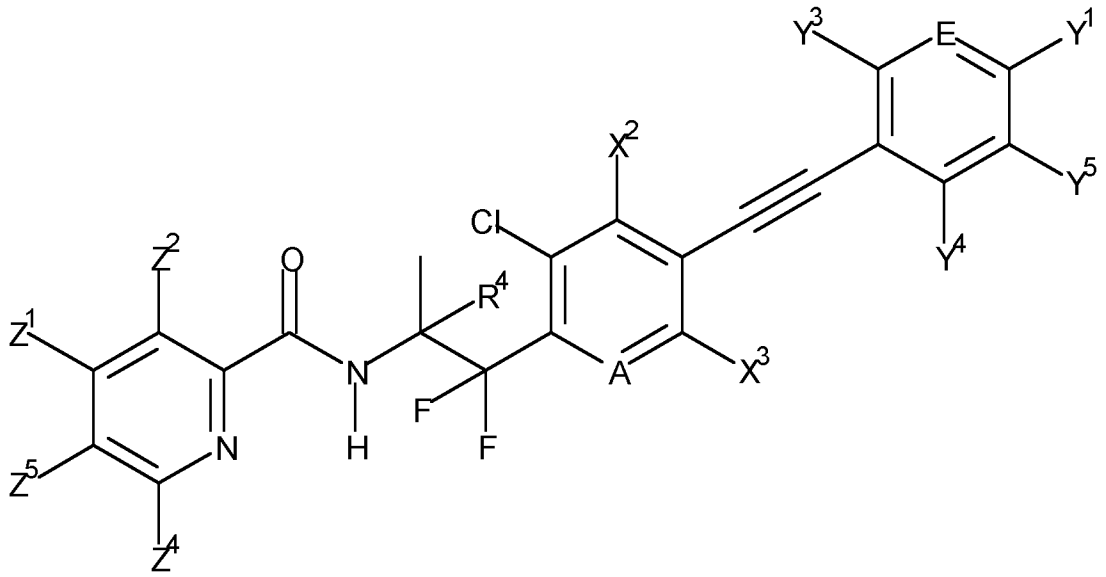


(XXXV)

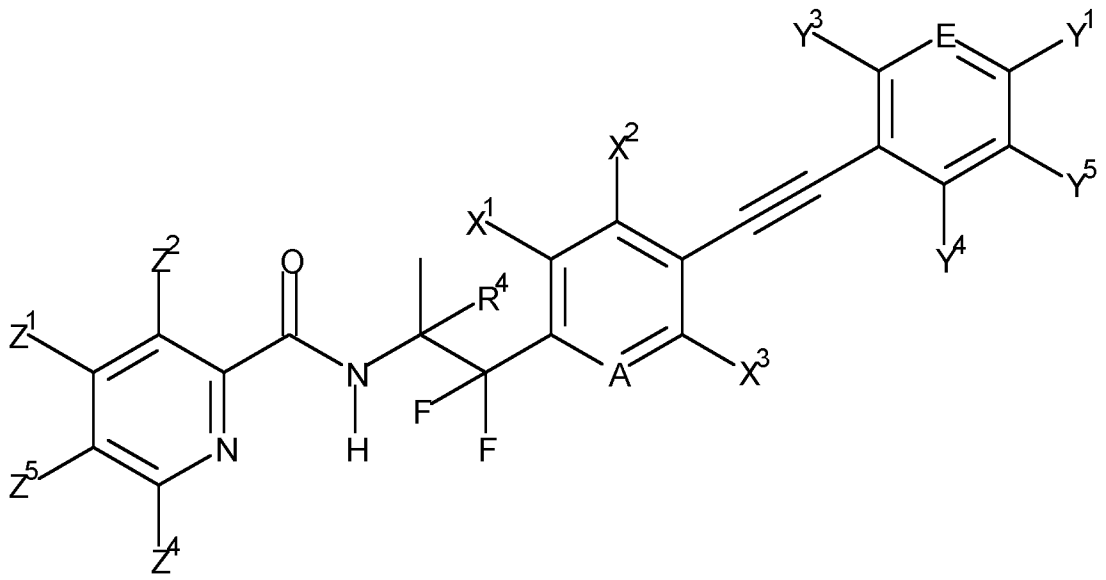
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXXVI) or (XXXVII)



(XXXVI)

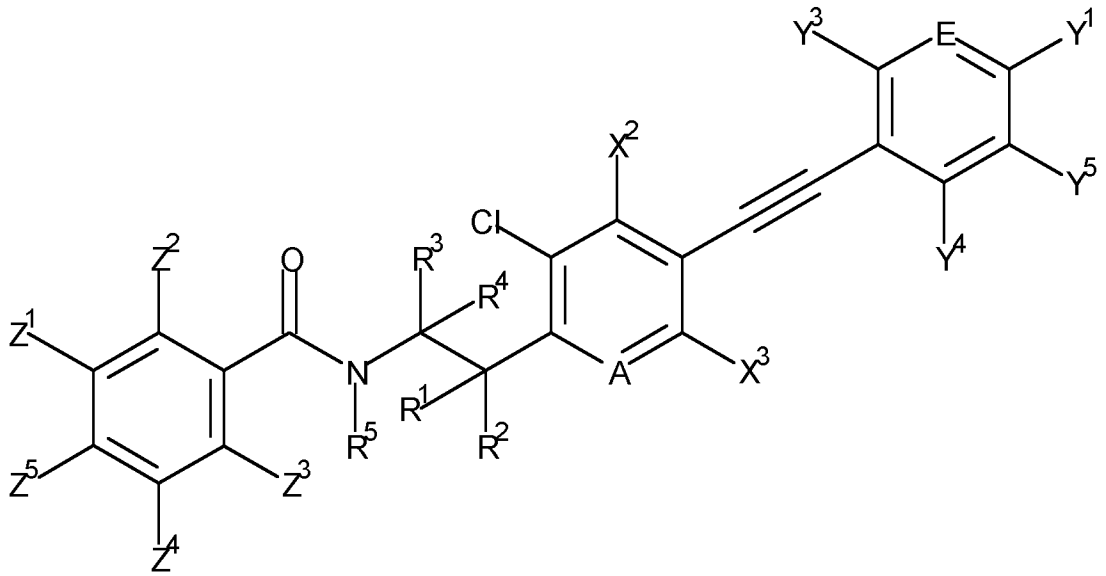


(XXXVII)

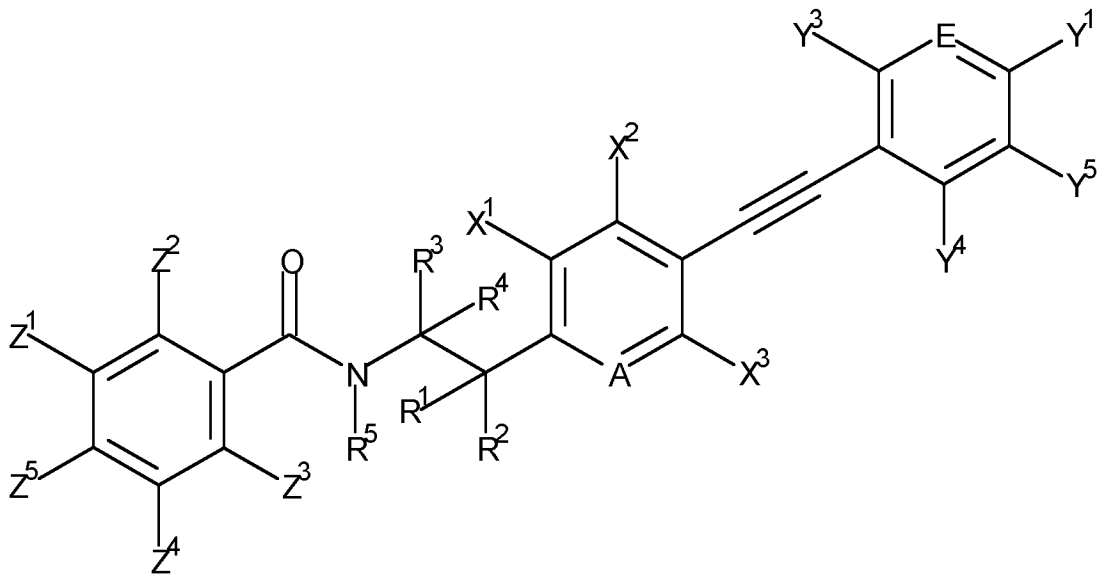
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is C-Y^2 or N; and wherein R^4, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XXXVIII) or (XXXIX)



(XXXVIII)

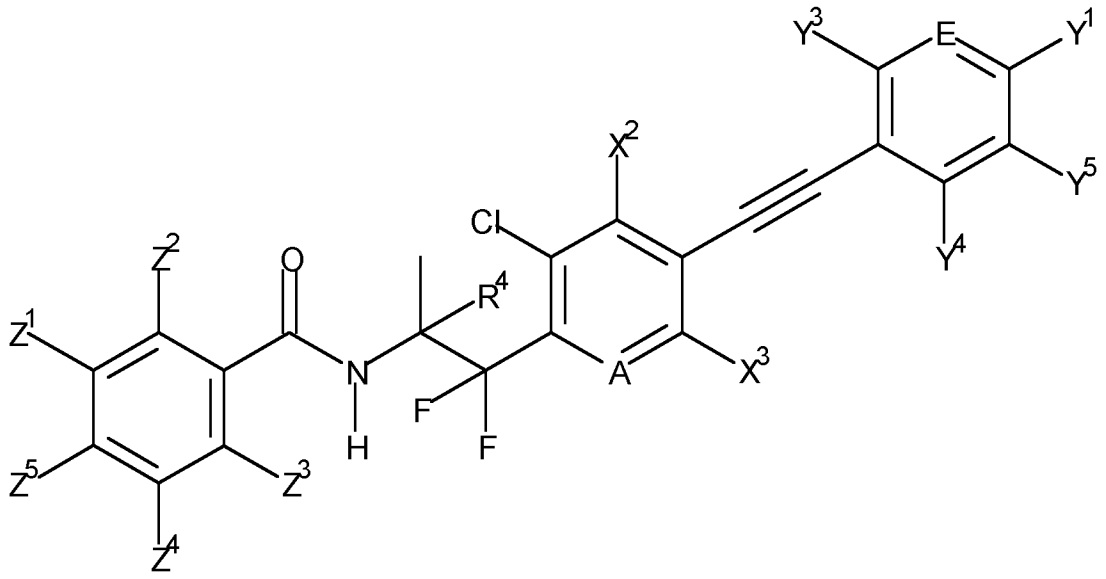


(XXXIX)

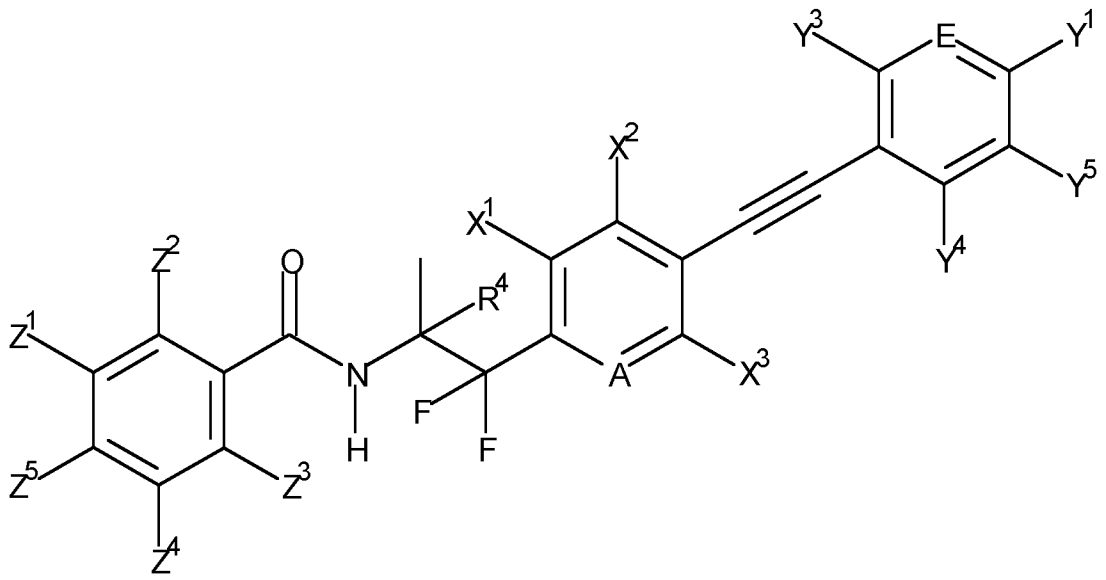
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is C-Y^2 or N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XL) or (XLI)



(XL)

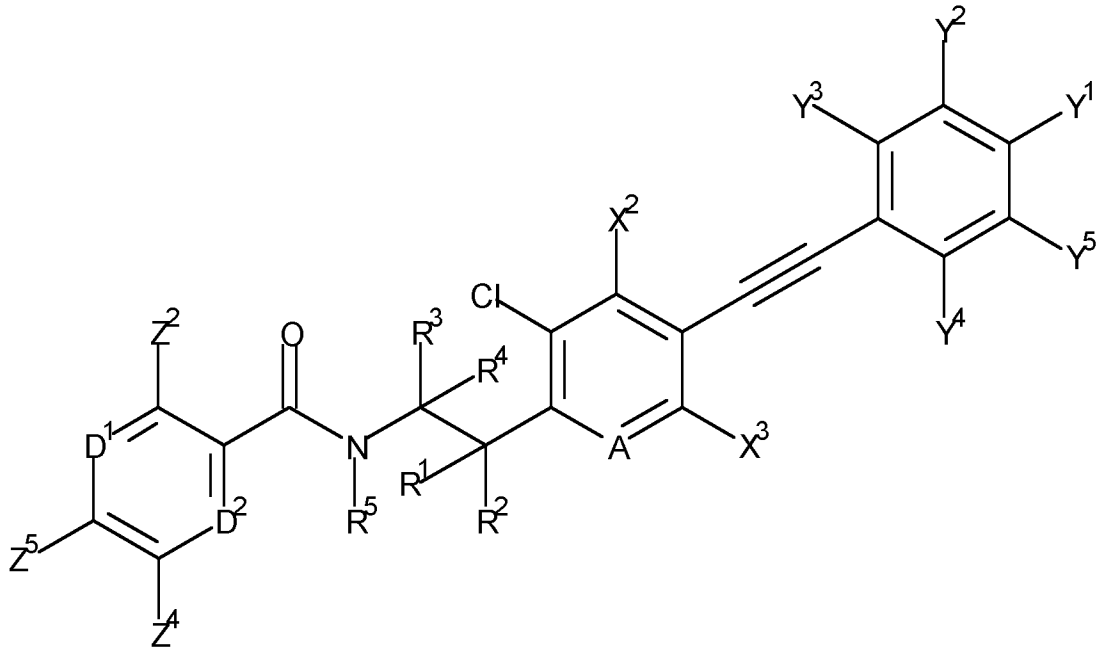


(XLI)

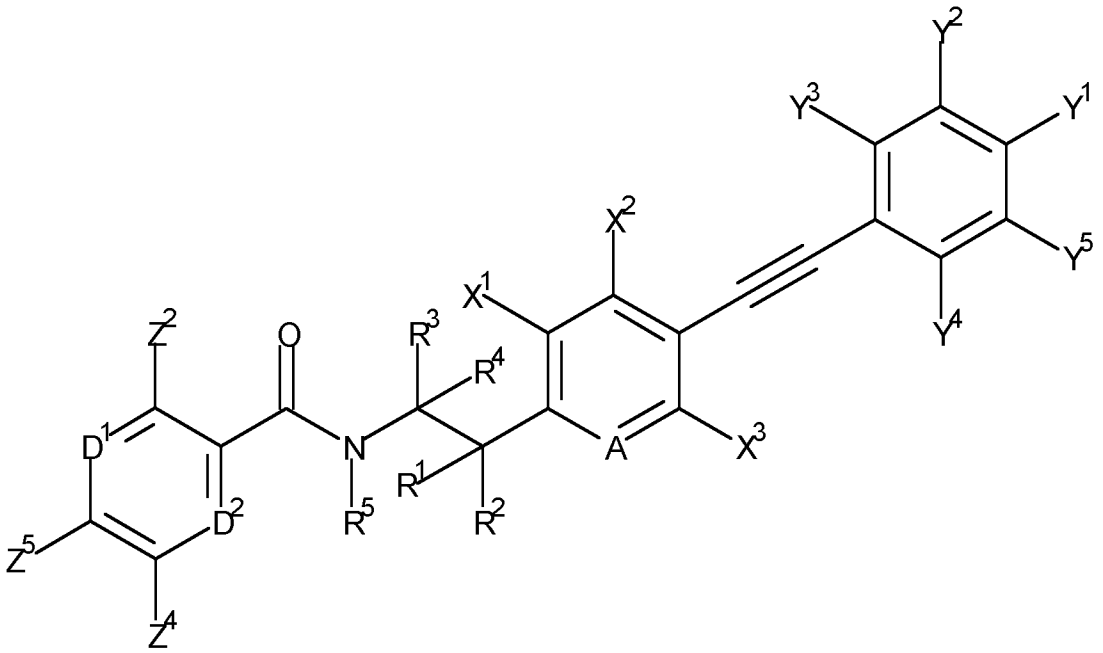
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is C-Y^2 or N; and wherein R^4, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2,Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XLII) or (XLIII)



(XLII)

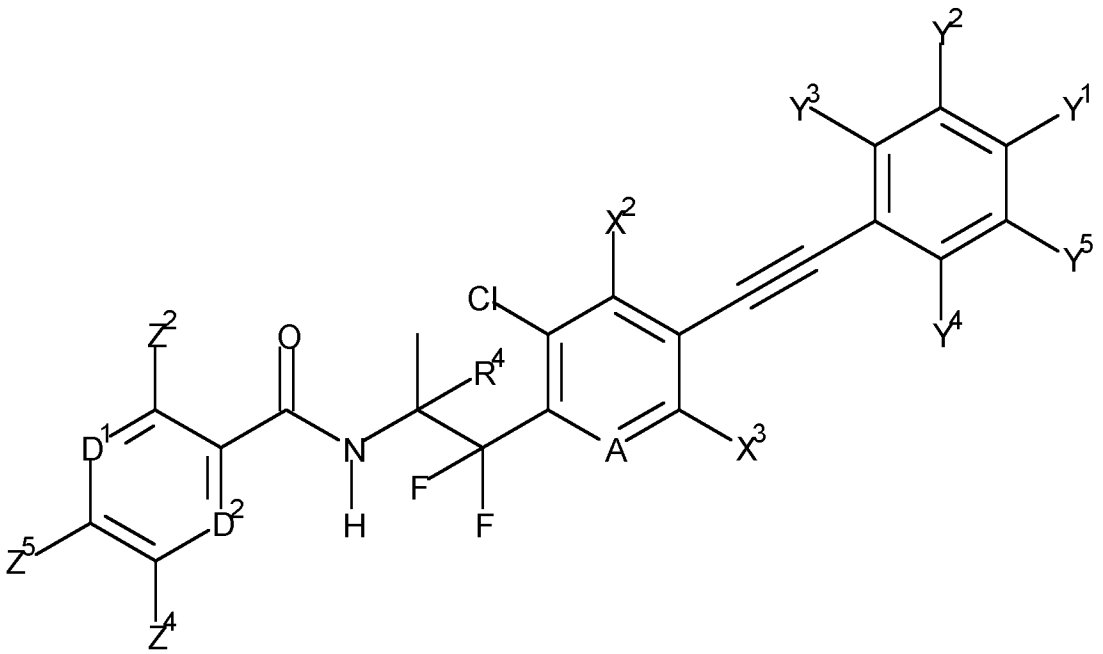


(XLIII)

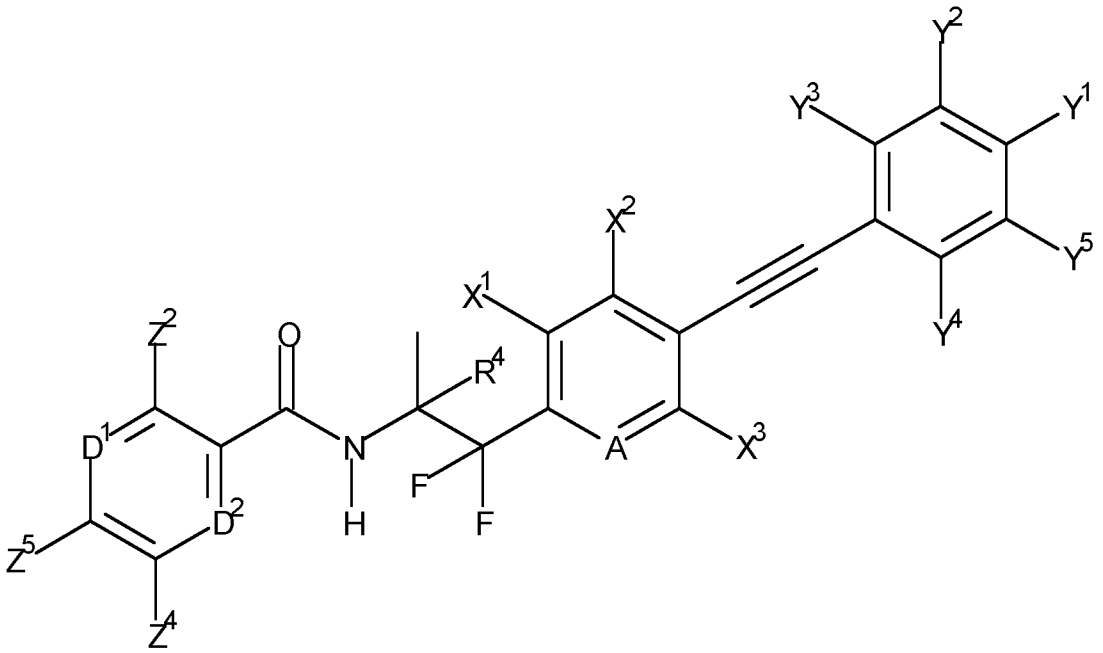
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XLIV) or (XLV)



(XLIV)

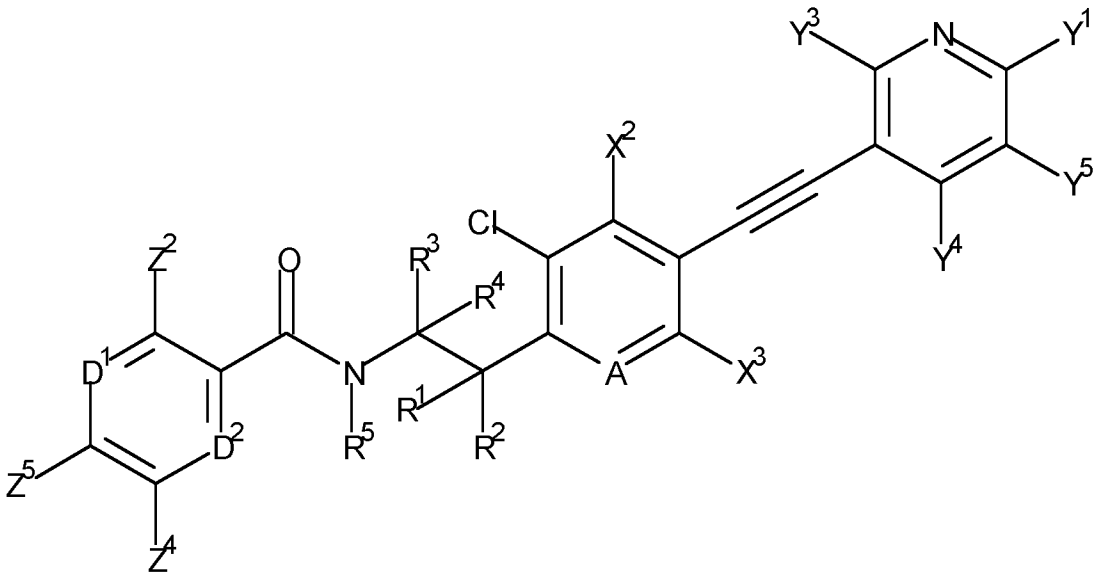


(XLV)

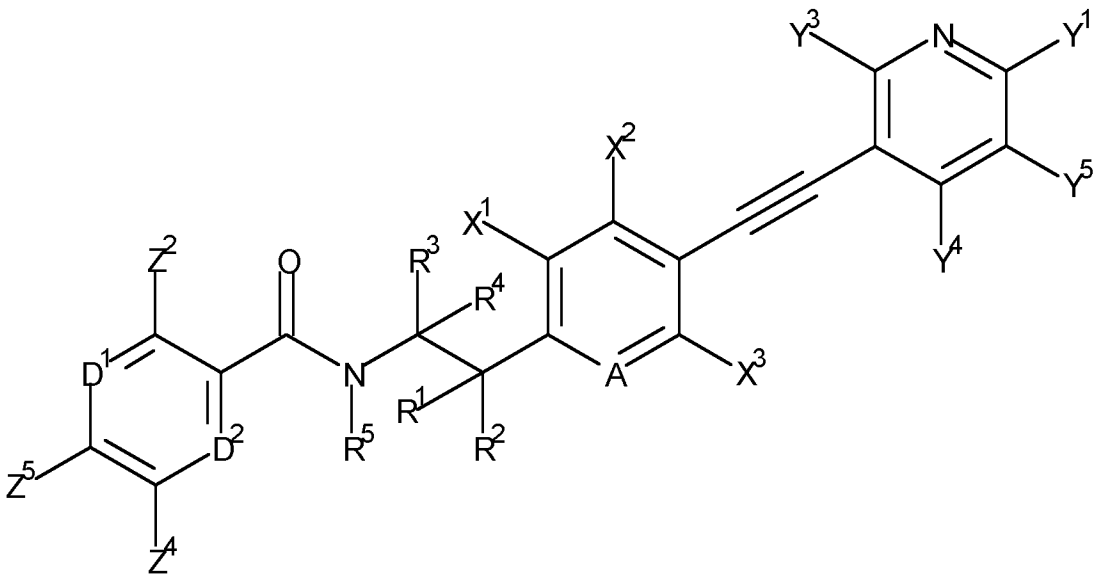
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; and wherein R^4, ,X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XLVI) or (XLVII)



(XLVI)

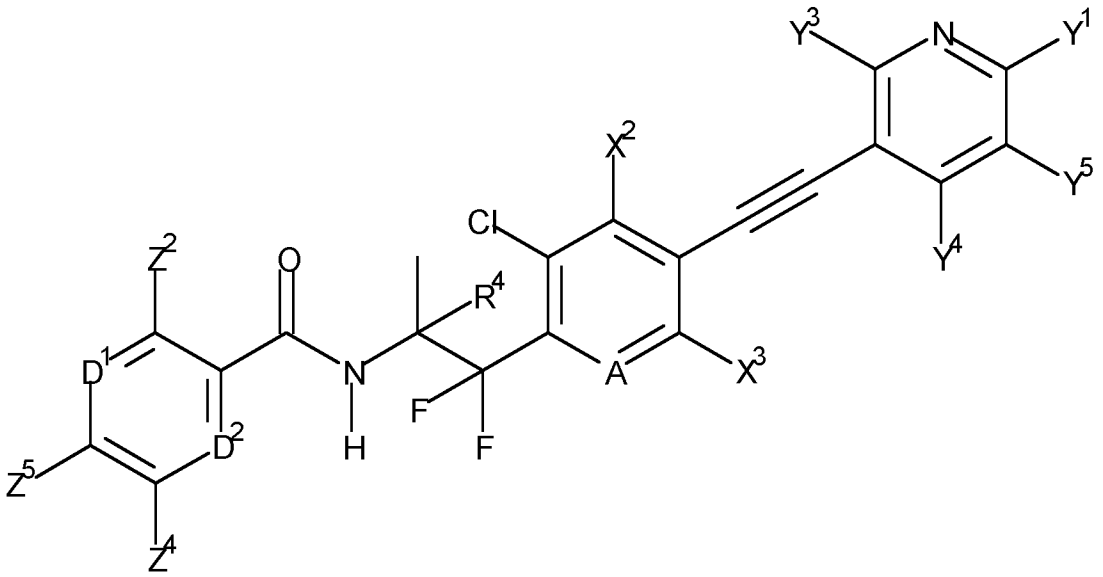


(XLVII)

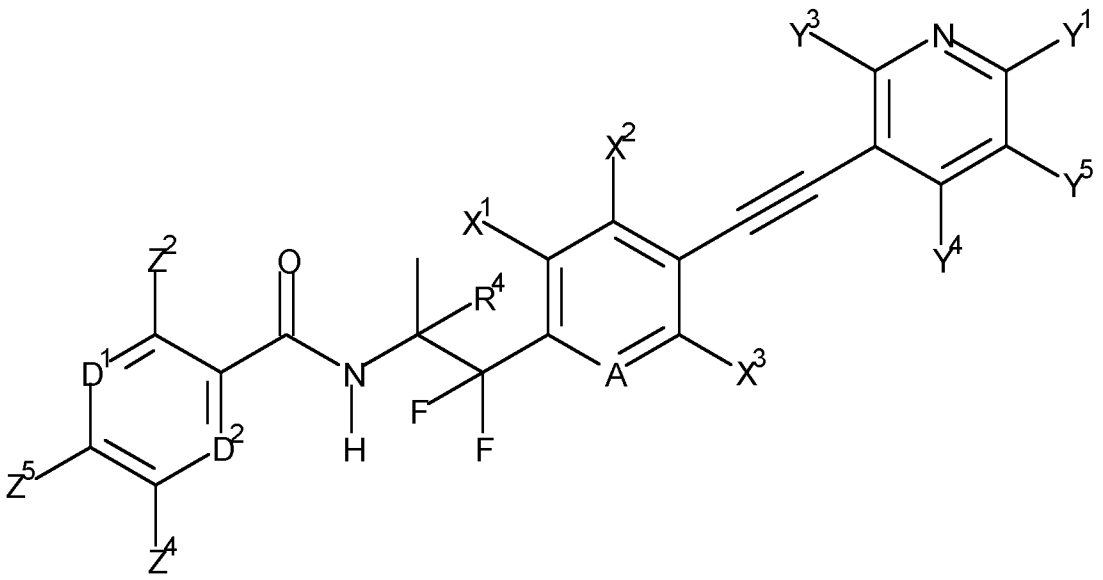
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; and wherein R^1, R^2, R^3 R^4, R^5,X^1, X^2, X^3, X^4, Y^1, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (XLVIII) or (XLIX)



(XLVIII)

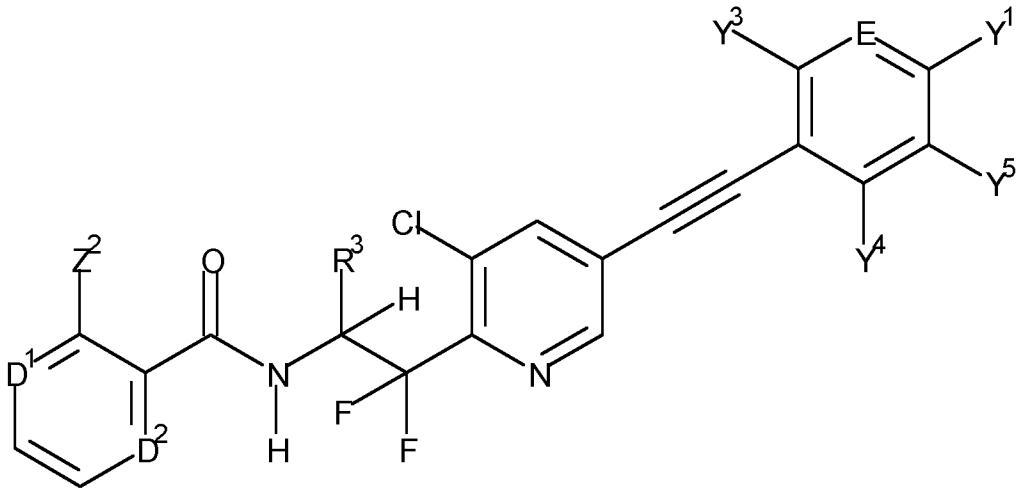


(XLIX)

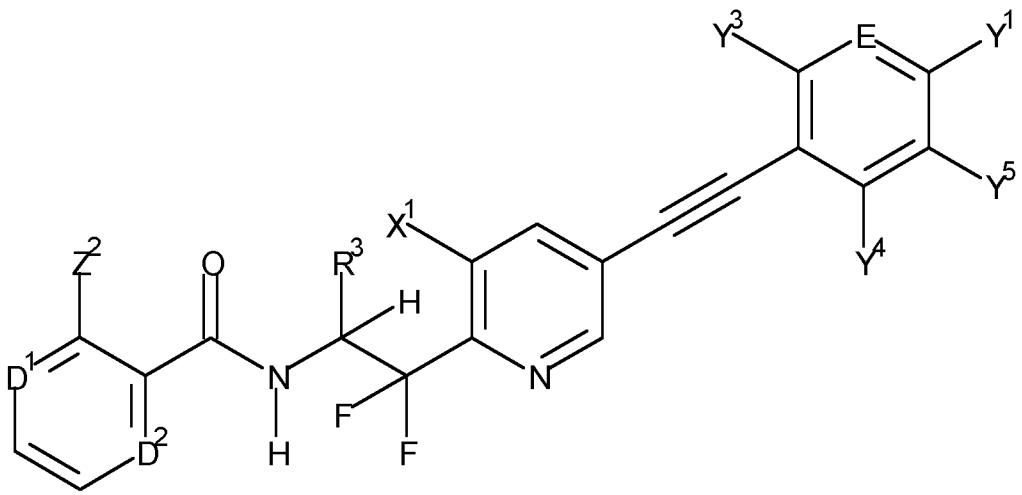
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; and wherein R^4, ,X^1, X^2, X^3, X^4, Y^1, Y^3, Y^4, Y^5, Z^1, Z^2, Z^3, Z^4, and Z^5 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (L) or (LI)



(L)

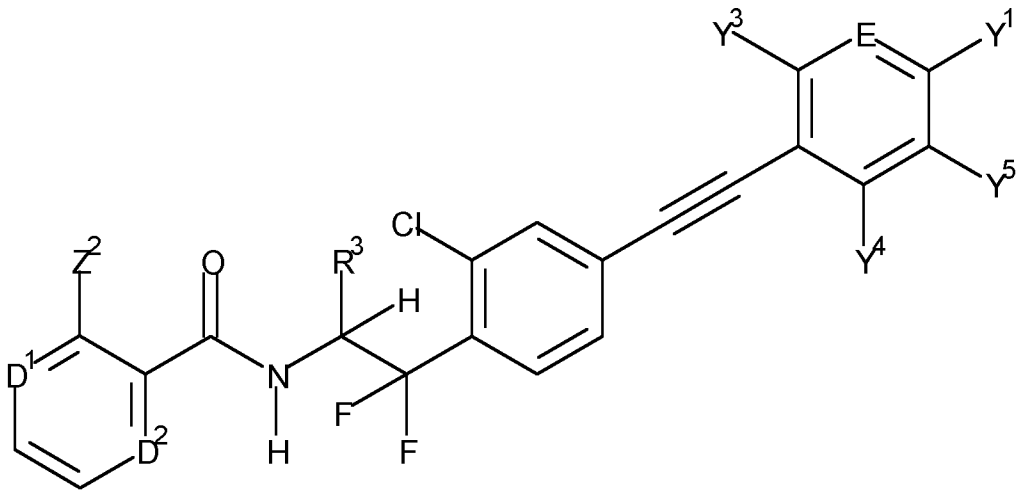


(LI)

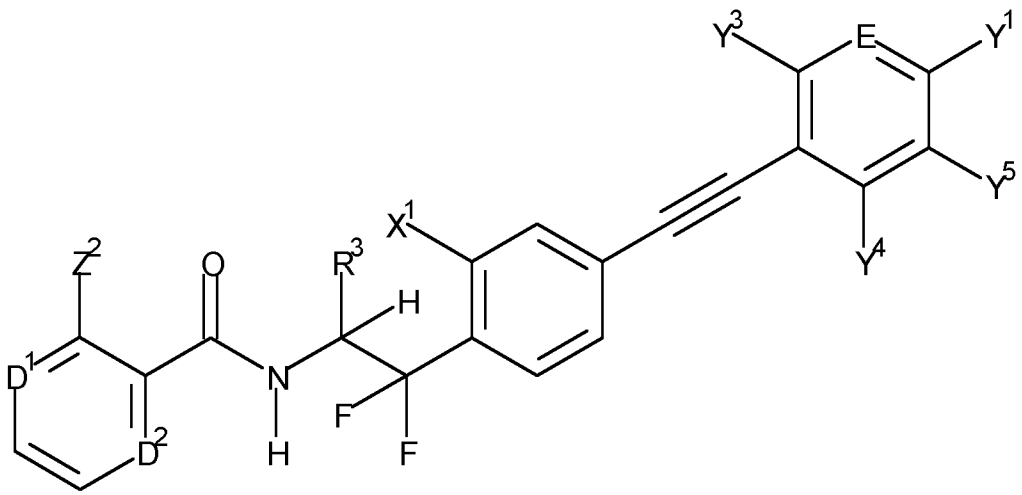
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 CH or N; D_2 CH or N and wherein maximum one of D_1 or D_2 is N; E is CH or N; and wherein Y^1, Y^3, Y^4, Y^5, Z^2, and R^3 are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LII) or (LIII)



(LII)

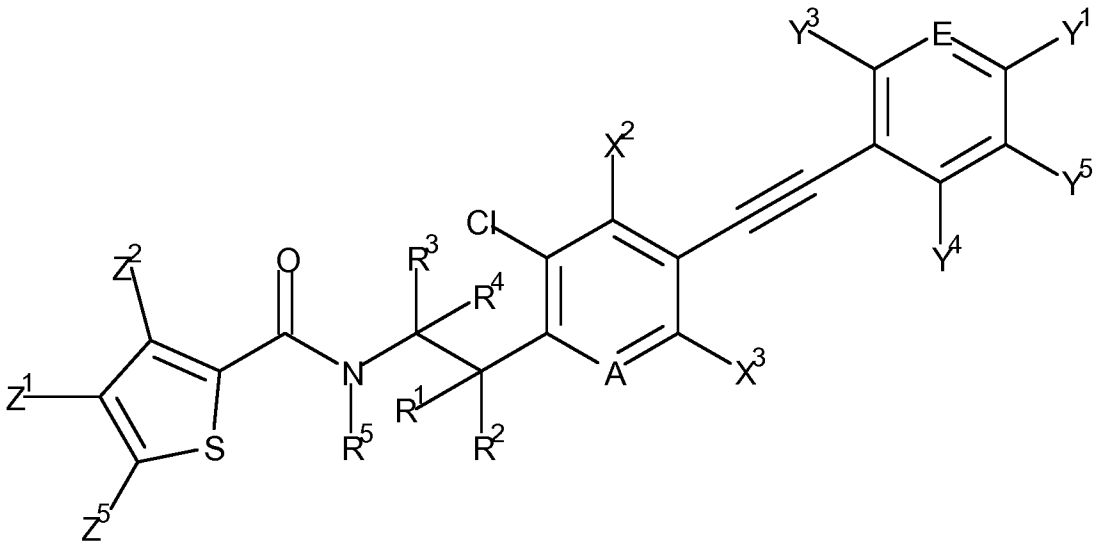


(LIII)

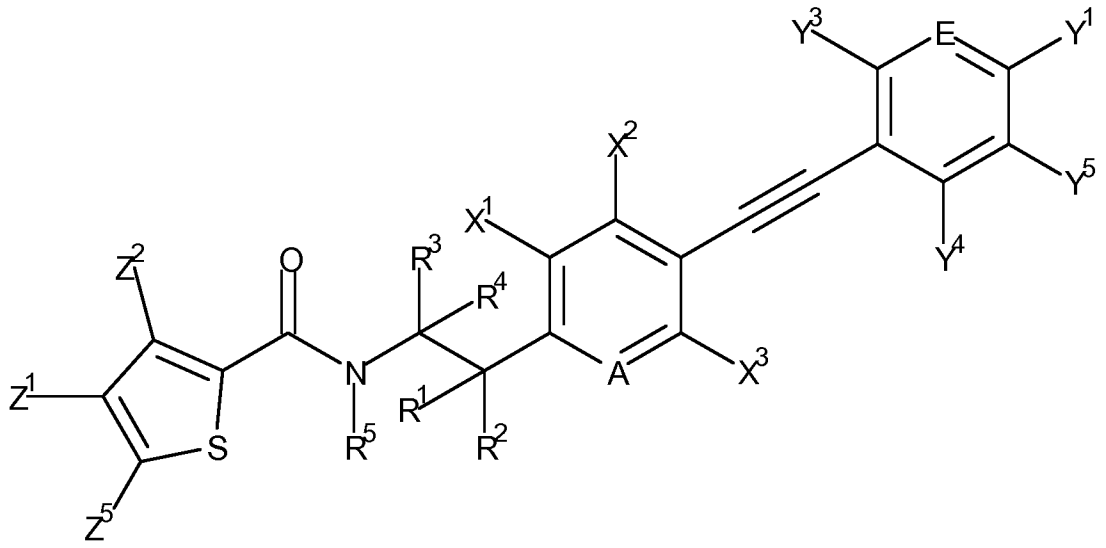
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; E is CH or N; and wherein X^1, Y^1, Y^3, Y^4, Y^5, Z^2, are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LIV) or (LV)



(LIV)

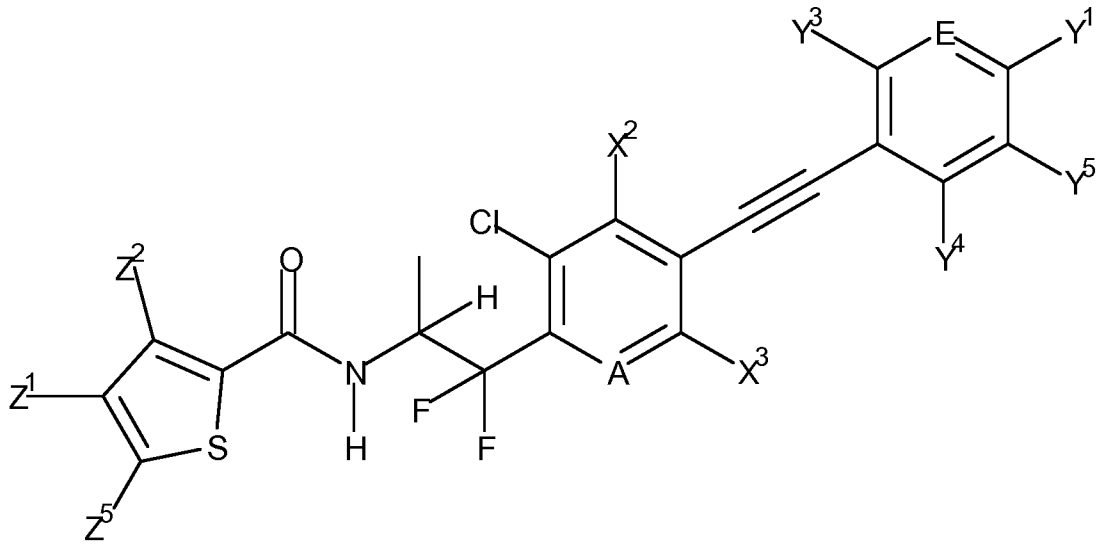


(LV)

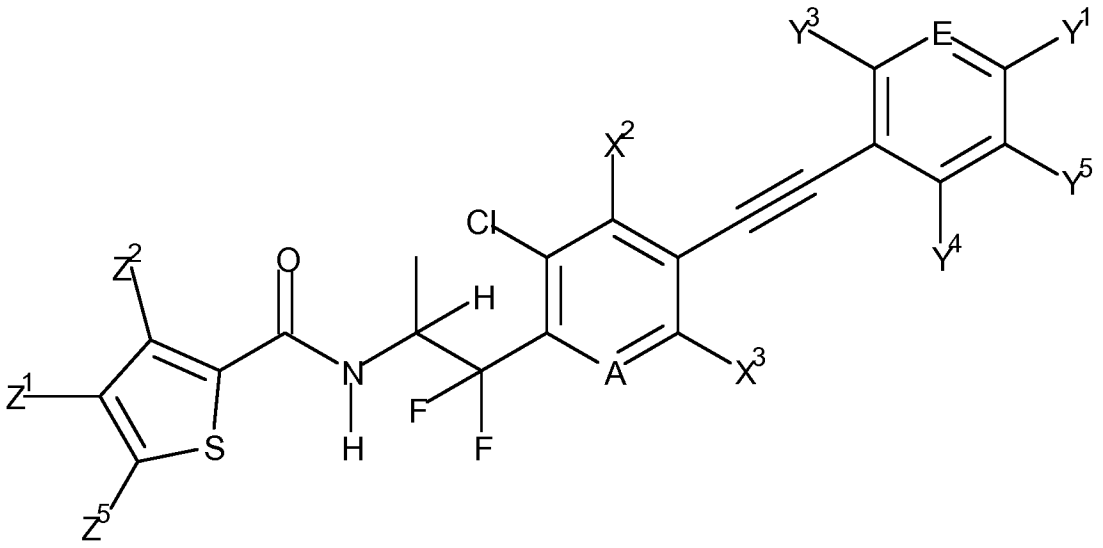
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is CH or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^1, Y^3, Y^4, Y^5, Z^1, Z^2, and Z^5, are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LVI) or (LVII)



(LVI)

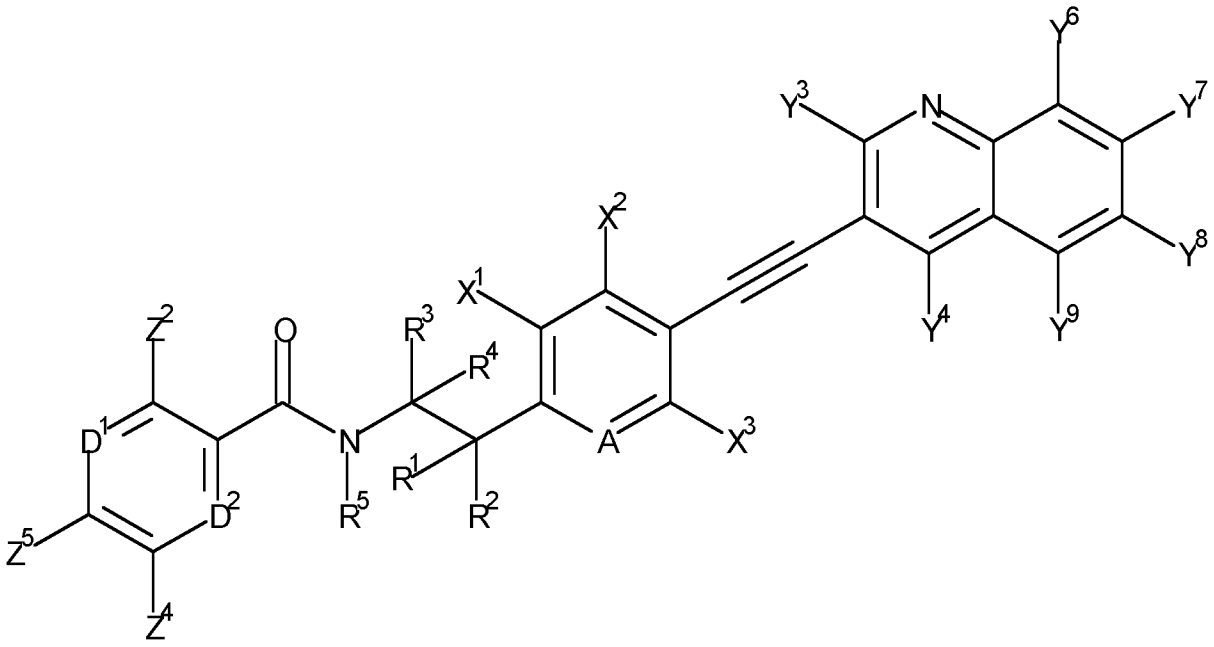


(LVII)

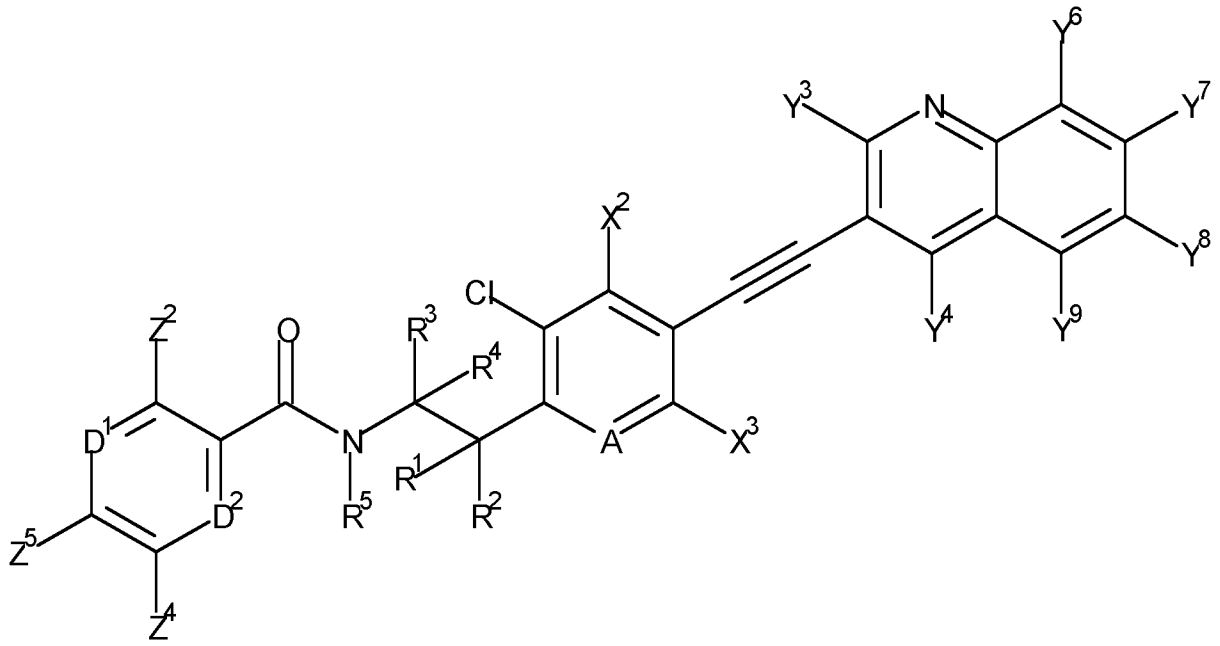
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

A is C-X^4 or N; E is CH or N; and wherein X^2, X^3, X^4, Y^1, Y^3, Y^4, Y^5, Z^1, Z^2, and Z^5, are as defined in any of the embodiments described herein.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LVIII) or (LIX)



(LVIII)

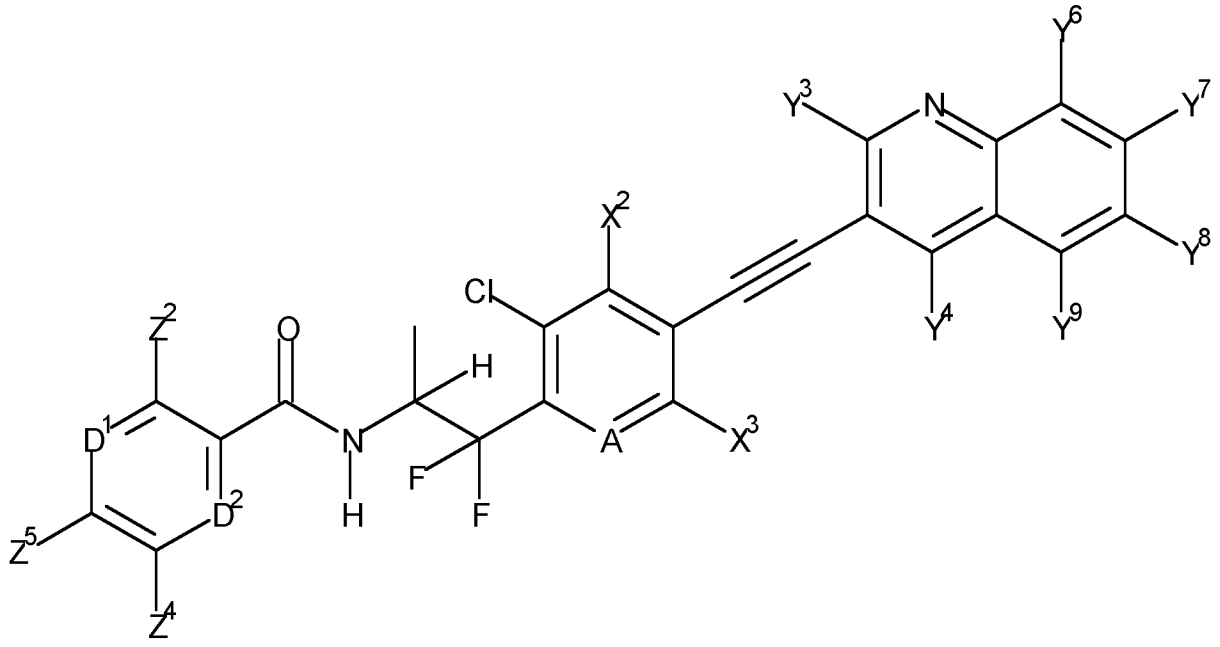


(VIX)

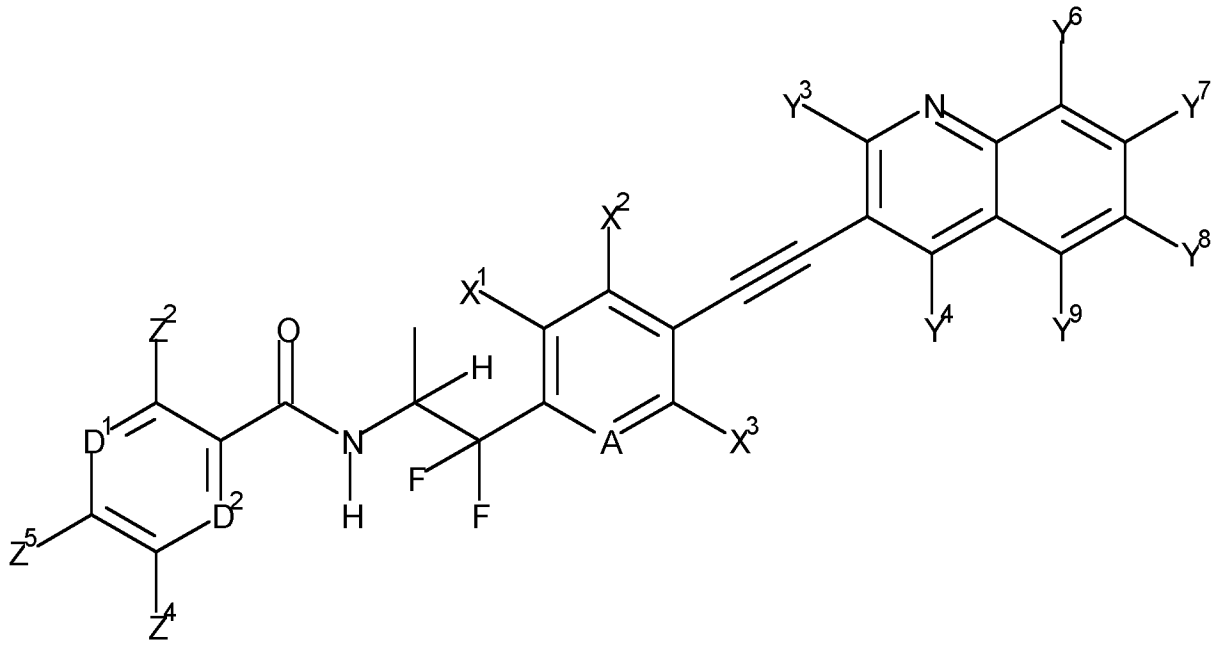
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^5, are as defined in any of the embodiments described herein, and wherein each of Y^2, Y^3, Y^4, Y^6, Y^7, Y^8, Y^9, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LX) or (LXI)



(LX)

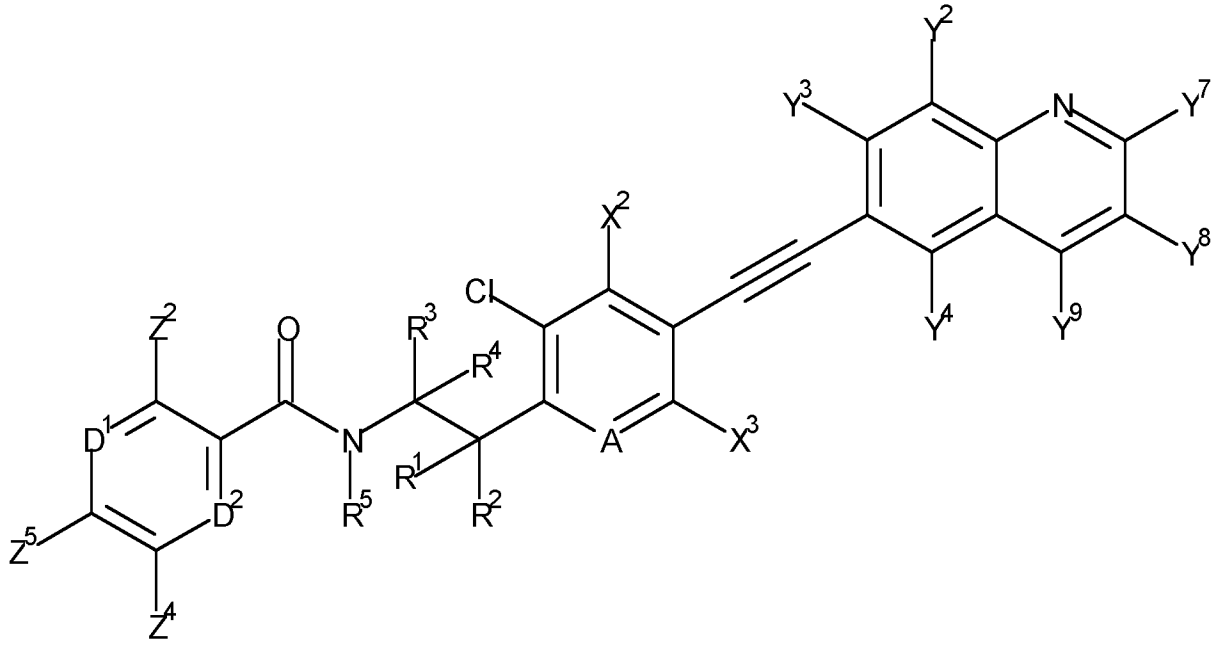


(LXI)

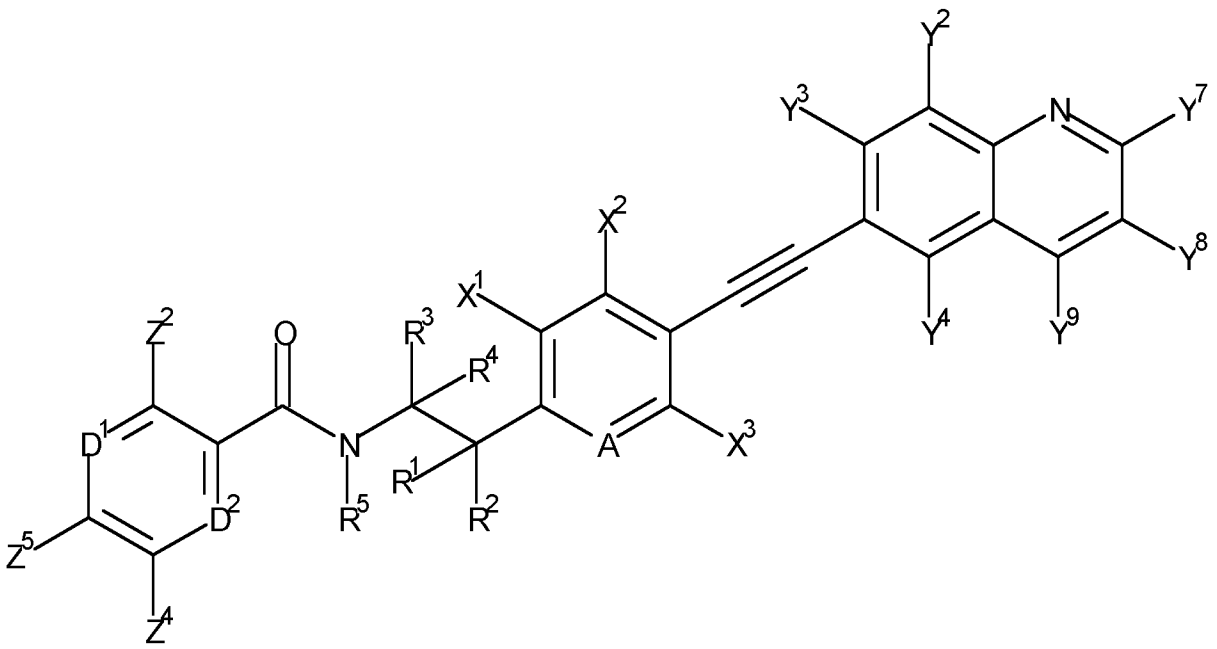
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; and wherein X^1, X^2, X^3, X^4, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^5, are as defined in any of the embodiments described herein, and wherein each of Y^2, Y^3, Y^4, Y^6, Y^7, Y^8, Y^9, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXII) or (LXIII)



(LXII)

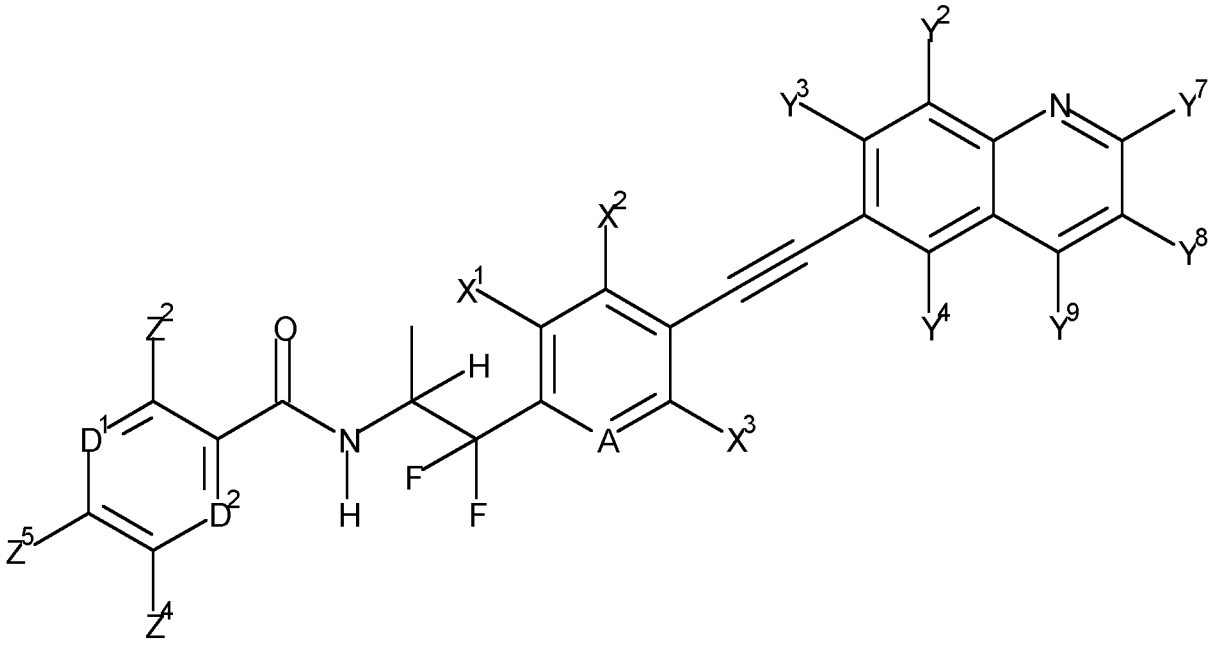


(LXIII)

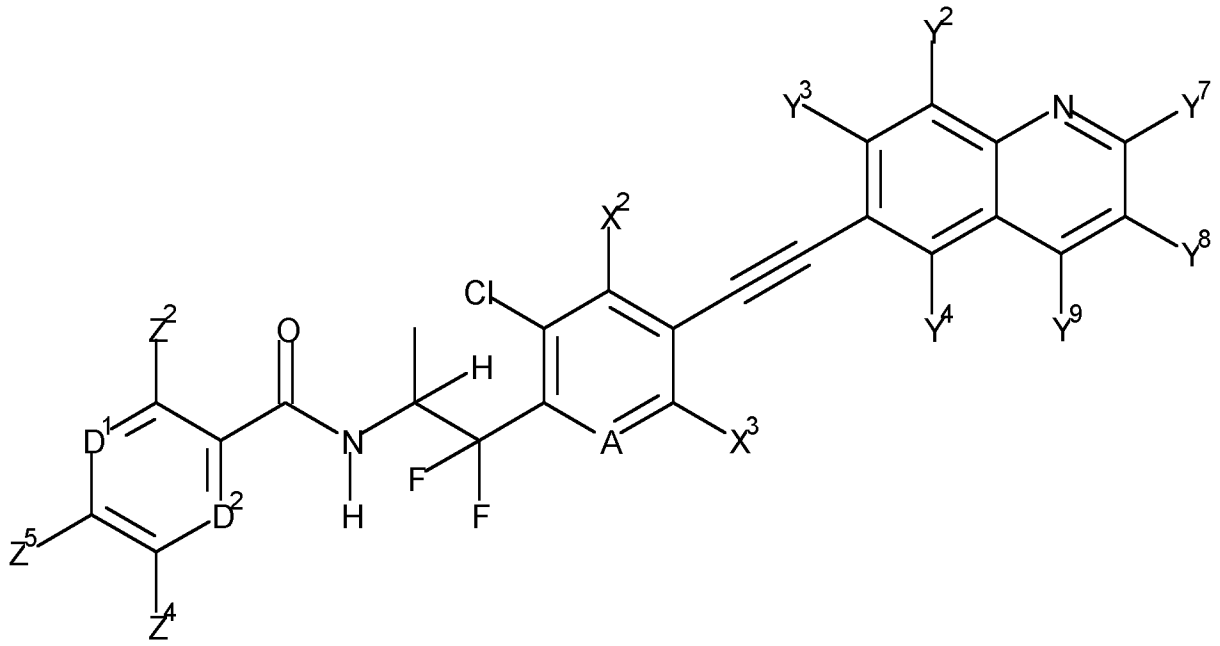
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^5, are as defined in any of the embodiments described herein, and wherein each of Y^2, Y^3, Y^4, Y^7, Y^8, Y^9, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXIX) or (LXX)



(LXIX)

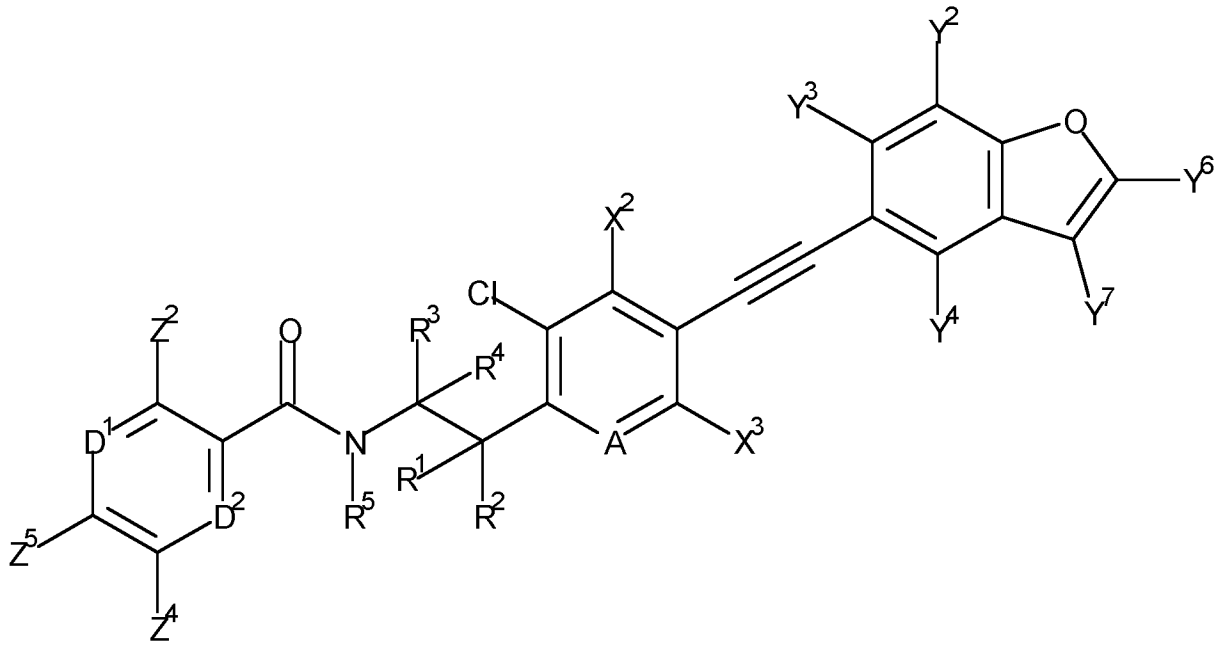


(LXX)

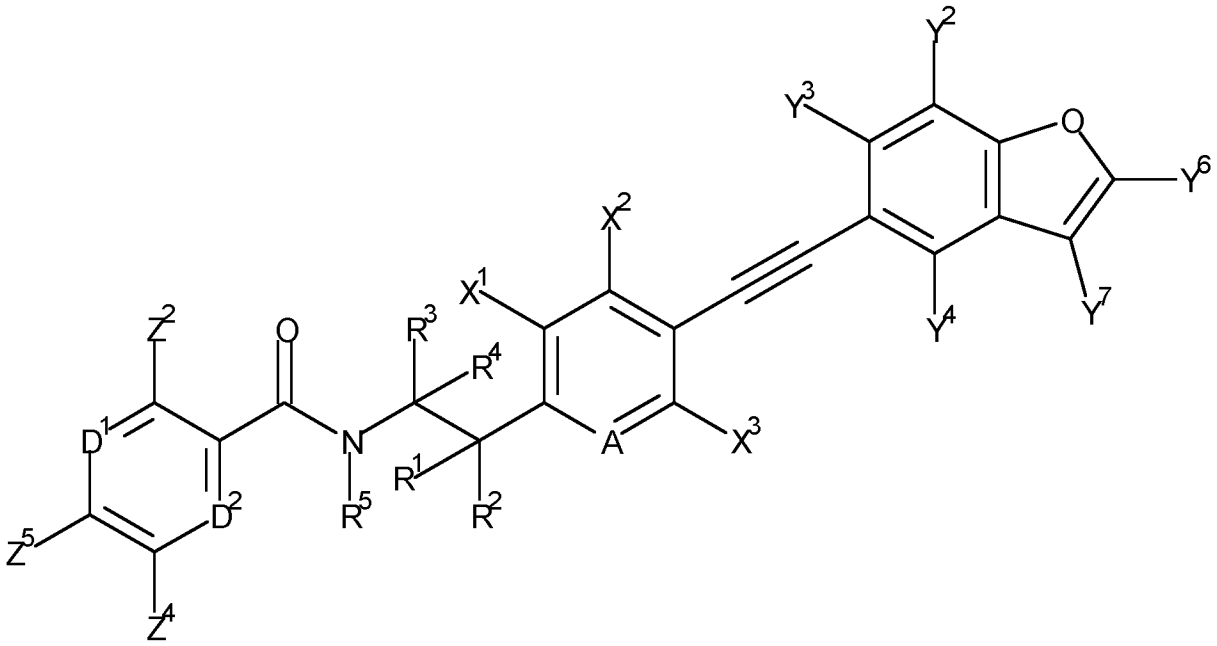
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; and wherein X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^5, are as defined in any of the embodiments described herein, and wherein each of Y^7, Y^8, Y^9, is defined as Y^1 as in in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXI) or (LXXII)



(LXXI)

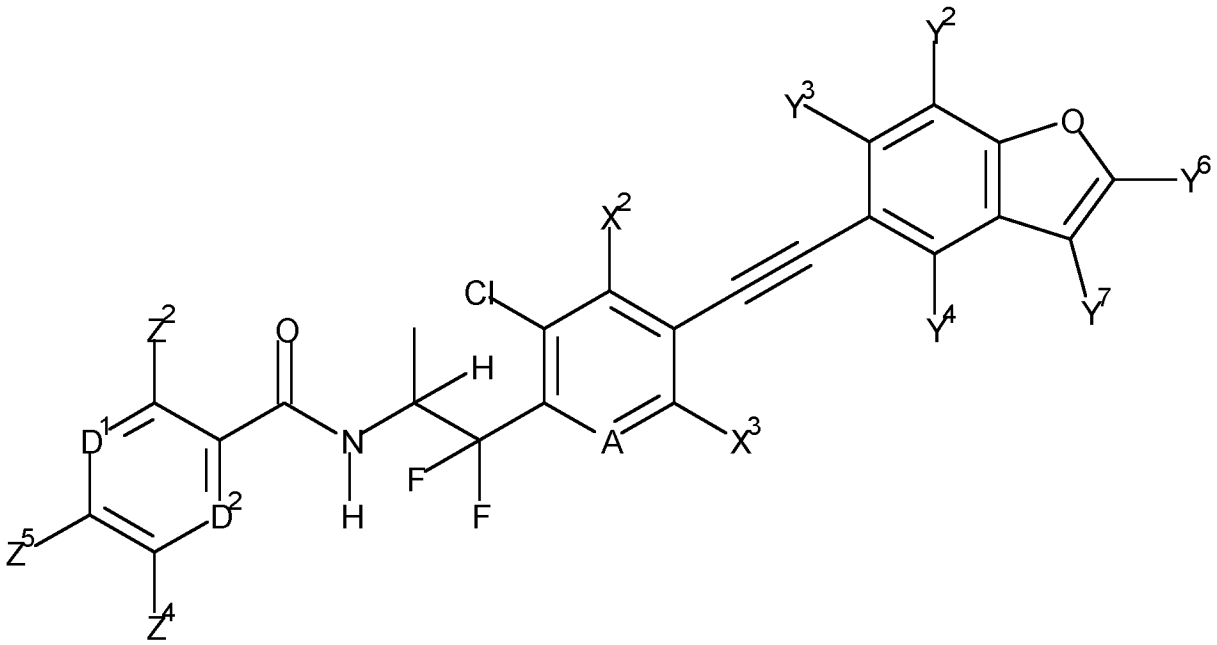


(LXXII)

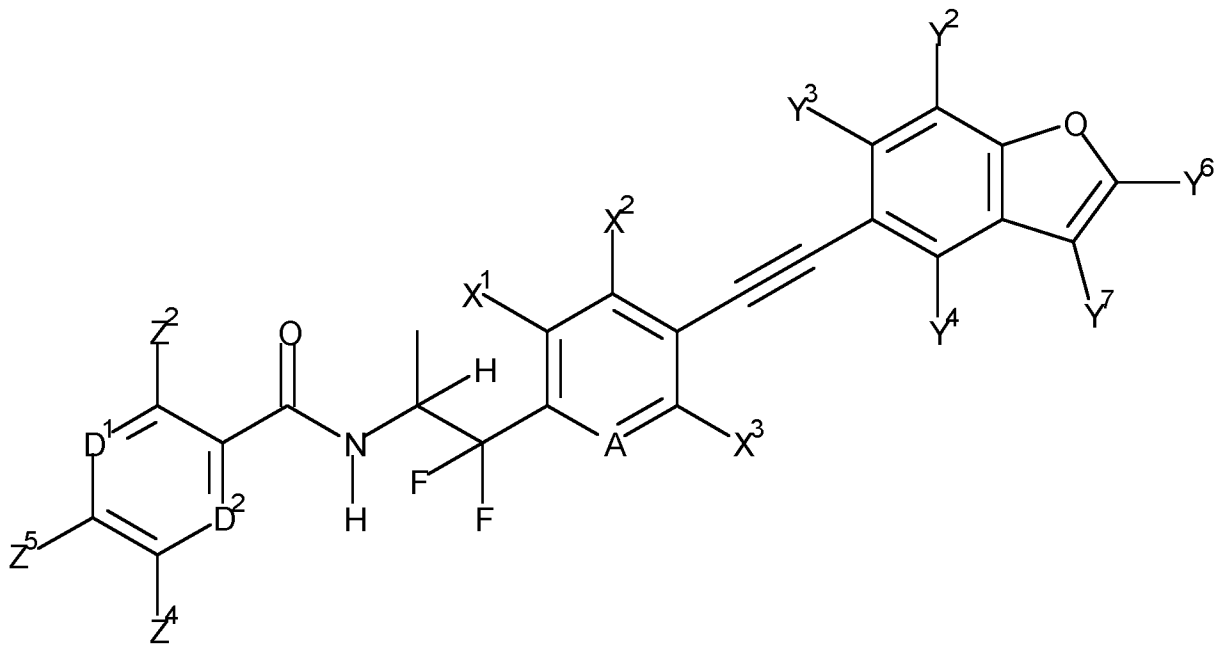
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein each of Y^6, Y^7, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXIII) or (LXXIV)



(LXXIII)

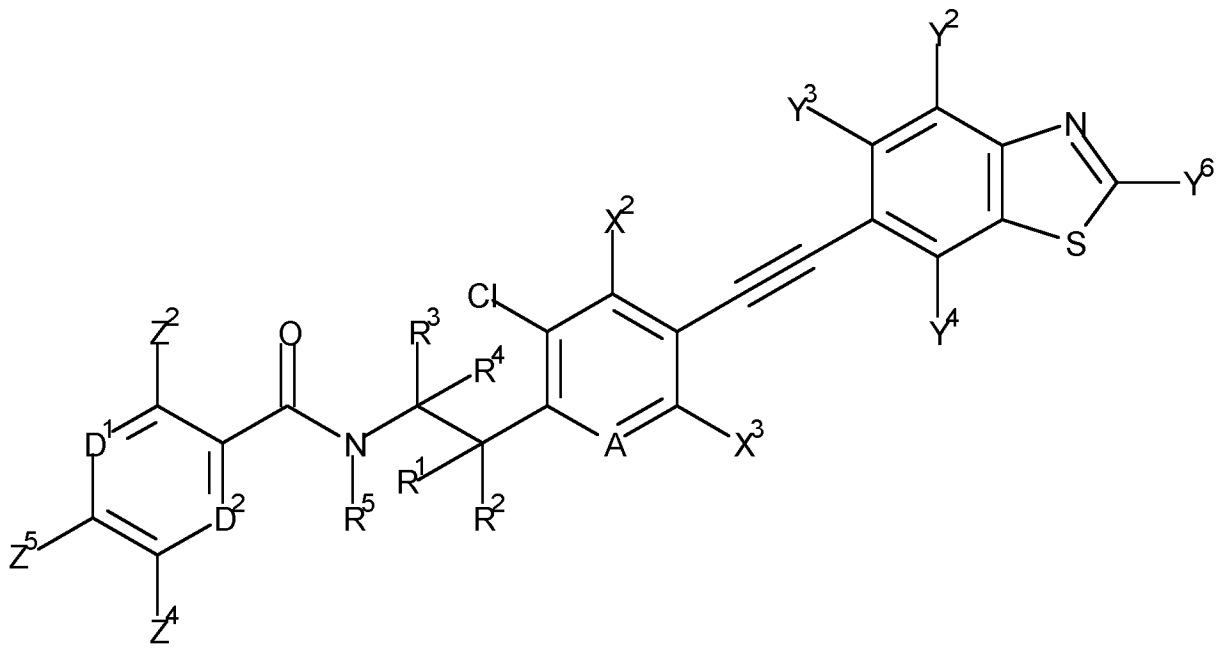


(LXXIV)

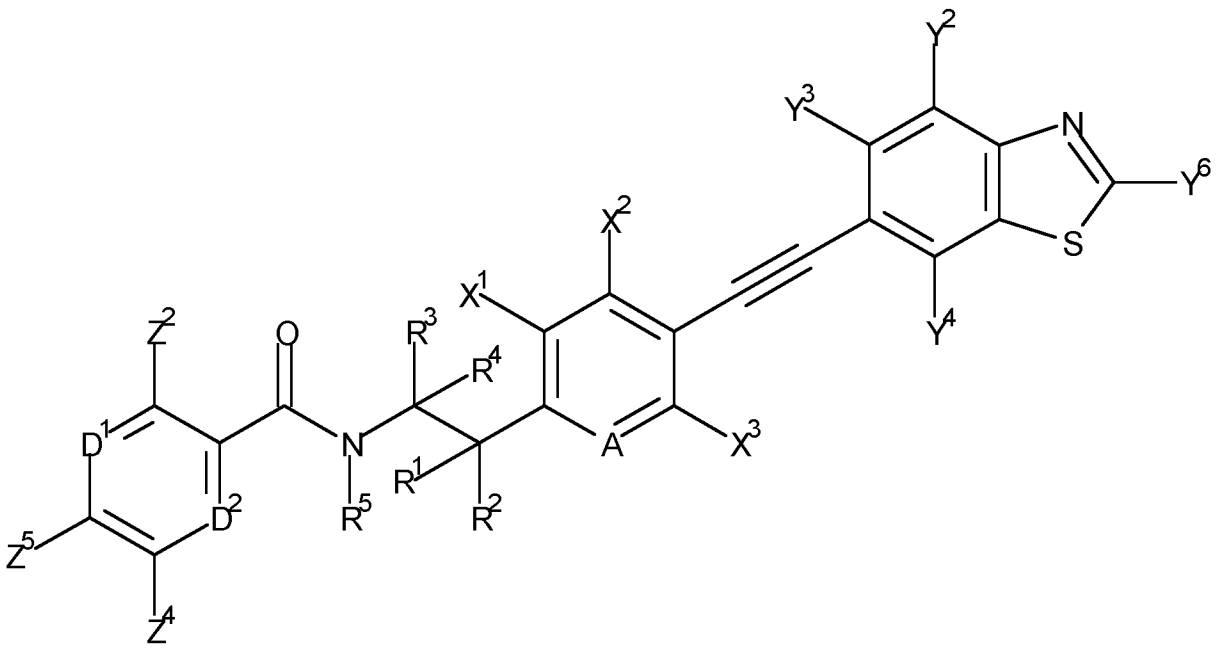
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; and wherein X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^5, are as defined in any of the embodiments described herein, and wherein each of Y^7, Y^8, Y^9, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXV) or (LXXVI)



(LXXV)

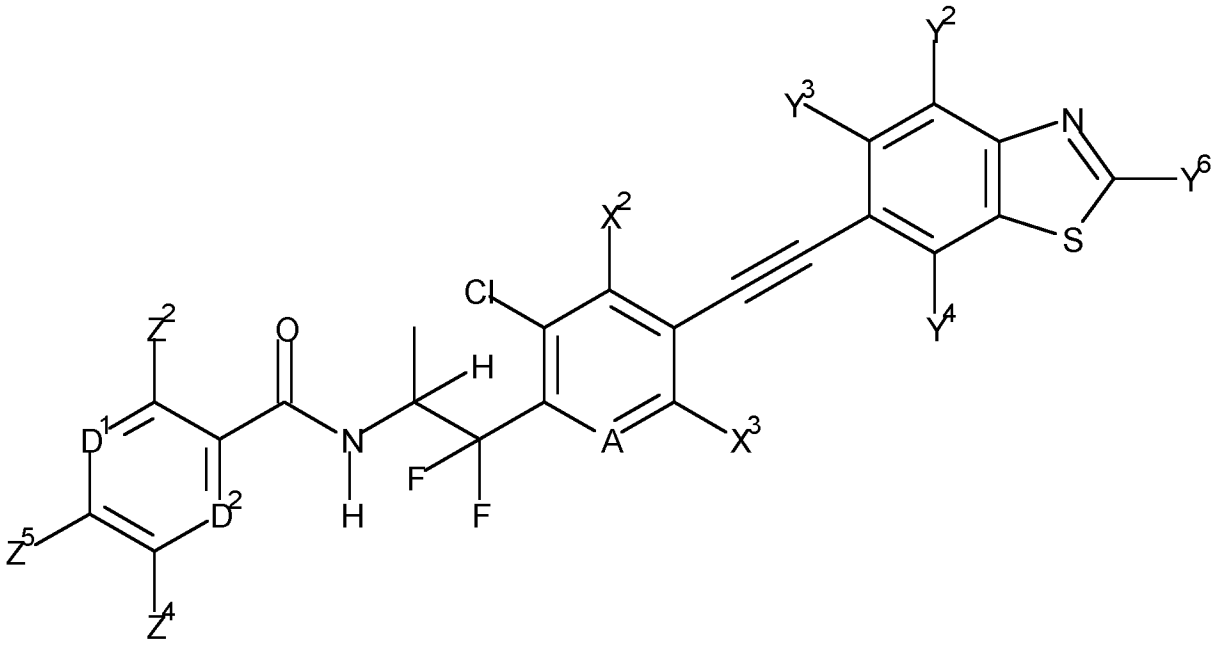


(LXXVI)

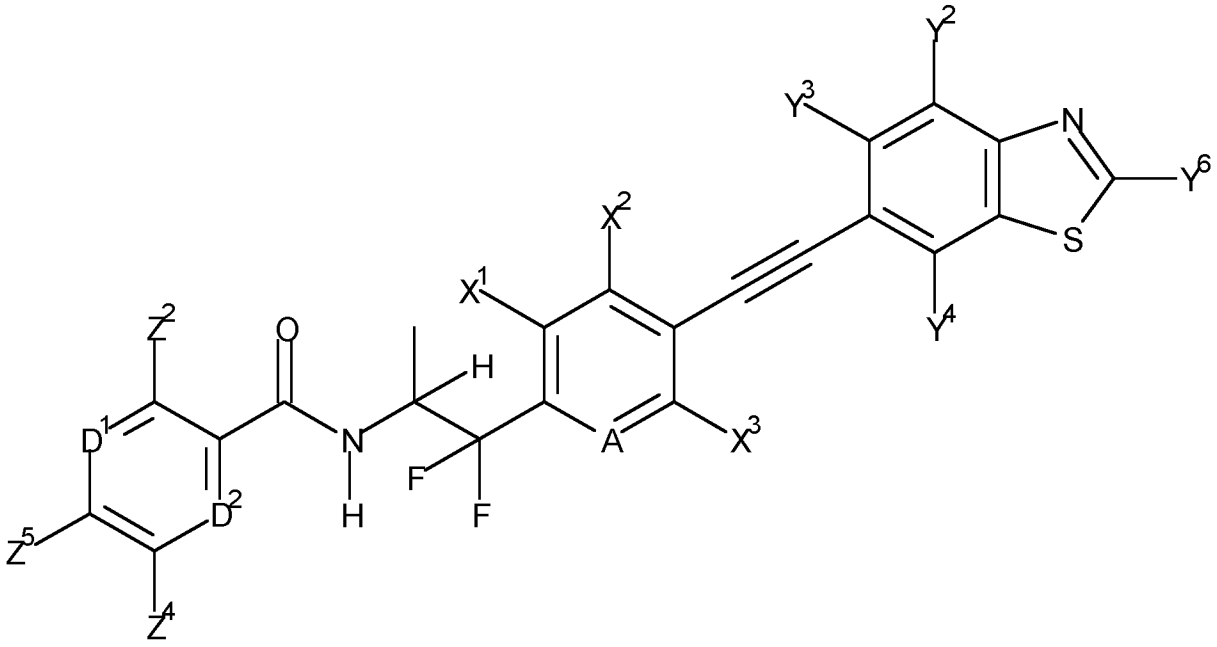
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein Y^6, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXVII) or (LXXVIII)



(LXXVII)

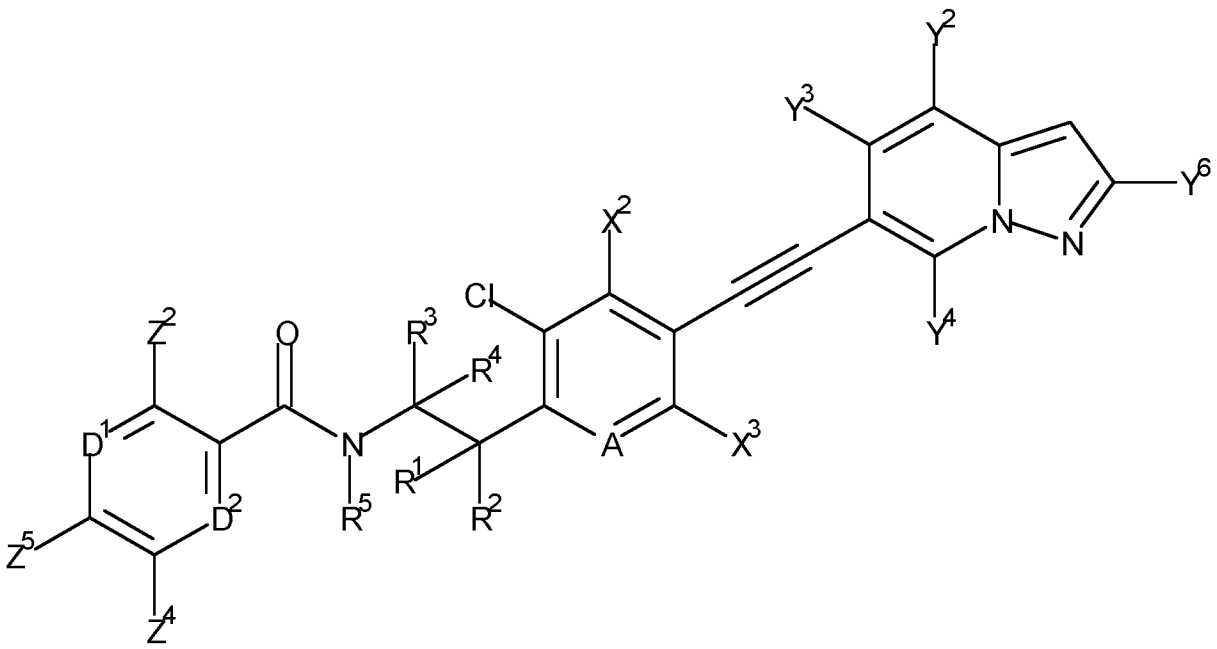


(LXXVIII)

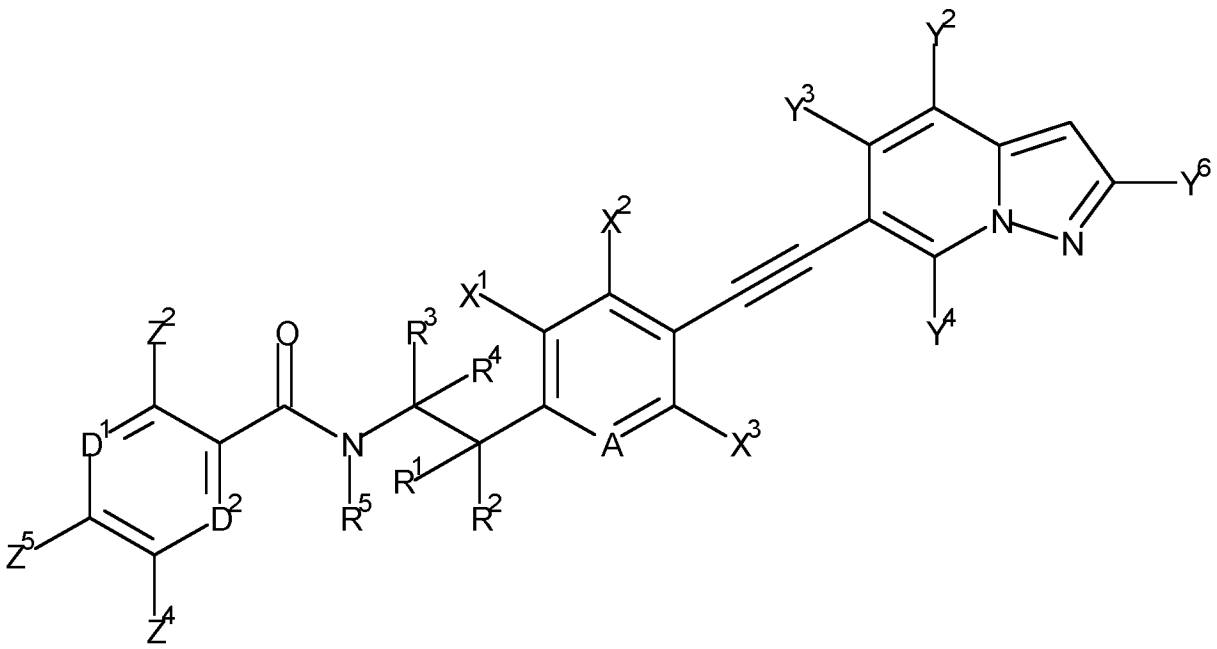
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein Y^6, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXIX) or (LXXX)



(LXXIX)

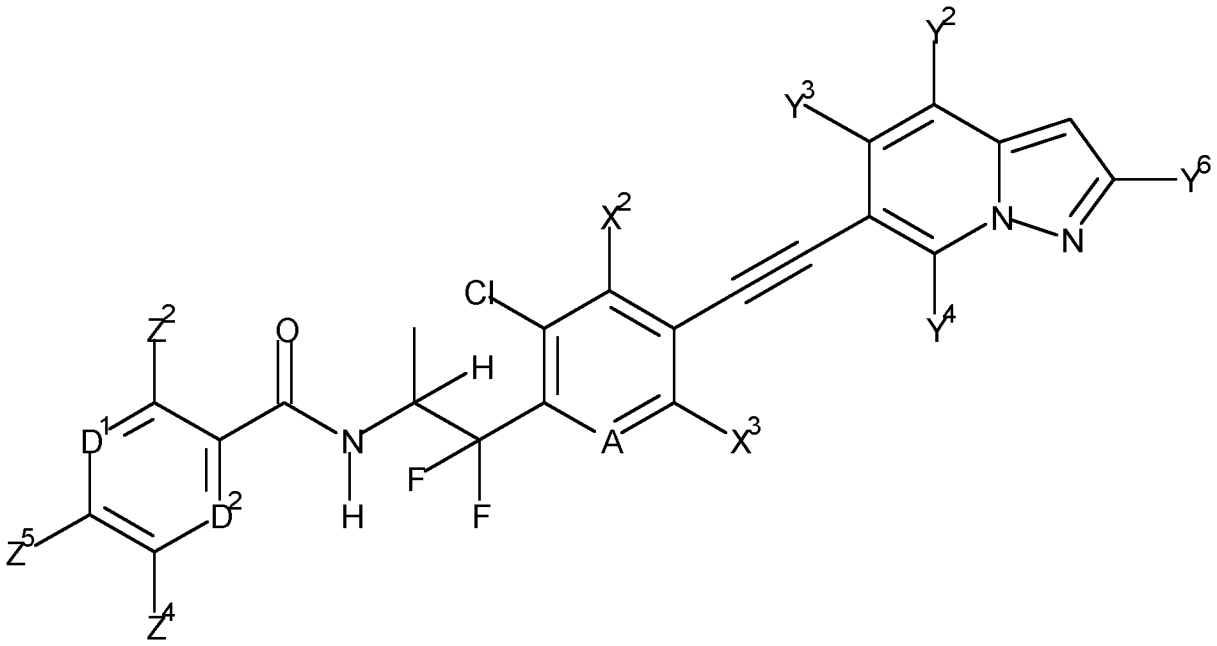


(LXXX)

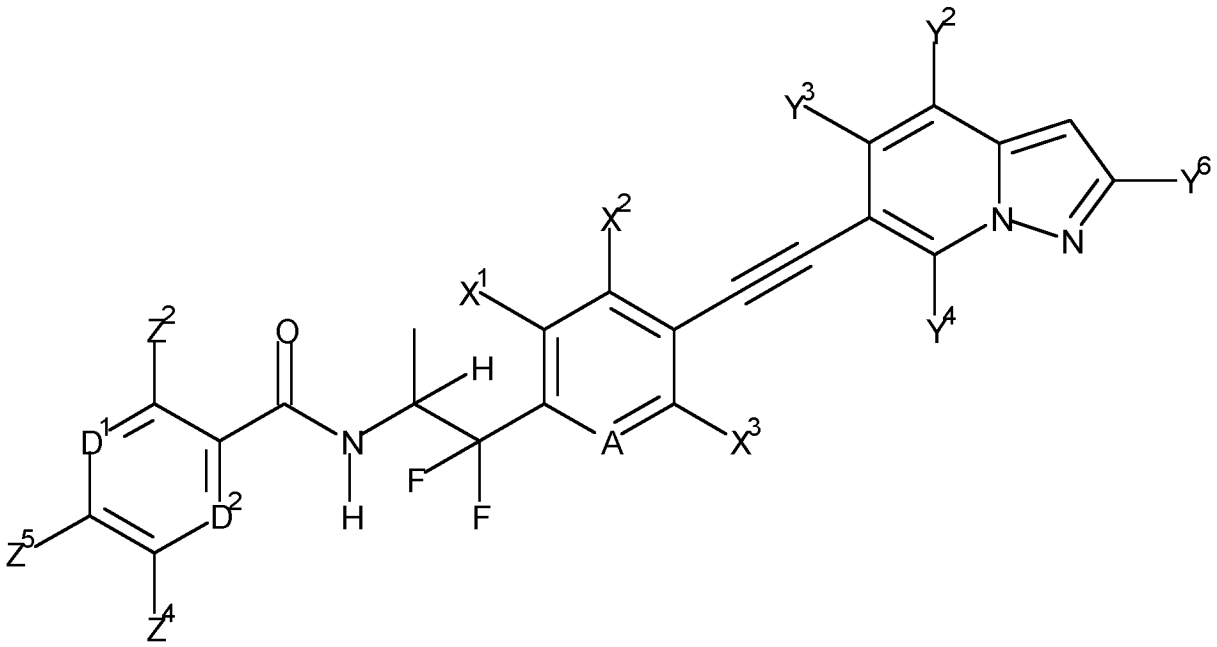
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein Y^6, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXX) or (LXXXI)



(LXXX)

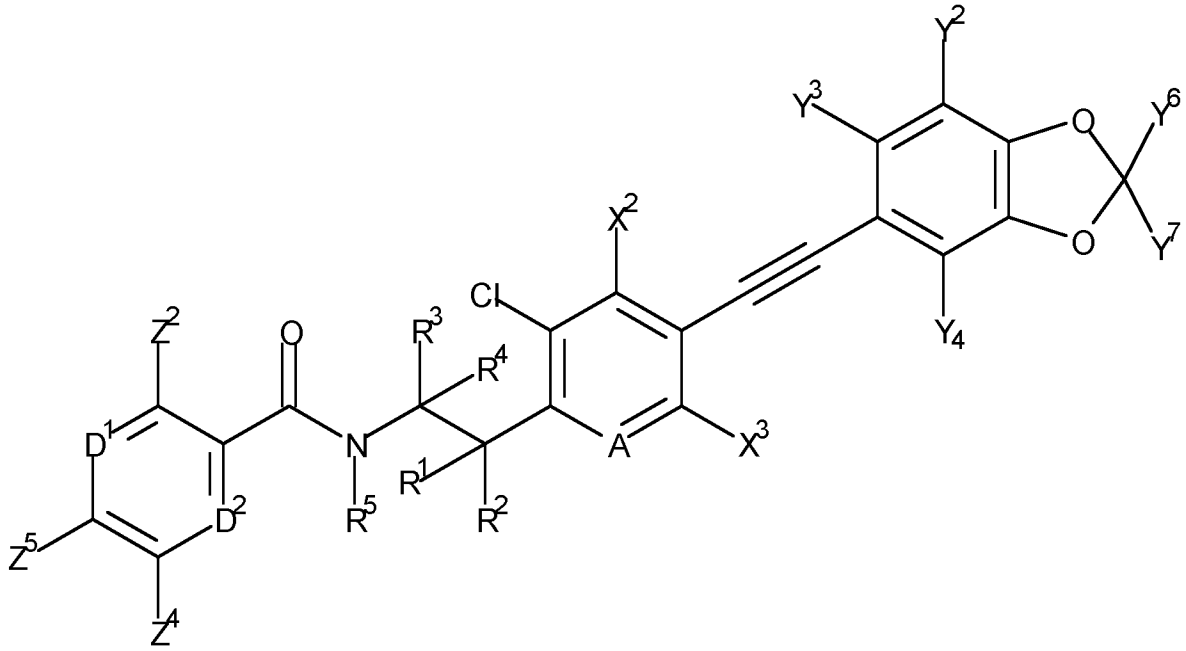


(LXXXI)

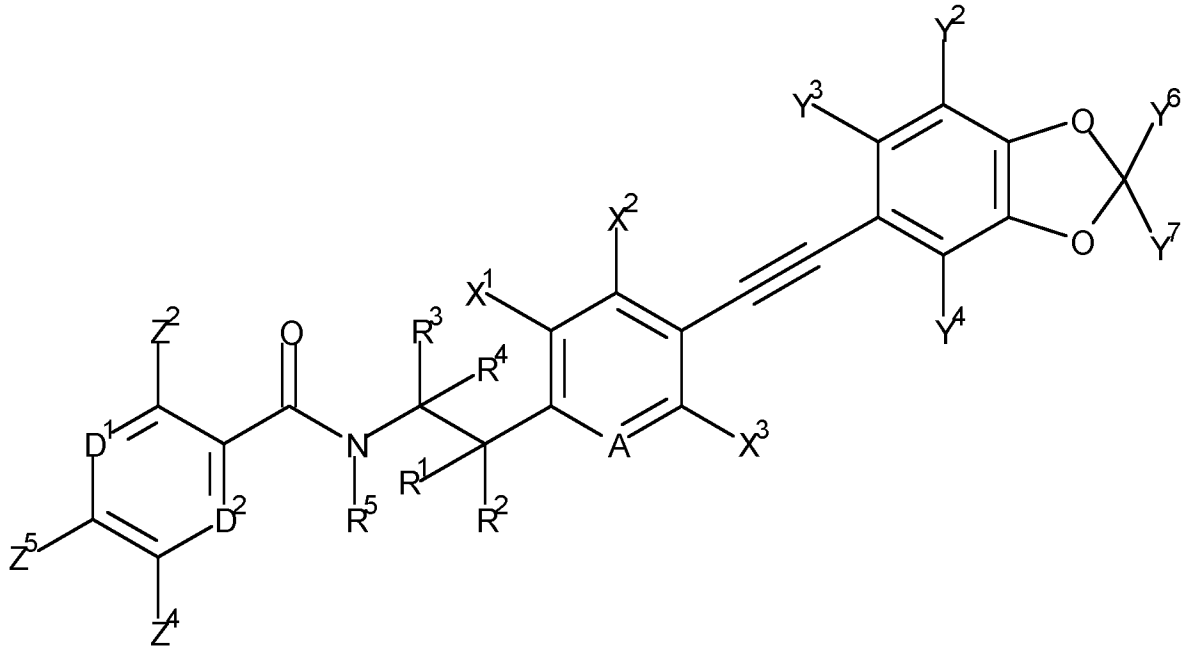
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein Y^6 is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXXII) or (LXXXIII)



(LXXXII)

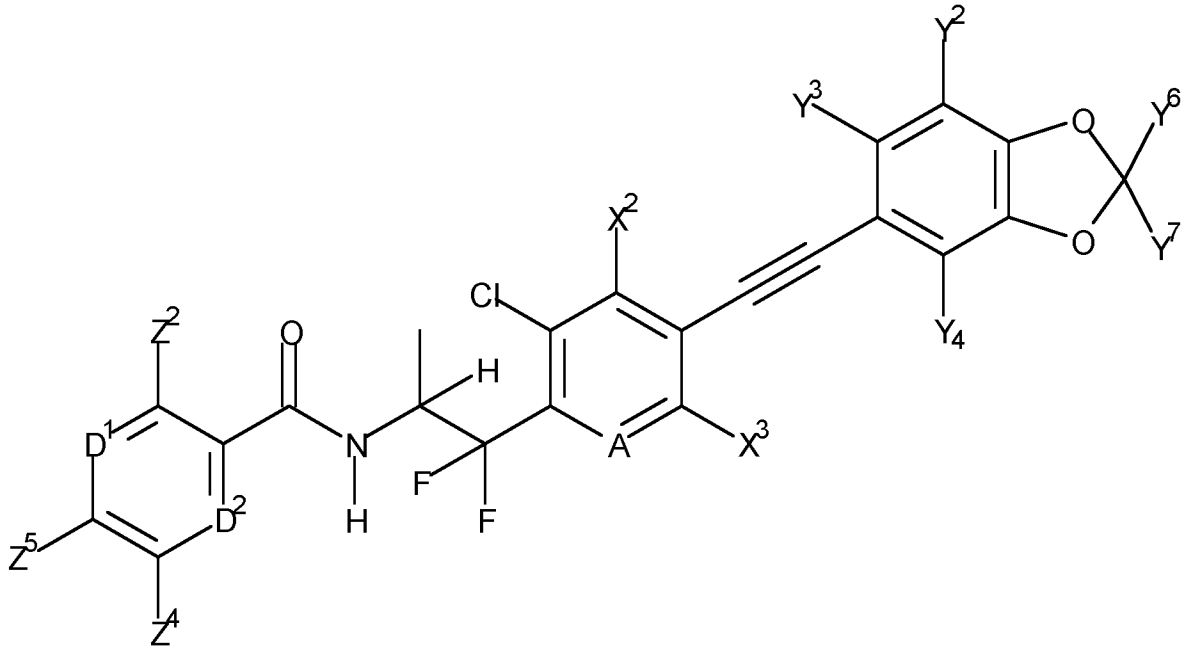


(LXXXIII)

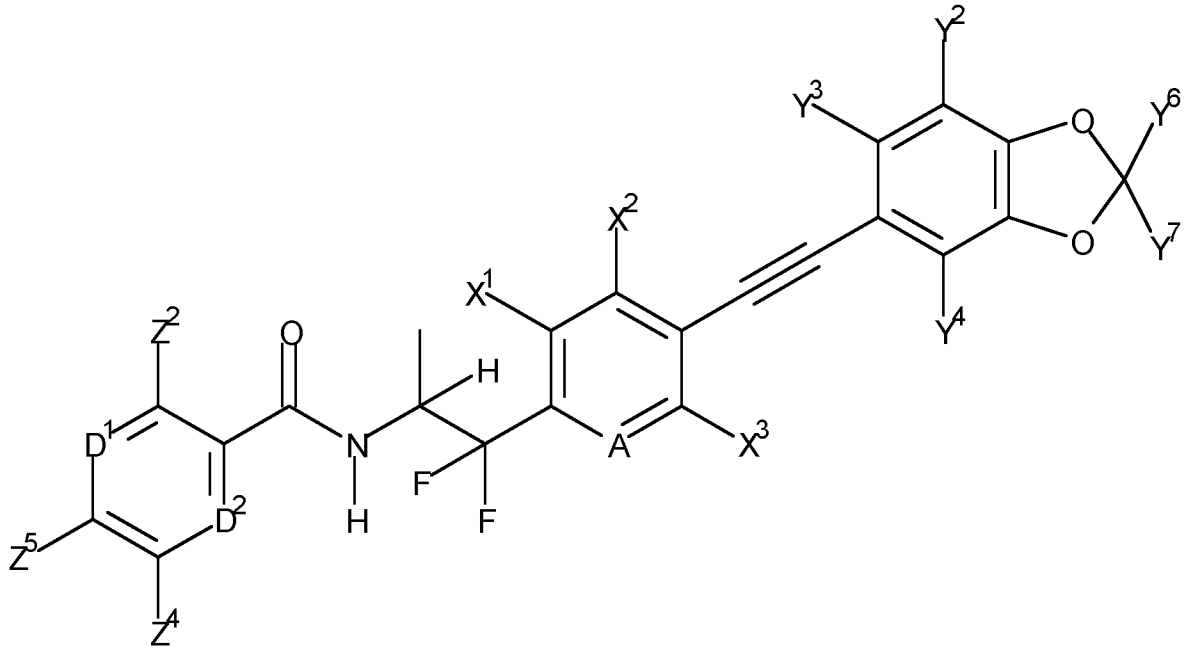
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein each of Y^6, Y^7, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXXIV) or (LXXXV)



(LXXXIV)

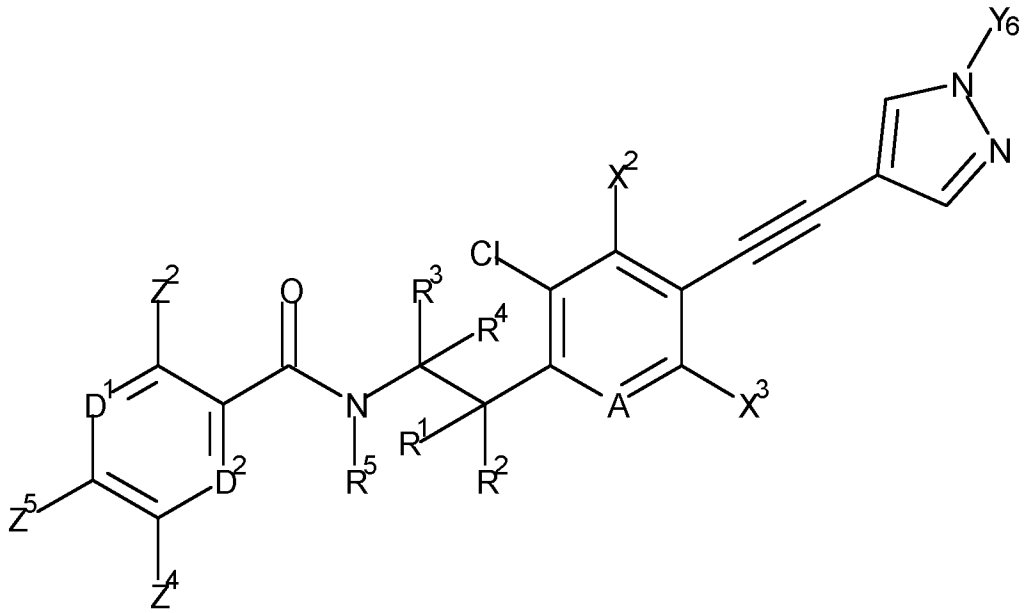


(LXXXV)

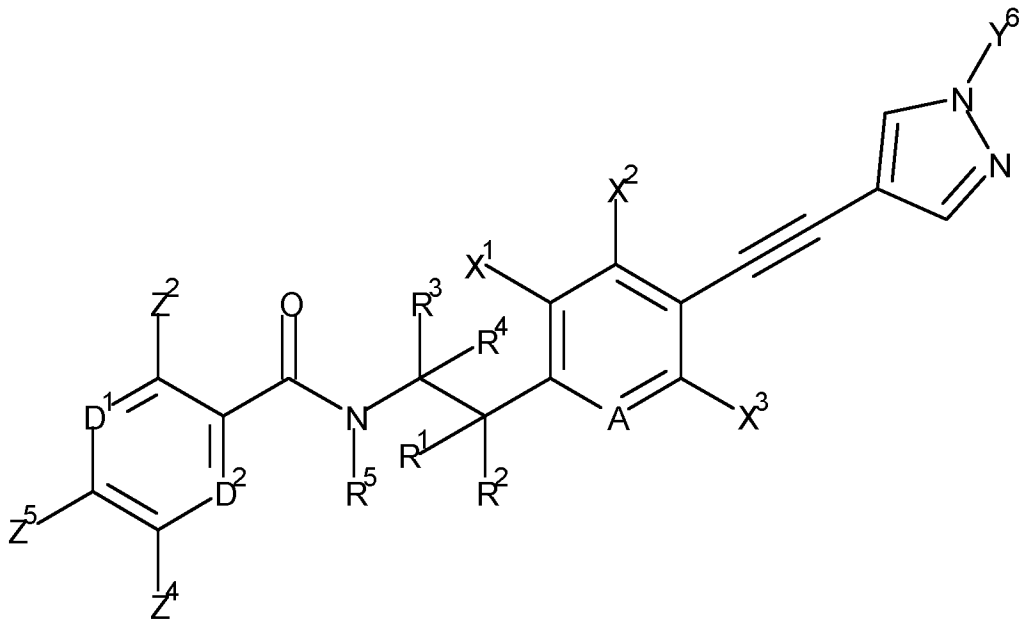
or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein each of Y^6, Y^7, is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXXVI) or (LXXXVII)



(LXXXVI)

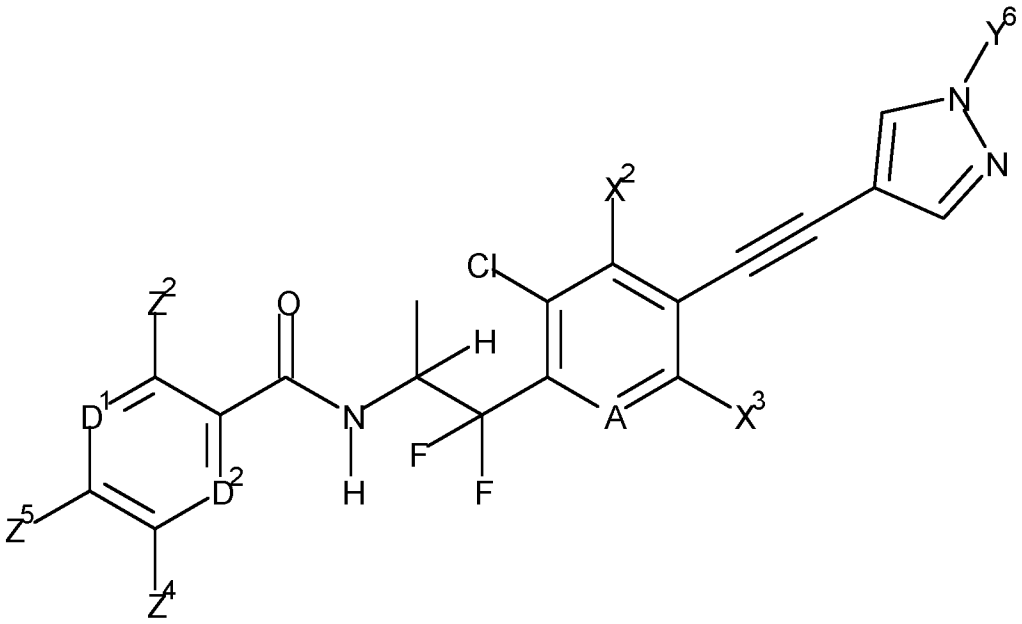


(LXXXVII)

or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein R^1, R^2, R^3, R^4, R^5, X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein Y^6 is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

In a suitable embodiment of the invention and/or embodiments thereof the compounds of the present invention are according to formula (LXXXVIII) or (LXXXIX)



(LXXXVIII)

(LXXXVIX

or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helminthic infection, wherein

D_1 is C-Z^1 or N; D_2 is C-Z^3 or N and wherein maximum one of D_1 or D_2 is N; A is C-X^4 or N; E is CH or N; and wherein X^1, X^2, X^3, X^4, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4 and Z^6, are as defined in any of the embodiments described herein, and wherein Y^6 is defined as in Y^1 in any of the embodiments of the invention and/or embodiments thereof described above.

The compound of the present invention and/or embodiments thereof may be administered orally, subcutaneously, or topically. Preferably, orally. Preferably subcutaneously. Preferably topically.

The compound of the present invention and/or embodiments thereof is useful against an infection caused by a nematode, cestode or trematode. Preferably the compound of the present invention and/or embodiments thereof is useful against a nematode. Preferably the compound of the present invention and/or embodiments thereof is useful against a trematode. Preferably the compound of the present invention and/or embodiments thereof is useful against *Fasciola*. Preferably the compound of the present invention and/or embodiments thereof is useful against *Dirofilaria* Preferably the compound of the present invention and/or embodiments thereof is useful against against *Haemonchus spp.* and/or *Trichostrongylus spp.*. Preferably the compound of the present invention and/or embodiments thereof is useful against against *Haemonchus contortus* and/or *Trichostrongylus colubriformis*.

The compound of the present invention and/or embodiments thereof is useful in the treatment of non-human animals. The compound of the present invention and/or embodiments thereof may be used for the treatment of an animal selected from the group consisting of ruminant, equine, companion animal,

swine, poultry or fish, preferable selected from the group consisting of sheep, bovine, horse. Preferably, sheep. Preferably ruminants. Preferably cow.

Suitably, the compound of the present invention and/or embodiments thereof is administered in a composition comprising a pharmaceutically acceptable carrier.

Suitably, the compound of the present invention and/or embodiments thereof is administered in an effective dose between about 0.01 and about 50 mg/ kg bodyweight of the animal.

Suitably, the compound is administered in combination with another anthelminthic agent.

Unless otherwise stated, a compound structure that does not indicate a particular conformation is intended to encompass compositions of all the possible conformational isomers of the compound, as well as compositions comprising fewer than all the possible conformational isomers.

In some embodiments of the invention and/or embodiments thereof, the compound of this invention is a chiral compound. In some embodiments of the invention and/or embodiments thereof, the compound of this invention is a non-chiral compound.

Salts, Solvates, N-Oxides and prodrugs

A salt of the above-described compounds may be advantageous due to one or more of the salt's physical properties, such as pharmaceutical stability in different temperatures and humidities; crystalline properties; and/or a desirable solubility in water, oil, or other solvent. In some instances, a salt may be used as an aid in the isolation, purification, and/or resolution of the compound. Acid and base salts can typically be formed by, for example, mixing the compound with an acid or base, respectively, using various known methods in the art. To the extent a salt of the compound is intended to be administered in vivo (i.e., to an animal) for a therapeutic benefit, the salt preferably is pharmaceutically acceptable.

In general, an acid addition salt can be prepared by reacting a free base compound with an approximately stoichiometric amount of an inorganic or organic acid. Examples of often suitable inorganic acids for making pharmaceutically acceptable salts include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Examples of often suitable organic acids for making pharmaceutically acceptable salts generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids. Specific examples of often suitable organic acids include cholic, sorbic, lauric, acetic, trifluoroacetic, formic, propionic, succinic, glycolic, gluconic, digluconic, lactic, malic, tartaric acid, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, aryl carboxylic acid (e.g., benzoic), anthranilic acid, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), alkylsulfonic (e.g., ethanesulfonic), arylsulfonic (e.g., benzenesulfonic), pantothenic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, β-hydroxybutyric, galactaric, galacturonic, adipic, alginic, butyric, camphoric, camphorsulfonic, cyclopentanepropionic, dodecylsulfic, glycoheptanoic, glycerophosphic, heptanoic, hexanoic, nicotinic, 2-

naphthalesulfonic, oxalic, palmoic, pectinic, 3-phenylpropionic, picric, pivalic, thiocyanic, tosylic, and undecanoic acid. In some embodiments of the invention and/or embodiments thereof, the salt comprises a trifluoroacetate, mesylate, or tosylate salt. In other embodiments of the invention and/or embodiments thereof, the salt comprises a hydrochloric acid salt.

In general, a base addition salt can be prepared by reacting a free acid compound with an approximately stoichiometric amount of an inorganic or organic base. Examples of base addition salts may include, for example, metallic salts and organic salts. Metallic salts, for example, include alkali metal (group Ia) salts, alkaline earth metal (group Ha) salts, and other physiologically acceptable metal salts. Such salts may be made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. For example, a free acid compound may be mixed with sodium hydroxide to form such a base addition salt. Organic salts may be made from amines, such as trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, ethanolamine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups may be quaternized with agents such as C1-C6-alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzylchloride and phenethyl bromides), and others.

A solvate of a compound of the formula (I)-(LXXXIX) or another compound may be formed by aggregation of said compound of the formula (I)-(LXXXIX) with solvent molecules such as water, alcohols, for example ethanol, aromatic solvents such as toluene, ethers, halogenated organic solvents such as dichloromethane, preferably in a definite proportion by weight.

An N-oxide of a compound of the formula (I)-(LXXXIX) or another compound may be formed by oxidation of an N-atom in an amine or N-heterocycle such as pyridine by oxidation agents such as hydrogen peroxide, peracids or inorganic oxidation agents such as potassium peroxymonosulfate (oxone). In preferred N-oxides a nitrogen atom in the group of formula (I) (LI) is oxidized, more preferred are N-oxides wherein the nitrogen atom in the para-position is oxidized.

This invention also encompasses prodrug derivatives of the compounds of the formula (I)-(LXXXIX). The term prodrug refers to compounds that are transformed in vivo to yield the parent compound of formula (I) or (Ib). In vivo means that in the case of, for example, treatment of a parasitic infection this transformation can occur in the host organism and/or the parasite. Various forms of prodrugs are well known in the art. For example, if the R^6, R^7, represents a pyridine, or if in formula (I) A_2 or A_4 is an N, it is possible to form pyridinium salts such as, for example, acyloxyalkylpyridinium salts, which can offer advantages in terms of higher solubility for parenteral dosage forms, which are described in S. K. Davidsen et al., J. of Med. Chem. 37 4423-4429 (1994). Other examples of possible prodrugs are compounds that form the double bond present in formula (I)-(LXXXIX) by elimination from a saturated precursor compound.Another example may be alkyloxycarbonyl substitutions in the R^5 position that may be cleaved by hydrolysis. A suitable example is methylformate.

The compounds according to this invention and/or embodiments thereof, their intermediates and compounds corresponding to the use according to the invention and/or embodiments thereof, may exist in various isomeric forms. A reference to a compound for use according to this invention and/or embodiments thereof, an intermediate thereof and a compound corresponding to the use according to the invention and/or embodiments thereof always includes all possible isomeric forms of such compound.

TREATMENT METHODS USING COMPOUNDS AND SALTS OF THIS INVENTION

Compounds and where applicable pharmaceutically acceptable solvates, N-oxides, salts and prodrugs thereof of this invention and/or embodiments thereof may generally be used as anthelmintics. In accordance with this invention, it has been discovered that these compounds and salts are particularly useful for treating nematode infections, such as infections by trematodes, cestodes and/or nematodes. The compounds of the present invention and/or embodiments thereof are suitable for use in treatment of infection from trematodes selected from the group consisting of *Dicrocoelium* spp., *Fasciola* spp. *Paramphistomum* spp., *Schistosoma* spp. The compounds of the present invention and/or embodiments thereof are suitable for use in treatment of infection from nematodes, selected from the group consisting of *Ancylostoma* spp., *Ascaridia* spp. *Ascaris* spp. *Bunostomum* spp. *Capillaria* spp., *Chabertia* spp. *Cooperia* spp. e.g. *Cooperia oncophora, Cooperia punctata, Cooperia curticei, Cooperia pectinata,*, *Dictyocaulus* spp., *Dirofilaria* spp. *Filaroides* spp., *Habronema* spp., *Haemonchus* spp, *Hyostrongylus* spp., *Nematodirus* spp. *Oesophagostomum* spp *Onchocerca* spp., *Ostertagia* spp. *Trichostrongylus* spp. ,
The compounds of the present invention and/or embodiments thereof are suitable for use in treatment of infection from trematodes selected from the group consisting of *Dicrocoelium dendriticum*, *Fasciola hepatica*, and *Schistosoma bovis*,.
The compounds of the present invention and/or embodiments thereof are suitable for use in treatment of infection from nematodes, selected from the group consisting of *Ascaridia galli*, *Ascaris suum*, *Bunostomum phleboptomum*, Chabertia ovina, *Cooperia oncophora, Cooperia punctata, Cooperia curticei, Cooperia pectinata,*, *Dirofilaria. immitis, Dirofilaria. repens*, *Haemonchus contortus.*, *Nematodirus helvetianus*, *Oesophagostomum dentatum.*, *Ostertagia ostertagi,*, *Ostertagia leptospicularis, Ostertagi circumcinata, Trichostrongylus axei, Trichostrongylus colubriformis, Trichostrongylus virinus,* and *Strongyloides papillosus.*

It is contemplated that the compound and salt of this invention and/or embodiments thereof may be used to treat a range of animals, especially mammals. Such mammals include, for example, humans. Other mammals include, for example, farm or livestock mammals (e.g., swine, bovines, sheep, goats, etc.), laboratory mammals (e.g., mice, rats, jirds, etc.), companion mammals (e.g., dogs, cats, equines, etc.), and wild and zoo mammals (e.g., buffalo, deer, etc.). In some embodiments of the invention and/or embodiments thereof, the compound and/or salt are used to treat cattle. In some embodiments of the invention and/or embodiments thereof, the compound and/or salt are used to treat bovine, such as cow. In some embodiments of the invention and/or embodiments thereof, the compound and/or salt are used to treat goats. In other embodiments of the invention and/or embodiments thereof, the compounds and salts are used to treat sheep. It is contemplated that the compounds and salts of this invention and/or

embodiments thereof also are suitable to treat non-mammals, such as birds (e.g., turkeys, chickens, etc.) and fish (e.g., salmon, trout, koi, etc.).

The term "(parasitic) infection" includes conditions associated with or caused by one or more (parasitic) pathogens; said conditions include clinical conditions (parasitoses) and sub-clinical conditions. The term "treatment of parasitic infection" thus includes both the treatment of parasitoses and the treatment of sub-clinical conditions. The treatment of a parasite infection generally implies the suppression of parasite (e.g. helminth) burdens in the animal below that level at which economic loss occurs.

Sub-clinical conditions are typically conditions not directly leading to clinical symptoms in the parasite infected animal but leading to economic losses. Such economic losses can be e.g. by depression of growth in young animals, lower feed efficiency, lower weight gain in meat producing animals, lower milk production in ruminants and equines, lower egg production in laying hens, or lower wool-production in sheep.

The term "parasitoses" relates to clinically manifest pathologic conditions and diseases associated with or caused by an infection by one or more parasites, such as, for example parasitic gastroenteritis or anemia in ruminants e.g. sheep and goats or colic in horses.

In general, the prevention or treatment of parasitic infection including parasitoses is achieved by administering one or more, preferably one compound according to this invention and/or embodiments thereof to treat a parasitic infection such as a helminth infection, the latter treatment being the sole treatment of the use according to the invention.

Thus the invention provides a method of treating a (parasitic) infection such as a helminth infection, including parasitoses, which comprises administering to the animal an antiparasitically, preferably an anthelmintically, effective amount of one or more compounds according to this invention and/or embodiments thereof,. Preferably nematode, cestode or trematode infections are treated, more preferably nematode infections.

"Treating (parasitic) infections" includes treating parasitoses and means to partially or completely inhibit the development of (parasitic) infections of an animal susceptible to (parasitic) infection, reduce or completely eliminate the symptoms of infections of an animal having infections, and/or partially or completely cure infections of an animal having infections. This can be achieved by alleviating or reducing pathogen numbers such as parasite numbers in an animal.

The effect of the compounds according to this invention or the use according to the invention can be e.g. ovicidal, larvicidal, and/or adulticidal or a combination thereof. The effect can manifest itself directly, i.e. killing the parasites either immediately or after some time has elapsed, for example when molting occurs, or by destroying their eggs, or indirectly, e.g. reducing the number of eggs laid and/or the hatching rate.

Alternatively the parasite is not killed but paralyzed and is then dislodged and excreted by the host animal.

In another aspect the present invention thus provides a pharmaceutical composition comprising an anthelmintically effective amount of one or more, preferably one compound for use according to this invention and/or embodiments thereof and one or more pharmaceutically acceptable excipients.

The compounds and pharmaceutical compositions according to this invention are useful in treating parasitic infections such as helminth infections of animals. An "effective amount," is the amount or quantity of a compound that is required to alleviate or reduce parasite numbers in an animal, and/or to inhibit the development of parasite infections in an animal, in whole or in part.

This amount is readily determined by observation or detection of the pathogen numbers such as parasite numbers both before and after contacting the sample of pathogens such as parasites including their stages with the compound for use according to this invention, directly and/or indirectly, e.g., by contacting articles, surfaces, foliage, or animals with the compound e.g. the parasite count is reduced, after a first administration, by an amount ranging from 5% to about 100%.

This can be evaluated by counting parasites (especially helminths) directly after necroscopy of the host animal.

The reduction of parasite numbers, especially gastrointestinal helminth parasites can be alternatively measured in-directly by faecal egg or differential larval counts. In this case the effective amount of the compound is determined by the reduction of the number of excreted helminth eggs or larvae in the faeces of the treated animal before and after treatment. For an in vivo administration the compound according to this invention and/or embodiments thereof, is preferably administered to an animal in an effective amount which is synonymous with "pharmaceutically effective amount" or "anthelmintically effective amount".

Optionally the compounds according to this invention are used to treat a helminth infection, such as an infection caused by one or more helminths selected from the group consisting of a) trematodes e.g. *Dicrocoelium* spp. e.g. *Dicrocoelium dentriticum*, *Fasciola* spp. *e.g. Fasciola hepatica*, *Paramphistomum* spp., *Schistosoma* spp., or b) nematodes, e.g. , *Ancylostoma* spp., *Ascaridia* spp., *Ascaris* spp., *Bunostomum* spp., *Capillaria* spp., *Chabertia* spp., *Cooperia* spp. e.g. *Cooperia oncophora, Cooperia punctata, Cooperia curticei, Cooperia pectinata,*, *Dictyocaulus* spp., *Dirofilaria* spp., *Filaroides* spp., *Habronema* spp., *Haemonchus* spp *e.g . Haemonchus contortus.*, *Hyostrongylus* spp., *Nematodirus* spp., *Oesophagostomum* spp *e.g. Oesophagostomum dentatum.*, *Onchocerca* spp., *Ostertagia* spp., *Schistosoma spp. Schistosoma bovis Trichostrongylus* spp *e.g. Trichostrongylus axei, Trichostrongylus colubriformis, Trichostrongylus virinus Trichostrongylus axei, Ascaridia galli*, and/or, *Strongyloides papillosus, Chabertia ovina, Bunostomum phleboptomumNematodirus helvetianus, Ostertagia ostertagi, Ostertagia leptospicularis,Ostertagi circumcinata, ,* and tematode infections by, *Dicrocoelium dentriticum, Schistosoma bovis,*

The compounds of this invention are particularly active against nematodes. For example, against nematodes of the genus *Trichostrongylus*, and/or *Haemonchus*, *Fasciola* and/or *Dirofilaria*.

In some embodiments of the invention and/or embodiments thereof, one or more compounds or salts of this invention are used to treat an infection by a nematode (for example, *H. contortus*) that is resistant to one or more other anthelmintic agents. In some embodiments of the invention and/or embodiments thereof, the compound or salt is active against a nematode (for example, *H. contortus*) resistant to one or more of the following: an avermectin (e.g., ivermectin, selamectin, doramectin, abamectin, and eprinomectin); a milbemycin (e.g. moxidectin and milbemycin oxime); a pro-benzimidazole (e.g., febantel, netobimin, and thiophanate); a benzimidazole derivative, such as a thiazole benzimidazole derivative (e.g., thiabendazole and cambendazole) or a carbamate benzimidazole derivative (e.g., fenbendazole, albendazole (oxide), mebendazole, oxfendazole, parbendazole, oxibendazole, flubendazole, and triclabendazole); an imidazothiazole (e.g., levamisole and tetramisole); a tetrahydropyrimidine (e.g. morantel and pyrantel), an organophosphate (e.g., trichlorphon, haloxon, dichlorvos, and naphthalophos); a salicylanilide (e.g., closantel, oxyclozanide, rafoxanide, and niclosamide); a nitrophenolic compound (e.g., nitroxynil and nitroscanate); benzoenedisulphonamide (e.g., clorsulon); a pyrazinaisoquinoline (e.g., praziquantel and epsiprantel); a heterocyclic compound (e.g., piperazine, diethylcarbamazine, dichlorophen, and phenothiazine); an arsenical (e.g., thiacetarsamide, melorsamine, and arsenamide); cyclooctadepsipeptide (e.g., emodepside); and a paraherquamide. In some embodiments of the invention and/or embodiments thereof, the compound or salt is active against a nematode (for example, *H. contortus*) resistant to an avermectin, such as ivermectin. In other embodiments of the invention and/or embodiments thereof, the compound or salt is alternatively or additionally active against a nematode (for example, *H. contortus*) resistant to a benzimidazole derivative, such as fenbendazole. In other embodiments of the invention and/or embodiments thereof, the compound or salt is alternatively or additionally active against a nematode (for example, *H. contortus*) resistant to levamisole. And, in other embodiments of the invention and/or embodiments thereof, the compound or salt is alternatively or additionally active against a nematode (for example, *H. contortus*) resistant to pyrantel. And, in other embodiments of the invention and/or embodiments thereof, the compound or salt is alternatively or additionally active against a nematode (for example, *H. contortus*) resistant to milbemycin, such as moxidectin

A dosage form may comprise one or more suitable excipients. Such excipients generally include, for example, sweetening agents, flavoring agents, coloring agents, preservative agents, inert diluents (e.g., calcium carbonate, sodium carbonate, lactose, calcium phosphate, sodium phosphate, or kaolin), granulating and disintegrating agents (e.g., corn starch or alginic acid), binding agents (e.g., gelatin, acacia, or carboxymethyl cellulose), and lubricating agents (e.g., magnesium stearate, stearic acid, or talc). Liquid compositions will generally comprise a solvent, such as, for example, one or more of dimethylformamide, N,N-dimethylacetamide, pyrrolidone, N-methylpyrrolidone, polyethyleneglycol, diethyleneglycolmonoethyl ester, dimethylsulfoxide, andethyl lactate. The solvent preferably has sufficient chemical properties and quantity to keep the compound or salt solubilized under normal storage

conditions. In some instances, it may be desirable for the compositions to comprise one or more preservatives. The presence of a preservative may, for example, allow for the compositions to be stored for longer periods. Every excipient in the composition preferably is pharmaceutically acceptable.

Dosage forms useful in the current invention may be liquid, semi-solid or solid dosage forms.

Liquid dosage forms of the compounds are generally solutions, suspensions or emulsions. A solution is a mixture of two or more components that form a single phase that is homogeneous down to the molecular level. A suspension consists of insoluble solid particles dispersed in a liquid medium, with the solid particles accounting for about 0.5% to about 30% of the suspension. The liquid may be aqueous, oily, or both. An emulsion is a heterogeneous dispersion of one immiscible liquid in another; it relies on an emulsifying agent for stability. A dry powder (or granule) for reconstitution is reconstituted as a solution or as a suspension immediately prior to injection. The principal advantage of this dosage form is that it overcomes the problem of instability in solution or suspension.

One possible dosage route is the oral dosage route, wherein the compound according to this invention is administered via the mouth. Oral dosage forms suitable for oral administration comprise liquids (e.g. drench or drinking water formulations), semi-solids (e.g. pastes, gels), and solids (e.g. tablets, capsules, powders, granules, chewable treats, premixes and medicated blocks).

A drench is a liquid oral formulation that is administered directly into the mouth/throat of an animal, especially a livestock animal, by means of a "drench gun" or syringe or another suitable device. When the composition is administered in the animal recipient's drinking water or as a drench, it may be convenient to use a solution or suspension formulation. This formulation can be, for example, a concentrated suspension that is mixed with water or a dry preparation that is mixed and suspended in the water.

Semi-solid oral formulations (pastes or gels) are generally administered via an applicator directly into the mouth of an animal or mixed with the feed.

Solid oral formulations are either administered directly to an animal (tablet, capsule) or mixed with the feed or via medicated feed blocks.

When the oral formulation is administered via a non-human animal's feed, it may, for example, be fed as a discrete feed or as a chewable treat. Alternatively (or additionally), it may, for example, be intimately dispersed in the animal recipient's regular feed, used as a top dressing, or in the form of solid pellets, paste or liquid that is added to the finished feed. When the oral formulation is administered as a feed additive, it may be convenient to prepare a "premix" in which the oral formulation is dispersed in a liquid or solid carrier. This "premix" is, in turn, dispersed in the animal's feed using, for example, a conventional mixer.

Several modified-release delivery systems have been developed, that take advantage of the unique anatomy of the ruminant forestomach, i.e. for intra-ruminal administration. An intraruminal bolus is a specific formulation for ruminants (cattle, sheep, goats, buffalos, camelids, deer etc). It is a veterinary delayed release delivery system which remains in the rumeno-reticular sac of a ruminant animal over an extended period of time and in which the therapeutically active substance has a predictable and delayed release pattern. Such intraruminal boluses are usually administered using a balling gun or another suitable device.

It is contemplated that the compounds and salts of this invention may alternatively be administered via non-oral routes, such as rectally, via inhalation (e.g., via a mist or aerosol), transdermally (e.g., via a transdermal patch), or parenterally (e.g., subcutaneous injection, intravenous injection, intramuscular injection, etc.).

For instance the compounds of this invention may be administered topically using a transdermal formulation (i.e. a formulation that passes through the skin). Alternatively the compounds of this invention may be administered topically via the mucosa. Typical formulations for transdermal and mucosal administration include, for example, pour-ons, spot-ons, dips, sprays, mousses, shampoos, powders, gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, limb bands, collars, ear tags, wafers, sponges, fibers, bandages, and microemulsions. The pour-on or spot-on methods, for example, comprise applying the composition to a specific location of the skin or coat, such as on the neck or backbone of the animal. This may be achieved by, for example, applying a swab or drop of the pour-on or spot- on formulation to a relatively small area of the recipient animal's skin or coat (i.e., generally no greater than about 10% of the animal recipient's skin or coat). In some embodiments of the invention and/or embodiments thereof, the compound of this invention is dispersed from the application site to wide areas of the fur due to the spreading nature of the components in the formulation and the animal's movements while, in parallel, being absorbed through the skin and distributed via the animal recipient's fluids and/or tissues.

The compounds and salts of this invention may be administered parenterally. Optionally the administration is a subcutaneous injection, an intravenous injection, or intramuscular injection. Preferably the compound of the present invention and/or embodiments thereof are administered by subcutaneous injection.

Parenteral dosage forms and delivery systems for non-oral routes include injectables (solutions, suspensions, emulsions, and dry powders for reconstitution), and implants. A solution for injection is a mixture of two or more components that form a single phase that is homogeneous down to the molecular level. A suspension for injection consists of insoluble solid particles dispersed in a liquid medium, with the solid particles accounting for about 0.5% to about 30% of the suspension. The liquid may be aqueous, oily, or both. An emulsion for injection is a heterogeneous dispersion of one immiscible liquid in another; it relies on an emulsifying agent for stability. A dry powder for parenteral administration is reconstituted as a solution or as a suspension immediately prior to injection. The principal advantage of this dosage form is

that it overcomes the problem of instability in solution. The majority of implants used in veterinary medicine are compressed tablets or dispersed matrix systems in which the drug is uniformly dispersed within a nondegradable polymer.

Pharmaceutical compositions of the present invention may be manufactured by, for example, processes known in the art. These processes include, for example, a variety of known mixing, dissolving, granulating, emulsifying, encapsulating, entrapping, and lyophilizing processes. Optimal formulation depends on, for example, the dosage route (e.g. oral, injection, topical).

Solid dosage forms, for example, may be prepared by, for example, intimately and uniformly mixing the compounds with fillers, binders, lubricants, glidants, disintegrants, flavoring agents (e.g., sweeteners), buffers, preservatives, pharmaceutical-grade dyes or pigments, and controlled release agents.

Oral dosage forms other than solids may be prepared by mixing the compounds with, for example, one or more solvents, viscosity-enhancing agents, surfactants, preservatives, stabilizers, resins, fillers, binders, lubricants, glidants, disintegrants, co-solvents, sweeteners, flavorings, perfuming agents, buffers, suspending agents, and pharmaceutical-grade dyes or pigments.

Contemplated binders include, for example, gelatin, acacia, and carboxymethyl cellulose.

Contemplated lubricants include, for example, magnesium stearate, stearic acid, and talc.

Contemplated disintegrants include, for example, corn starch, alginic acid, sodium carboxymethylcellulose, and sodium croscarmellose.

Contemplated buffers include, for example, sodium citrate, and magnesium and calcium carbonate and bicarbonate.

Contemplated solvents include, for example, water, petroleum, animal oils, vegetable oils, mineral oil, and synthetic oil. Physiological saline solution or glycols (e.g., ethylene glycol, propylene glycol, or polyethylene glycol) also may be included. The solvent preferably has sufficient chemical properties and quantity to keep the compounds solubilized at temperatures in which the composition is stored and used.

Contemplated viscosity-enhancing agents include, for example, polyethylene, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl- methylcellulose, hydroxypropylcellulose, sodium alginate, carbomer, povidone, acacia, guar gum, xanthan gum, tragacanth, methylcellulose, carbomer, xanthan gum, guar gum, povidone, sodium carboxymethylcellulose, magnesium aluminum silicate, carboxyvinyl polymers, carrageenan, hydroxyethyl cellulose, laponite, water-soluble salts of cellulose ethers, natural gums, colloidal magnesium aluminum silicateor finely divided silica, homopolymers of acrylic acid crosslinked with an alkyl ether of pentaerythritol or an alkyl ether of sucrose, and carbomers.

Contemplated surfactants include, for example, polyoxyethylene sorbitan fatty acid esters; polyoxyethylene monoalkyl ethers; sucrose monoesters; lanolin esters and ethers; alkyl sulfate salts; and sodium, potassium, and ammonium salts of fatty acids.

Contemplated preservatives include, for example, phenol, alkyl esters of parahydroxybenzoic acid (e.g., methyl p-hydroxybenzoate (or "methylparaben") and propyl p-hydroxybenzoate (or "propylparaben")), sorbic acid, o-phenylphenol benzoic acid and the salts thereof, chlorobutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, and cetylpyridinium chloride.

Contemplated stabilizers include, for example, chelating agents and antioxidants.

Solid dosage forms also may comprise, for example, one or more excipients to control the release of the compounds. For example, it is contemplated that the compounds may be dispersed in, for example, hydroxypropylmethylcellulose. Some oral dosage forms (e.g., tablets and pills) also may be prepared with enteric coatings.

Topical dosage route uses, for example, a concentrated liquid or semi-liquid solution, suspension (aqueous or non-aqueous), emulsion (water-in-oil or oil-in- water), or microemulsion comprising a compounds dissolved, suspended, or emulgated in a pharmaceutically-acceptable liquid vehicle. In such embodiments of the invention and/or embodiments thereof, a crystallization inhibitor optionally may generally be present.

Such a pour-on or spot-on formulation can be prepared by dissolving, suspending, or emulsifying the compounds in a suitable skin-fitted solvent or solvent mixture. Other excipients may be included as well, such as, for example, a surfactant, colorant, antioxidant, stabilizer, adhesive, etc. Contemplated solvents include, for example, water, alkanol, glycol, polyethylene glycol, polypropylene glycol, glycerin, benzyl alcohol, phenylethanol, phenoxyethanol, ethyl acetate, butyl acetate, benzyl benzoate, dipropylene glycol monomethyl ether, diethylene glycol monobutyl ether, acetone, methyl ethyl ketone, aromatic and/or aliphatic hydrocarbons, vegetable or synthetic oil, dimethylformamide (DMF), liquid paraffin, silicone, dimethylacetamide, N-methylpyrrolidone, or 2,2-dimethyl-4-oxy- methylene-1 ,3-dioxolane.

A topical formulation (particularly a pour-on or spot- on formulation) may comprise a carrier that promotes the absorption or penetration of the compounds through the skin into the blood stream, other bodily fluids (lymph), and/or body tissue (fat tissue). Contemplated examples of dermal penetration enhancers include, for example, dimethylsulfoxide, isopropyl myristate, dipropylene glycol pelargonate, silicone oil, aliphatic esters, triglycerides, and fatty alcohols.

Topical formulations also (or alternatively) may comprise, for example, one or more spreading agents. These substances act as carriers that assist in distributing an active ingredient over the animal recipient's coat or skin. They may include, for example, isopropyl myristate, dipropylene glycol pelargonate, silicone oils, fatty acid esters, triglycerides, and/or fatty alcohols. Various spreading oil/solvent combinations also

may be suitable, such as, for example, oily solutions, alcoholic and isopropanolic solutions (e.g., solutions of 2-octyl dodecanol or oleyl alcohol), solutions of esters of monocarboxylic acids (e.g., isopropyl myristate, isopropyl palmitate, lauric acid oxalic ester, oleic acid oleyl ester, oleic acid decyl ester, hexyl laurate, oleyl oleate, decyl oleate, and caproic acid esters of saturated fatty alcohols having a carbon chain of 12 to 18 carbons), solutions of esters of dicarboxylic acids (e.g., dibutyl phthalate, diisopropyl isophthalate, adipic acid diisopropyl ester, and di-n-butyl adipate), or solutions of esters of aliphatic acids (e.g., glycols). When the formulation comprises a spreading agent, it also may be advantageous to include a dispersant, such as, for example, pyrrolidin-2-one, N- alkylpyrrolidin-2-one, acetone, polyethylene glycol or ether or ester thereof, propylene glycol, or synthetic triglycerides.

When formulated in, for example, an ointment, it is contemplated that the compounds may be mixed with, for example, either a paraffinic or a water-miscible ointment base. When formulated in a cream, it is contemplated that the compounds may be formulated with, for example, an oil-in-water cream base. In some instances, the aqueous phase of the cream base includes, for example at least about 30% (w/w) of a polyhydric alcohol, such as propylene glycol, butane-1, 3-diol, mannitol, sorbitol, glycerol, polyethylene glycol, or a mixture thereof.

Injectable formulations may be prepared according to, for example, the known art using suitable solvents, solubilizing agents, protecting agents, dispersing agents, wetting agents, and/or suspending agents. Contemplated carrier materials include, for example, water, ethanol, butanol, benzyl alcohol, glycerin, 1, 3-butanediol, Ringer's solution, isotonic sodium chloride solution, bland fixed oils (e.g., synthetic mono- or diglycerides), vegetable oil (e.g., corn oil), dextrose, mannitol, fatty acids (e.g., oleic acid), dimethyl acetamide, surfactants (e.g., ionic and non-ionic detergents), N- methylpyrrolidone, propylene glycol, and/or polyethylene glycols (e.g., PEG 400).

Contemplated solubilizing agents include, for example, polyvinyl pyrrolidone, polyoxyethylated castor oil, polyoxyethylated sorbitan ester, and the like. Contemplated protecting agents include, for example, benzyl alcohol, trichlorobutanol, p-hydroxybenzoic acid ester, n-butanol, and the like.

In some embodiments of the invention and/or embodiments thereof, a parenteral formulation is, for example, prepared from sterile powders or granules having one or more of the carrier materials discussed above for other formulations. The compound is, for example, dissolved or suspended in a liquid comprising water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. The pH generally may be adjusted, if necessary, with a suitable acid, base, or buffer.

Other inert ingredients may generally be added to the composition as desired. To illustrate, it is contemplated that these may include, for example, lactose, mannitol, sorbitol, calcium carbonate, sodium carbonate, tribasic calcium phosphate, dibasic calcium phosphate, sodium phosphate, kaolin, compressible sugar, starch, calcium sulfate, dextro or microcrystalline cellulose, colloidal silicon dioxide, starch, sodium starch glycolate, crospovidone, microcrystalline cellulose, tragacanth,

hydroxypropylcellulose, pregelatinized starch, povidone, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and methylcellulose.

Further aspects regarding formulation of drugs and various excipients are found in, for example, Gennaro, A.R., et al., eds., Remington: The Science and Practice of Pharmacy (Lippincott Williams & Wilkins, 20th Ed., 2000). Another source regarding formulation of drugs and various excipients is found in, for example, Liberman, H. A., et al., eds., Pharmaceutical Dosage Forms (Marcel Decker, New York, N.Y., 1980).

The concentration of the compounds according to this invention in the applied dosage form may vary widely depending on, for example, the dosage route. In general, the concentration is from about 1 to about 70% (by weight). In some embodiments of the invention and/or embodiments thereof, for example, the concentration is from about 1 to about 50% (by weight), or from about 10 to about 50% (by weight). In other embodiments of the invention and/or embodiments thereof, the concentration is from about 35 to about 65% (by weight), from about 40 to about 60% (by weight), from about 45 to about 55% (by weight), or about 50% (by weight).

In another aspect the present invention thus provides a pharmaceutical composition comprising an anthelmintically effective amount of one or more, preferably one compound according to this invention and/or embodiments thereof and one or more pharmaceutically acceptable excipients.

The formulation type chosen for a dosage form in any instance will depend upon the particular purpose envisaged and the physical, chemical and biological properties of the compound according to this invention.

The compounds and pharmaceutical compositions according to this invention are useful in treating parasitic infections such as helminth infections of animals. An "effective amount," is the amount or quantity of a compound that is required to alleviate or reduce parasite numbers in an animal, and/or to inhibit the development of parasite infections in an animal, in whole or in part.

This amount is readily determined by observation or detection of the pathogen numbers such as parasite numbers both before and after contacting the sample of pathogens such as parasites including their stages with the compound according to this invention and/or embodiments thereof, directly and/or indirectly, e.g., by contacting articles, surfaces, foliage, or animals with the compound.

This can be evaluated by counting parasites (especially helminths) directly after necroscopy of the host animal.

The reduction of parasite numbers, especially gastrointestinal helminth parasites can be alternatively measured in-directly by faecal egg or differential larval counts. In this case the effective amount of the compound is determined by the reduction of the number of excreted helminth eggs or larvae in the faeces

of the treated animal before and after treatment. For an in vivo administration the compound according to this invention and/or embodiments thereof, is preferably administered to an animal in an effective amount which is synonymous with "pharmaceutically effective amount" or "anthelmintically effective amount".

In general, the compositions of this invention are administered in a dosage form that provides a therapeutically effective amount of the compound or salt to the site of infection. A "therapeutically effective amount" is an amount that is sufficient to ameliorate, suppress, or eradicate a target pathogen(s) infection. Generally, the therapeutically effective amount is defined as the amount necessary to achieve a concentration efficacious to control the target pathogen(s) at the site of infection. The concentration at the site of infection is preferably at least equal to the MIC90 level (minimum inhibitory concentration, i.e., the concentration that inhibits the growth of 90% of the target pathogen) of the compound or salt thereof for the target pathogen. To the extent the compound or salt is administered with another active ingredient(s) (e.g., one or more other anthelmintics), the dosage preferably comprises an amount of the compound or salt that, together with the amount of other active ingredient(s), constitutes a therapeutically effective amount.

A single administration of the compound or salt is typically sufficient to treat a nematode infection. Although such a single dose is typically preferred, it is contemplated that multiple doses can be used. When the compound or salt is orally administered, the total dose to treat an infection is generally greater than about 0.01 mg/kg (i.e., milligram of compound or salt per kilogram body weight). In some such embodiments of the invention and/or embodiments thereof, the total dose is from about 0.01 to about 100 mg/kg, from about 0.01 to about 50 mg/kg, from about 0.1 to about 25 mg/kg, or from about 1 to about 20. For sheep, for example, the dose is generally from about 1 to about 15 mg/kg, from about 8 to about 12 mg/kg, or about 10 mg/kg. The same dose range may be suitable for other routes of administration. For example, in some embodiments of the invention and/or embodiments thereof, the same dose range is used for subcutaneous administration. The desired dose, however, may be less in some instances where the compound or salt is administered parenterally, particularly intravenously. For example, in some such embodiments of the invention and/or embodiments thereof, the dose is from about 0.01 to about 50 mg/kg, from about 0.01 to about 15 mg/kg, or from about 0.1 to about 10. For sheep, for example, a suitable intravenous dose may be from about 0.01 to about 10 mg/kg, from about 0.1 to about 5 mg/kg, or about 1 mg/kg.

If the compound or salt is administered parenterally via an injection, the concentration of the compound or salt in the dosage form preferably is sufficient to provide the desired therapeutically effective amount of the compound or salt in a volume that is acceptable for parenteral administration.

It may advantageous if the compounds of the present invention could be given subcutaneously because subcutaneous administration is a minimally invasive mode of administration. Subcutaneous administration is also the most versatile mode of administration that can be used for short term and long term therapies. Subcutaneous administration can be performed by injection or by implantation of a sustained or timed release device beneath the surface of the skin. The site of the injection or device can be rotated when

multiple injections or devices are needed. Accordingly, subcutaneous formulations are much easier to handle, especially since the formulation may have to be taken regularly and for a large group of animals. Furthermore, the easy and speed of subcutaneous delivery allows increased compliance and quicker access to medication when needed.

Factors affecting the preferred dosage may include, for example, the type (e.g., species and breed), age, size, sex, diet, activity, and condition of the intended recipient; the administration route; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular composition administered; and whether the compound or salt is being administered as part of a combination of active ingredients. Thus, the preferred amount of the compound or salt can vary, and, therefore, can deviate from the typical dosages set forth above. Determining such dosage adjustments is generally within the skill of those in the art.

This invention also is directed to kits that are, for example, suitable for use in performing the methods of treatment described above. The kit comprises a therapeutically effective amount of at least one compound or salt of this invention, and an additional component. The additional component(s) may be, for example, one or more of the following: another ingredient (e.g., an excipient or active ingredient), instructions for combining the compound or salt with another ingredient, an apparatus for combining the compound or salt with another ingredient and/or administering the compound or salt, instructions for using an apparatus to combine the compound or salt with another ingredient and/or administer the compound or salt, or a diagnostic tool.

Examples of contemplated combination therapies

The methods and pharmaceutical compositions of this invention encompass methods wherein a compound according to this invention and/or embodiments thereof or a compound corresponding to the use according to the invention and/or embodiments thereof is the sole active ingredient administered to the recipient animal. It is contemplated, however, that the methods and pharmaceutical compositions also encompass combination therapies wherein a compound is administered in combination with one or more other pharmaceutically acceptable active ingredients. The other active ingredient(s) may be, for example, one or more other compounds according to this invention and/or embodiments thereof or one or more other compounds corresponding to the use according to the invention and/or embodiments thereof. Alternatively (or additionally), the other active ingredient(s) may be one or more pharmaceutically acceptable compounds that are not compounds according to this invention or compounds corresponding to the use according to the invention. The other active ingredient(s) may target the same and/or different parasites and conditions.

Contemplated active ingredient(s) that may be administered in combination with the compounds include, for example, pharmaceutically acceptable anthelmintics, insecticides and acaricides, insect growth regulators, anti-inflammatories, anti-infectives, anti-protozoals, hormones, dermatological preparations

(e.g., antiseptics and disinfectants), and immunobiologicals (e.g., vaccines and antisera) for disease prevention.

Therefore this invention is also directed to the use as a medicament of combinations comprising a) one or more compounds according to this invention or one or more compounds corresponding to the use according to this invention with b) one or more pharmaceutically acceptable active compounds which differ in structure from component a). The active compounds b) are preferably anthelmintic compounds, more preferably selected from the group consisting of avermectins (e.g., ivermectin, selamectin, doramectin, abamectin, and eprinomectin); milbemycins (e.g. moxidectin and milbemycin oxime); pro-benzimidazoles (e.g., febantel, netobimin, and thiophanate); benzimidazole derivatives, such as triclabendazole or a thiazole benzimidazole derivative (e.g., thiabendazole and cambendazole) or a carbamate benzimidazole derivatives (e.g., fenbendazole, albendazole (oxide), mebendazole, oxfendazole, parbendazole, oxibendazole, flubendazole); an imidazothiazoles (e.g., levamisole and tetramisole); a tetrahydropyrimidine (e.g. morantel and pyrantel), organophosphates (e.g., trichlorphon, haloxon, dichlorvos, and naphthalophos); salicylanilides (e.g., closantel, oxyclozanide, rafoxanide, and niclosamide); nitrophenolic compounds (e.g., nitroxynil and nitroscanate); benzenedisulphonamides (e.g., clorsulon); pyrazineisoquinolines (e.g., praziquantel and epsiprantel); heterocyclic compounds (e.g. , piperazine, diethylcarbamazine, dichlorophen, and phenothiazine); arsenicals (e.g. , thiacetarsamide, melorsamine, and arsenamide); cyclooctadepsipeptides (e.g., emodepside); paraherquamides (e.g. derquantel); and amino-acetonitrile compounds (e.g. monepantel, AAD 1566); amidine compounds (e.g., amidantel and tribendimidin), including all pharmaceutically acceptable forms, such as salts, solvates or N-oxides.

Preferred combinations are comprising a) one compound selected from the group of compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof such as salts, solvates, N-oxides. or prodrugs thereof and b) one compound selected from the group consisting of anthelmintic avermectins (e.g., ivermectin, selamectin, doramectin, abamectin, emamectin and eprinomectin); milbemycins (e.g. moxidectin and milbemycin oxime); pro-benzimidazoles (e.g., febantel, netobimin, and thiophanate); benzimidazole derivatives, such as thiazole benzimidazole derivatives (e.g., thiabendazole and cambendazole), carbamate benzimidazole derivatives (e.g., fenbendazole, albendazole (oxide), mebendazole, oxfendazole, parbendazole, oxibendazole, flubendazole, and triclabendazole); imidazothiazoles (e.g., levamisole and tetramisole); tetrahydropyrimidines (e.g. morantel and pyrantel), organophosphates (e.g., trichlorphon, haloxon, dichlorvos, and naphthalophos); salicylanilides (e.g., closantel, oxyclozanide, rafoxanide, and niclosamide); nitrophenolic compounds (e.g., nitroxynil and nitroscanate); benzenedisulphonamides (e.g., clorsulon); pyrazineisoquinolines (e.g., praziquantel and epsiprantel); heterocyclic compounds (e.g., piperazine, diethylcarbamazine, dichlorophen, and phenothiazine); arsenicals (e.g., thiacetarsamide, melorsamine, and arsenamide); cyclooctadepsipeptides (e.g., emodepside); paraherquamides (e.g. derquantel); amino-acetonitrile compounds (e.g. monepantel, AAD 1566); tribendimidine (amidine compound); and amidantel (amidine compound); including all pharmaceutically acceptable forms, such as salts.

Preferred combinations comprise at least one compound selected from the group of compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof s and

1) abamectin, ivermectin, emamectin, eprinomectin, doramectin, moxidectin, milbemycin oxime; or .

2) closantel, oxyclozanide, rafoxanide, niclosamide; or

3) nitroxynil, nitroscanate, clorsulon; or

4) praziquantel, epsiprantel; or

5) emodepside, derquantel, monepantel or.

6) benzimidazole, mebendazole, fenbendazole, febantel, oxfendazole, oxibendazole, and flubendazole.

Examples of such combinations are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with abamectin.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with ivermectin.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with emamectin.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with eprinomectin.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with doramectin.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with moxidectin.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with milbemycin oxime.

Other examples are combinations of one of the according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with closantel.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with oxyclozanide.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with rafoxanide.

Other examples are combinations of one of the according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with niclosamide.

Other examples are combinations of one of the according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with nitroxynil.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with nitroscanate.

Other examples are combinations of one of the according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with clorsulon.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with praziquantel.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with epsiprantel.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with emodepside.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with derquantel.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof withthereof with monepantel.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with mebendazole.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with fenbendazole.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with febantel.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxfendazole.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxibendazole.

Other examples are combinations of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with flubendazole.

Examples of such combinations are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with abamectin.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with ivermectin.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with emamectin.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with eprinomectin.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with doramectin.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with moxidectin.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with milbemycin oxime.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with closantel.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxyclozanide.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with rafoxanide.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with niclosamide.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with nitroxynil.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with nitroscanate.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with clorsulon.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with praziquantel.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with epsiprantel.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with emodepside.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with derquantel.

Other examples are combinations of a salt of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with monepantel.

Examples of such combinations are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with abamectin.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with ivermectin.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with emamectin.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with eprinomectin.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with doramectin.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with moxidectin.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with milbemycin oxime.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with closantel.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxyclozanide.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with rafoxanide.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with niclosamide.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with nitroxynil.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with nitroscanate.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with clorsulon.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with praziquantel.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with epsiprantel.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with emodepside.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with derquantel.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with monepantel.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with mebendazole.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with fenbendazole.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with febantel.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxfendazole.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxibendazole.

Other examples are combinations of a solvate of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with flubendazole.

Examples of such combinations are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with abamectin.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with ivermectin.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with emamectin.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with eprinomectin.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with doramectin.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with moxidectin.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with milbemycin oxime.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with closantel.

Other examples are combinations of a N-oxide of one of the according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxyclozanide.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with rafoxanide.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with niclosamide.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with nitroxynil.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with nitroscanate.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with clorsulon.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with praziquantel.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with epsiprantel.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with emodepside.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with derquantel.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with monepantel.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with mebendazole.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with fenbendazole.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with febantel.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxfendazole.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with oxibendazole.

Other examples are combinations of a N-oxide of one of the compounds according to any of the formula (I)-(LXXXIX), compounds according to table I and/or variants thereof with flubendazole.

The compounds as described herein can be combined with pharmaceutically acceptable insecticides or acaricides. Such pharmaceutically acceptable insecticides and acaricides include, for example, acetamiprid, acetoprole, amitraz, amidoflumet, avermectin, azadirachtin, bifenthrin, bifenazate, buprofezin, bistrifluron, chlorfenapyr, chlorfluazuron, chlorantraniliprole, chlorpyrifos, chromafenozide, clothianidin, cyantraniliprole, cyflumetofen, β-cyfluthrin, cyhalothrin, λ-cyhalothrin, cymiazole cypermethrin, cyromazine, deltamethrin, demiditraz, diafenthiuron, diazinon, diflubenzuron, dimefluthrin, dinotefuran, emamectin, esfenvalerate, ethiprole, fenoxycarb, fenpropathrin, fenvalerate, fipronil, flonicamid, flubendiamide, flucythrinate, tau- fluvalinate, flufenoxuron, halofenozide, hexaflumuron, imidacloprid, indoxacarb, lufenuron, metaflumizone, methoprene, metofluthrin, methoxyfenozide, nitenpyram, novaluron, noviflumuron, permethrin, phosmet, profluthrin, protrifenbute, pymetrozine, pyrafluprole, pyrethrin, pyridalyl, pyrifluquinazon, pyriprole, pyriproxyfen, rotenone, ryanodine, spinetoram, spinosad, spirodiclofen, spiromesifen, spirotetramat, sulfoxaflor, tebufenozide, tebufenpyrad, teflubenzuron, tefluthrin, tetrachlorvinphos, tetramethylfluthrin, thiacloprid, thiamethoxam, tolfenpyrad, tralomethrin, triflumuron, isoxazalines such as afoxolaner, fluralaner, sarolaner and lotilaner. General references discussing antiparasitic agents, such as insecticides and acaricides, include, for example, The Pesticide Manual, 17th Edition, J. A. Turner, Ed., British Crop Protection Council, 7 Omni Business Centre, Omega Park, Alton Hampshire, GU34 2QD, UK (2015).

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The compounds as described herein can be combined with pharmaceutically acceptable insect growth regulators. Such pharmaceutically acceptable insect growth regulators include, for example, methoprene, pyriproxyfen, tetrahydroazadirachtin, chlorfluazuron, cyromazine, diflubenzuron, fluazuron, flucycloxuron, flufenoxuron, hexaflumuron, lufenuron, ifenuron, tebufenozide, and triflumuron. These compounds tend to provide both initial and sustained treatment of parasite infections at all stages of insect development, including eggs, on the animal subject, as well as within the environment of the animal subject.

The compounds as described herein can be combined with pharmaceutically acceptable anti-protozoals. Such pharmaceutically acceptable anti-protozoals include, for example, triazintriones like toltrazuril and ponazuril and triazindiones such as clazuril, diclazuril and letrazuril.

In some contemplated embodiments of the invention and/or embodiments thereof, the compounds are administered with pyridylmethylamine derivatives, such as, for example, pyridylmethylamine derivatives discussed in European Patent Appl. EP0539588 or Int'l Patent Appl. Publ. WO2007/115643.

In some contemplated embodiments of the invention and/or embodiments thereof, the compounds is administered with nodulisporic acids and derivatives thereof, such as, for example, compounds discussed in US Patent 5,399,582; 5,945,317; 5,962,499; 5,834,260; 6,221 ,894; or 5,595,991 ; or Int'l Patent Appl. Publ. 1996/29073.

In some contemplated embodiments of the invention and/or embodiments thereof, the compounds are administered with dihydroazole compounds, such as, for example, compounds discussed in WO 2010/75591.

In some contemplated embodiments of the invention and/or embodiments thereof, the compounds are administered with anthelminic proteins, such as, for example *Bacillus thuringensis* crystal proteins e.g. described in WO 2010/053517.

Other antiparasitic compounds contemplated to be useful in combination therapies with the compounds include, for example, imidazo[1 ,2-b] pyridazine compounds discussed in US Patent Appl. Publ. No. 2005-0182059; 1-(4-Mono and di- halomethylsulphonylphenyl)-2-acylamino-3-fluoropropanol compounds discussed US Patent 7,361 ,689; trifluoromethanesulfonanilide oxime ether compounds discussed in US Patent 7,312,248; n-[(phenyloxy)phenyl]-1, 1, 1-trifluoromethanesulfonamide and n-[(phenylsulfanyl)phenyl]-1, 1, 1-trifluoromethanesulfonamide compounds discussed in US Patent Appl. Publ. 2006-0281695; and 2-phenyl-3-(1 H-pyrrol-2-yl)acrylonitrile compounds discussed in US Appl. Publ. 2006/0128779; isoxazoline compounds discussed in WO Patent Appl, Publ. 2005-085216, WO 2007-026965, WO 2007-070606, WO 2007- 075459, WO 2007-079162, WO 2007-105814, WO 2007-125984, WO 2008-019760, WO 2008-122375, WO 2008-150393, WO 2009-002809, WO 2009-003075, WO 2009- 022746, WO 2009-035004, WO 2009-045999, WO 2009-051956, WO 2009-035004.

In the contemplated combination therapies, the compounds according to this invention may be administered before, simultaneously, and/or after the other active ingredient(s). In addition, the compounds according to this invention may be administered in the same composition as the other active ingredient(s) and/or in separate compositions from the other active ingredient(s). Further, the compounds according to this invention and other active ingredient(s) may be administered via the same and/or different dosage route.

When the compounds according to this invention are administered in a combination therapy, the weight ratio of the active ingredients may vary widely. Factors influencing this ratio include, for example, the particular compounds; the identity of the other active ingredient(s) be administered in the combination therapy; the dosage route of the compounds and other active ingredient(s); the target condition and pathogen; the type (e.g., species and breed), age, size, sex, diet, activity, and condition of the animal; and pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the compounds and other active ingredient(s). In some contemplated embodiments of the invention and/or embodiments thereof, for example, the weight ratio of the compounds to the other active ingredient(s) is, for example, from about 1 :3000 to about 3000: 1. In some such instances, the weight ratio is from about 1 :300 to about 300: 1. In other such instances, the weight ratio is from about 1 :30 and about 30: 1.

In addition to other active ingredients, it is contemplated that the compounds may be administered with one or more other compounds that beneficially affects (e.g. enhances or prolongs) the activity (or other characteristic, such as safety) of the compounds. For example, it is contemplated that the compounds may be administered with one or more synergists, such as, for example, piperonyl butoxide (PBO) and triphenyl phosphate (TPP). Other synergists include, for example, N-(2- ethylhexyl)-8,9, 10-trinorborn-5-ene-2,3-dicarboxamide (also known as "ENT 8184" or "MGK 264") and Verbutin (also known as "MB-599").

This invention also is directed to kits that are, for example, suitable for use in performing the methods of treatment described above. The kit comprises a therapeutically effective amount of one or more compounds of this invention, and an additional component. The additional component(s) may be, for example, one or more of the following: another ingredient (e.g., an excipient or active ingredient), an apparatus for combining the compound of this invention with another ingredient and/or for administering the compound of this invention, or a diagnostic tool.

The compounds used according to this invention show an excellent activity in treating parasite infections and in addition are acceptable for the animals treated.

Compounds may be synthesised as described in WO2018003924, JP2017134111 and Japanese patent application JP2017/134111.. The content of which are incorporated herein in its entirety.

The invention will now be further described by the following, non-limiting, examples.

Examples

Example 1:

Compounds are synthesised as described in WO2018003924 and JP2017134111and Japanese patent application JP2017/134111. Table 1 below refers to the compound in WO2018003924.

Synthetic Example 1A; Compound 1

N-[2-[3-Chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]-2-(trifluoromethyl)benzamide (Compound No.1-004 of WO2018003924)

Step 1: Preparation of 2-(5-bromo-3-chloropyridine-2-yl)-2,2-difluoroacetonitrile

To a stirred solution of 2-(5-bromo-3-chloropyridine-2-yl) acetonitrile (2.00g) in tetrahydrofuran (40ml) at -78°C was added dropwise 1.3M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (16ml). After stirring at same temperature for 0.5h, *N*-fluorobenzenesulfonimide (6.00g) was added dropwise to the reaction mixture at -78°C, which was stirred at same temperature for additional 3h. After the completion of the reaction, to the resulting mixture was added water (50ml), and extracted with hexane (50ml x 3). The organic extracts were combined, washed with water (50ml x 1) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with ethyl acetate-hexane (volume ratio 0:100 to 5:95 gradient composition) to afford the title compound as a pale yellow oil (0.81g).

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.66 (d, J=2.1Hz, 1H), 8.08 (d, J=2.1Hz, 1H).

Step 2: Preparation of 2-(5-bromo-3-chloropyridine-2-yl)-2,2-difluoroethylamine

To a stirred solution of 2-(5-bromo-3-chloropyridine-2-yl)-2,2-difluoroacetonitrile (810mg) in dichloromethane (20ml) at -78°C was added dropwise 1.0M solution of diisobutylaluminium hydride in hexane (9ml). After stirring at same temperature for 2h, to the reaction mixture was added saturated aqueous potassium sodium tartrate (Rochelle salt) solution (20ml) and dichloromethane (20ml), and then stirred at room temperature for 2h. After the completion of the reaction, to the resulting mixture was added water (30ml), and the organic layer was separated. The organic phase was washed with saturated aqueous Rochelle salt solution (20ml x 1) and water (20ml x 2), and concentrated under reduced pressure to afford the title compound as a brown oil (607mg), which was used in the next step without purification.

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.56 (d, J=2.1Hz, 1H), 8.00 (d, J=2.1Hz, 1H), 3.49 (t, J=13.8Hz, 2H).

Step 3: Preparation of *N*-[2-(5-bromo-3-chloropyridine-2-yl)-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester

To a stirred solution of 2-(5-bromo-3-chloropyridine-2-yl)-2,2-difluoroethylamine (607mg) and triethylamine (271mg) in dichloromethane (5ml) was added di-*tert*-butyl dicarbonate (584mg). After stirring at room temperature for 1h, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with ethyl acetate-hexane (volume ratio 0:10 to 1:9 gradient composition) to afford the title compound as a pale yellow oil (430mg).

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.55 (d, J=2.1Hz, 1H), 8.00 (d, J=2.1Hz, 1H), 5.05 (bs, 1H), 4.0-4.2 (m, 2H), 1.40 (s, 9H).

Step 4: Preparation of *N*-[2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester

To a stirred solution of *N*-[2-(5-bromo-3-chloropyridine-2-yl)-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester (1.50g) in *N*,*N*-dimethylformamide (4ml) was added triethylamine (1.64g), 1-ethynyl-4-fluorobenzene (631mg) and copper(I) iodide (231mg) followed by the addition of dichlorobis(triphenylphosphine)palladium(II) (283mg). The mixture was stirred at room temperature under nitrogen atmosphere for 2h. After the completion of the reaction, to the resulting mixture was added saturated aqueous ammonium chlorine solution (15ml), extracted with ethyl acetate (20ml x 1). The organic extract was washed with water (10ml x 2) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with ethyl acetate-hexane (volume ratio 0:10 to 2:8 gradient composition) to afford the title compound as a white solid (1.40g).

m.p.107.0-108.0°C

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.57 (d, J=1.5Hz, 1H), 7.92 (d, J=1.5Hz, 1H), 7.5-7.6 (m, 2H), 7.05-7.15 (m, 2H), 5.10 (bs, 1H), 4.0-4.2 (m, 2H), 1.41 (s, 9H).

Step 5: Preparation of 2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2,2-difluoroethylamine

To a stirred solution of *N*-[2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester (1.40g) in dichloromethane (5ml) at 0°C was added trifluoroacetic acid (3ml). After stirring at room temperature for 1h, the reaction mixture was then concentrated under reduced pressure. To the residue was added saturated aqueous sodium carbonate solution (10ml), and then extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with water (10ml) and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the crude title compound as a brown resin (1.01g), which was used in the next step without purification.

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.59 (d, J=1.5Hz, 1H), 7.91 (d, J=1.5Hz, 1H), 7.5-7.6 (m, 2H), 7.0-7.15 (m, 2H), 3.4-3.6 (m, 2H).

Step 6: Preparation of *N*-[2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]-2-(trifluoromethyl)benzamide

To a stirred solution of 2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2,2-difluoroethylamine (90mg) in ethyl acetate (2ml) at 0°C was added 10 wt% potassium carbonate solution (2ml) and 2-(trifluoromethyl)benzoyl chlorine (67mg), then stirred at room temperature for 1h. After the completion of the reaction, to the resulting mixture was added water (10ml), then extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with water (10ml x 1) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (volume ratio 0:10 to 2:8 gradient composition) to afford the title compound as an white solid (105mg).

m.p.164.0-166.0°C

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.54 (d, J=1.8Hz, 1H), 7.95 (d, J=1.8Hz, 1H), 7.45-7.7 (m, 6H), 7.0-7.15 (m, 2H), 6.45 (bs, 1H), 4.4-4.55 (m, 2H).

Synthesis Example 1B: Compound 5

2-Chloro-*N*-[2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2-fluoropropyl]nicotinamide (Compound No. 3- 010 of WO2018003924).

Step 1: Preparation of 5-bromo-3-chloro-2-(2-methyloxlane-2-yl)pyridine

To a stirred solution of trimethylsulfoxonium iodide (5.2g) in DMSO (15ml) at 0°C was added sodium hydride (55 wt%, dispersion in Paraffin Liquid) (1.1g). After stirring at same temperature for 0.5h, the reaction mixture was added dropwise to a stirred solution of 1-(5-bromo-3-chloropyridine-2-yl)ethane-1-on (5.0g) in DMSO (10ml) at 0°C, which was stirred at room temperature for additional 15h. After the completion of the reaction, the reaction mixture was added with water (20ml) and extracted with ethyl acetate (30ml x 1). The organic extract was washed with water (30ml x 1) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide a residue. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (volume ratio 0:10 to 3:7 gradient composition) to afford the title compound as a brown resin (5.7g).

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.66 (d, J=1.8Hz, 1H), 8.36 (d, J=1.8Hz, 1H), 3.03 (d, J=5.2Hz, 1H), 2.92 (d, J=5.2Hz, 1H), 1.58 (s, 3H).

Step 2:Preparation of *N*-[2- (5-bromo-3-chloropyridine-2-yl)-2-hydroxypropyl]phthalimide

To a solution of 5-bromo-3-chloro-2-(2-methyloxyrane-2-yl)pyridine (5.70g) in DMSO (40ml) was added potassium phthalimide (4.48g). The mixture was stirred at 100°C for 6h and then cooled to room temperature. The resulting mixture was diluted with water (30ml), extracted with ethyl acetate (20ml x 2). The organic extracts were combined, washed with water (40ml x 1) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (volume ratio 1:9 to 3:7 gradient composition) to afford the title compound as a brown resin (3.90g).

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.3-8.4 (m, 1H), 7.9-7.95 (m, 1H), 7.7-7.8 (m, 2H), 7.65-7.7 (m, 2H), 5.64 (s, 1H), 4.31 (d, J=14.0Hz, 1H), 4.21 (d, J=14.0Hz, 1H), 1.80 (s, 3H).

Step 3: Preparation of *N*-[2-(5-bromo-3-chloropyridine-2-yl)-2-fluoropropyl]phthalimide

To a stirred solution of *N*-[2-(5-bromo-3-chloropyridine-2-yl)-2-hydroxypropyl]phthalimide (3.90g) in dichloromethane (20ml) at 0°C was added dropwise bis(2-methoxyethyl)aminosulfur trifluorine (2.62g). After stirring at 50°C for 12h, the reaction mixture was allowed to cool to ambient temperature. To the resulting mixture was added saturated aqueous sodium hydrogencarbonate solution (30ml), and then extracted with dichloromethane (20ml x 2). The organic extracts were combined, washed with water (40ml x 1) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual solid was washed with diisopropyl ether (10ml x 1) to afford the title compound as a pale yellow solid (3.50g).

m.p.134.0-136.0°C

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.45-8.55 (m, 1H), 7.85-7.9 (m, 1H), 7.8-7.85 (m, 2H), 7.7-7.8 (m, 2H), 4.3-4.55 (m, 2H), 1.82 (d, J=22.4Hz, 3H).

Step 4: Preparation of *N*-[2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2-fluoropropyl]phthalimide

To a stirred solution of *N*-[2-(5-bromo-3-chloropyridine-2-yl)-2-fluoropropyl]phthalimide (1.0g) in *N*,*N*-dimethylformamide (4ml) was added triethylamine (762mg), 1-ethynyl-4-fluorobenzene (452mg) and copper(I) iodide (143mg) followed by the addition of dichlorobis(triphenylphosphine)palladium(II) (176mg). The mixture was stirred at 60°C under nitrogen atmosphere for 5h. After the completion of the reaction, the resulting mixture was allowed to cool to ambient temperature, added saturated aqueous ammonium chlorine solution (10ml), and extracted with ethyl acetate (10ml x 1). The organic extract was washed with water (10ml x 1) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with ethyl acetate-hexane (volume ratio 5:95 to 10:90 gradient composition) to afford the title compound as a brown solid (1.2g).

m.p.153.0-155.0°C

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.45-8.55 (m, 1H), 7.8-7.9 (m, 3H), 7.7-7.75 (m, 2H), 7.45-7.6 (m, 2H), 7.0-7.15 (m, 2H), 4.3-4.6 (m, 2H), 1.86 (d, J=23.0Hz, 3H).

Step 5:Preparation of 2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2- fluoropropylamine

To a solution of *N*-[2-[3-chloro-5-[(4-fluorophenyl)ethynyllpyridine-2-yl]-2-fluoropropyl]phthalimide (1.2g) in ethanol (4ml) was added hydrazine monohydrate (432mg). The mixture was stirred at 80°C for 5h. The resulting mixture was concentrated under reduced pressure.

To the residue was added saturated aqueous sodium hydrogencarbonate solution (5ml), and then extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with water (10ml x 1) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide a residue. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (volume ratio 5:5 to 9:1 gradient composition) to afford the title compound as a brown resin (323mg).

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.45-8.75 (m, 1H), 7.75-8.05 (m, 1H), 7.45-7.75 (m, 2H), 7.0-7.3 (m, 2H), 3.05-3.8 (m, 2H), 1.74 (d, J=23.0Hz, 3H), 1.05-1.45 (m, 2H).

Step 6: Preparation of 2-Chloro-*N*-[2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2-fluoropropyl]nicotinamide

To a stirred solution of 2-[3-chloro-5-[(4-fluorophenyl)ethynyl]pyridine-2-yl]-2-fluoropropylamine (100mg) and triethylamine (50mg) in dichloromethane (1ml) at 0°C was added dropwise 2-chloronicotinyl chlorine (63mg), then stirred at room temperature for 1h. After the completion of the reaction, to the resulting mixture was added water (2ml), then extracted with dichloromethane (5ml x 1). The organic extracts was washed with water (5ml x 1) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (volume ratio 2:8 to 5:5 gradient composition) to afford the title compound as an white solid (69mg).

m.p.149.0-151.0°C

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.54 (d, J=1.7Hz, 1H), 8.4-8.45 (m, 1H), 8.05-8.1 (m, 1H), 7.86 (d, J=1.7Hz, 1H), 7.45-7.6 (m, 2H), 7.3-7.35 (m, 1H), 7.2-7.25 (m, 1H), 7.05-7.15 (m, 2H), 4.15-4.4 (m, 2H), 1.90 (d, J=21.0Hz, 3H).

Example 1C: Compound 7
N-[2-[3-Chloro-5-[(6-fluoropyridine-3-yl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]-2-(trifluoromethyl)benzamide (Compound No.1-011 of WO2018003924).

Step 1: Preparation of *N*-[2-[3-chloro-5-(trimethylsilylethynyl)pyridine-2-yl]-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester
To a stirred solution of *N*-[2-(5-bromo-3-chloropyridine-2-yl)-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester (see Synthesis Example 1, Step 3) (1.86g) in *N*,*N*-dimethylformamide (15ml) was added triethylamine (1.52g), trimethylsilylacetylene (0.59g) and copper(I) iodide (285mg) followed by the addition of dichlorobis(triphenylphosphine)palladium(II) (350mg). The reaction mixture was stirred at room temperature for 1 h under nitrogen atmosphere. After the completion of the reaction, to the resulting mixture was added saturated aqueous ammonium chlorine solution (20ml) and ethyl acetate (20ml), then the layers were separated, and the aqueous phase was extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with saturated aqueous ammonium chlorine solution (20ml) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (volume ratio 0:10 to 2:8 gradient composition) to afford the title compound as an yellow solid (1.44g).
m.p.93.0-97.0°C
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.50 (d, J=1.5Hz, 1H), 7.85 (d, J=1.5Hz, 1H), 5.08 (bs, 1H), 4.07 (td, J=12.9, 6.6Hz, 2H), 1.41 (s, 9H), 0.27 (s, 9H).

Step 2: Preparation of *N*-[2-[3-chloro-5-[(6-fluoropyridine-3-yl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester
To a stirred solution of *N*-[2-[3-chloro-5-(trimethylsilylethynyl)pyridine-2-yl]-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester (480mg), triethylamine (375mg), 2-fluoro-5-iodopyridine (303mg) and copper(I) iodide (71mg) in *N*,*N*-dimethylformamide (6ml) was added dichlorobis(triphenylphosphine)palladium(II) (87mg), followed by the addition of tetra-*n*-butylammonium fluorine (1.0M tetrahydrofuran solution) (1.3ml). The reaction mixture was stirred at room temperature for 16h under nitrogen atmosphere. After the completion of the reaction, to the resulting mixture was added saturated aqueous ammonium chlorine solution (10ml) and ethyl acetate (10ml), then the layers were separated, and the aqueous phase was extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with saturated aqueous ammonium chlorine solution (20ml) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (volume ratio 0:10 to 2:8 gradient composition) to afford the title compound as a colorless resin (324mg).
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.55-8.65 (m, 1H), 8.4-8.5 (m, 1H), 7.9-8.0 (m, 2H), 6.95-7.05 (m, 1H), 5.05-5.2 (m, 1H), 4.0-4.2 (m, 2H), 1.41 (s, 9H).

Step 3: Preparation of 2-[3-chloro-5-[(6-fluoropyridine-3-yl)ethynyl]pyridine-2-yl]-2,2-difluoroethylamine
To a stirred solution of *N*-[2-[3-chloro-5-[(6-fluoropyridine-3-yl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]carbamic acid 1,1-dimethylethyl ester (324mg) in dichloromethane (3ml) at 0°C was added trifluoroacetic acid (1ml). After stirring at room temperature for 1h, the reaction mixture was then concentrated under reduced pressure. To the residue was added saturated aqueous sodium hydrogencarbonate solution (10ml), and then extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with water (10ml) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude title compound as a yellow solid (253mg), which was used in the next step without purification.
m.p.109.0-111.0°C
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.61 (d, J=1.2Hz, 1H), 8.43 (d, J=2.4Hz, 1H), 7.9-8.0 (m, 2H), 7.00 (dd, J=8.4, 3.0Hz, 1H), 3.52 (t, J=14.1Hz, 2H), 1.58 (bs, 2H).

Step 4: Preparation of *N*-[2-[3-chloro-5-[(6-fluoropyridine-3-yl)ethynyl]pyridine-2-yl]-2,2-difluoroethyl]-2-(trifluoromethyl)benzamide
To a stirred solution of 2-[3-chloro-5-[(6-fluoropyridine-3-yl)ethynyl]pyridine-2-yl]-2,2-difluoroethylamine (119mg) and triethylamine (77mg) in dichloromethane (2ml) at 0°C was added dropwise 2-(trifluoromethyl)benzoyl chlorine (88mg), then stirred at room temperature for 16h. After the completion of the reaction, to the resulting mixture was added water (2ml), then the layers were separated, and the aqueous phase was extracted with dichloromethane (5ml x 1). The organic extracts were combined, washed with water (10ml x 1) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual solid was washed with diisopropyl ether (10ml x 1) to afford the title compound as a white solid (148mg).
m.p.155.0-157.0°C
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.55-8.6 (m, 1H), 8.4-8.45 (m, 1H), 7.97 (d, J=1.8Hz, 1H), 7.93 (ddd, J=8.7, 7.5, 2.4Hz, 1H), 7.5-7.7 (m, 4H), 6.99 (ddd, J=8.7, 3.3, 0.9Hz, 1H), 6.42 (t, J=6.6Hz, 1H), 4.47 (td, J=13.5, 6.6Hz, 2H).

Synthesis Example 1D: compound 43
N-[2-[2-chloro-4-[[6-(trifluoromethyl)pyridine-3-yl]ethynyl]phenyl]-2,2-difluoro-1-methylethyl]-2-(trifluoromethyl)nicotinamide (Compound No.3-025 of PCT JP1017/046693)

Step 1: Preparation of ethyl 2-(4-bromo-2-chlorophenyl)-2,2-difluoroacetate
To a stirred solution of 4-bromo-2-chloro-1-iodobenzene (3.20g) and ethyl bromodifluoroacetate (3.25g) in dimethylsulfoxide (20ml) was added copper (4.40g). The mixture was stirred under nitrogen atmosphere at 60°C for 2h, and then at room temperature for 16h. The resulting mixture was diluted with saturated aqueous ammonium chloride solution (30ml), filtered through Celite®, and extracted with diethyl ether (10ml x 2). The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography

eluted with ethyl acetate-hexane (0:10 to 2:8 gradient composition) to afford the title compound as a brown resin (2.40g).
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ7.45-7.6 (m, 3H), 4.25-4.4 (m, 2H), 1.2-1.35 (m, 3H).

Step 2: Preparation of 2-(4-bromo-2-chlorophenyl)-2,2-difluoroacetamide
Ethyl 2-(4-bromo-2-chlorophenyl)-2,2-difluoroacetate (2.4g) was dissolved in 4% ammonia-methanol solution (20ml). After stirring at room temperature for 16h, the mixture was concentrated under reduced pressure to afford the title compound as a white solid (2.1g).
Melting Point: 158.0-160.0°C
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ7.55-7.65 (m, 2H), 7.45-7.55 (m, 1H), 6.51 (bs, 1H), 6.14 (bs, 1H).

Step 3: Preparation of 2-(4-bromo-2-chlorophenyl)-2,2-difluoroacetonitrile
To a stirred solution of 2-(4-bromo-2-chlorophenyl)-2,2-difluoroacetamide (3.80g) and pyridine (4.77g) in tetrahydrofuran (30ml) at 0°C was added dropwise trifluoroacetic anhydride (5.63g). After stirring at the same temperature for 1h, the reaction mixture was poured into water (20ml) and extracted with ethyl acetate (10ml x 2). The organic extracts were combined, sequentially washed with water (20ml), saturated aqueous sodium hydrogencarbonate solution (20ml) and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude title compound as a brown resin (3.20g), which was used in the next step without purification.
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ7.65-7.8 (m, 1H), 7.5-7.6 (m, 2H).

Step 4: Preparation of 2-(4-bromo-2-chlorophenyl)-2,2-difluoro-1-(methyl)ethylamineTo a stirred solution of 2-(4-bromo-2-chlorophenyl)-2,2-difluoroacetonitrile (1.8g) in diethyl ether (10ml) at 0°C was added dropwise methylmagnesium bromide (35% in diethyl ether) (5ml). After stirring at same temperature for 1h, methanol (10ml) was added dropwise. After stirring further 30 minutes at same temperature, sodium borohydride (1.1g) was added portionwise (divide into three) to the reaction mixture, which was stirred at 0°C for additional 5h. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous ammonium chloride solution (20ml) and extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with water (20ml) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the crude title compound as a brown resin (1.5g), which was used in the next step without purification.
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ7.55-7.65 (m, 1H), 7.35-7.5 (m, 2H), 3.55-3.85 (m, 1H), 1.15-1.4 (m, 2H), 1.0-1.15 (m, 3H).

Step 5: Preparation of N-[2-(4-bromo-2-chlorophenyl)-2,2-difluoro-1-methylethyl]carbamic acid 1,1-dimethylethyl esterTo a stirred solution of 2-(4-bromo-2-chlorophenyl)-2,2-difluoro-1-(methyl)ethylamine (1.50g) and triethylamine (1.60g) in dichloromethane (5ml) was added di-tert-butyl dicarbonate (1.30g). After stirring at room temperature for 16h, the reaction mixture was diluted with water (10ml) and extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography eluted with ethyl acetate-hexane (0:100 to 25:75 gradient composition) to afford the title compound as a yellow resin (1.15g).
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ7.55-7.65 (m, 1H), 7.3-7.5 (m, 2H), 4.55-4.8 (m, 2H), 1.15-1.35 (m, 12H).

Step 6: Preparation of tert-butyl N-[2-[2-chloro-4-(trimethylsilylethynyl)phenyl]-2,2-difluoro-1-methylethyl]carbamateTo a stirred solution of tert-butyl N-[2-(4-bromo-2-chlorophenyl)-2,2-difluoro-1-methylethyl]carbamate 1,1-dimethylethyl ester (900mg) and triethylamine (0.4ml) in N,N-dimethylformamide (2ml) was added trimethylsilylacetylene (346mg) and copper(I) iodide (90mg) followed by the addition of dichlorobis(triphenylphosphine)palladium(II) (82mg). The reaction mixture was stirred at 60°C for 3 h under nitrogen atmosphere and then cooled to room temperature. The resulting mixture was diluted with saturated aqueous ammonium chloride solution (5ml) and extracted with ethyl acetate (10ml x 1). The organic extracts was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide a residue. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (0:100 to 25:75 gradient composition) to afford the title compound as a brown resin (540mg).
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ7.3-7.8 (m, 3H), 4.6-4.9 (m, 1H), 4.64 (bs, 1H), 1.1-1.45 (m, 12H), 0.23 (s, 9H).

Step 7: Preparation of tert-butyl N-[2-[2-chloro-4-[[6-(trifluoromethyl)pyridine-3-yl]ethynyl]phenyl]-2,2-difluoro-1-methylethyl]carbamateTo a stirred solution of tert-butyl N-[2-[2-chloro-4-(trimethylsilylethynyl)phenyl]-2,2-difluoro-1-methylethyl]carbamate (1.60g), triethylamine (1.2ml) and 5-bromo-2-(trifluoromethyl)pyridine (1.08g) in toluene (4ml) was added copper(I) iodide (152mg) and dichlorobis(triphenylphosphine)palladium(II) (140mg), followed by the addition of tetra-n-butylammonium fluoride (1M tetrahydrofuran solution) (346mg). The reaction mixture was stirred at room temperature for 16h under nitrogen atmosphere. After the completion of the reaction, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (5ml) and extracted with ethyl acetate (10ml x 1). The organic extracts was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide a residue. The residue was purified by column chromatography on silica gel eluted with ethyl acetate-hexane (0:100 to 25:75 gradient composition) to afford the title compound as a brown resin (450mg).
^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.7-8.9 (m, 1H), 7.9-8.05 (m, 1H), 7.65-7.8 (m, 1H), 7.35-7.6 (m, 3H), 4.65-4.95 (m, 1H), 4.5-4.65 (m, 1H), 1.15-1.4 (m, 12H).

Step 8: Preparation of 2-[2-chloro-4-[[6-(trifluoromethyl)pyridine-3-yl]ethynyl]phenyl]-2,2-difluoro-1-(methyl)ethylamineTo a stirred solution of tert-butyl N-[2-[2-chloro-4-[[6-(trifluoromethyl)pyridine-3-yl]ethynyl]phenyl]-2,2-difluoro-1-methylethyl]carbamate (450mg) in dichloromethane (3ml) at 0°C was added trifluoroacetic acid (1ml). After stirring at room temperature for 1h, the reaction mixture was then concentrated under reduced pressure. To the residue was added saturated aqueous sodium hydrogencarbonate solution (10ml), and then extracted with ethyl acetate (10ml x 2). The organic extracts were combined, washed with water (10ml) and brine, dried over anhydrous magnesium sulfate and

concentrated under reduced pressure to afford the crude title compound as a brown resin (390mg), which was used in the next step without purification.

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.75-8.85 (m, 1H), 7.85-8.0 (m, 1H), 7.65-7.75 (m, 1H), 7.4-7.6 (m, 3H), 3.65-3.95 (m, 1H), 1.3-1.45 (m, 2H), 1.05-1.15 (m, 3H).

Step 9: Preparation of N-[2-[2-chloro-4-[[6-(trifluoromethyl)pyridine-3-yl]ethynyl]phenyl]-2,2-difluoro-1-methylethyl]-2-(trifluoromethyl)nicotinamideTo a stirred solution of 2-[2-chloro-4-[[6-(trifluoromethyl)pyridine-3-yl]ethynyl]phenyl]-2,2-difluoro-1-(methyl)ethylamine (130mg), 2-(trifluoromethyl)nicotinic acid (74mg), triethylamine (0.5ml) and 4-(dimethylamino)pyridine (5mg) in dichloromethane (1ml) was added O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (170mg). After stirring at room temperature for 16h, water (10ml) was added, and then extracted with ethyl acetate (10ml x 1). The organic extracts were washed with 1M aqueous hydrochloric acid (10ml x 2) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with ethyl acetate-hexane (0:100 to 25:75 gradient composition) to afford the title compound as a colorless resin (45mg).

^{1}H NMR ($CDCl_3$, Me_4Si, 300MHz) δ8.8-8.85 (m, 1H), 8.7-8.75 (m, 1H), 7.95-8.25 (m, 1H), 7.65-7.75 (m, 3H), 7.55-7.6 (m, 1H), 7.5-7.55 (m, 2H), 5.9-6.05 (m, 1H), 5.35-5.55 (m, 1H), 1.34 (d, J=6.7Hz, 3H).

The compound of the present invention can be produced according to the above-mentioned production methods and examples. Examples of alkynylpyridine-substituted amide compounds included in the present invention are prepared in the same manner as in Synthesis Example 1A to Synthesis Example 1D are shown in Table 1.

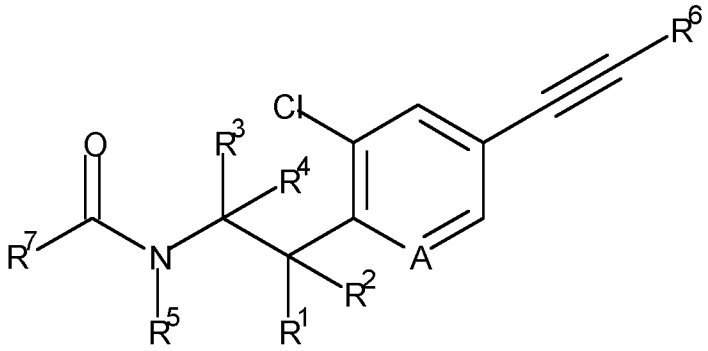


Table 1:

#	R^1	R^2	R^3	R^4	R^5	R^6	R^7	A
1	F	F	H	H	H	4-fluorophenyl	2-(trifluoromethyl)phenyl	N
2	F	F	methyl	H	H	4-fluorophenyl	2-(trifluoromethyl)phenyl	N
3	F	F	H	H	H	4-fluorophenyl	2-chloro-3-pyridyl	N
4	F	F	H	H	H	4-(trifluoromethyl) phenyl	2-(trifluoromethyl)phenyl	N
5	H	F	H	H	H	4-fluorophenyl	2-chloro-3-pyridyl	N
6	F	F	methyl	H	H	4-fluorophenyl	2-chloro-3-pyridyl	N
7	F	F	H	H	H	6-fluoro-3-pyridyl	2-(trifluoromethyl)phenyl	N

8	F	F	methyl	H	H	4-chlorophenyl	2-(trifluoromethyl)phenyl	N
9	F	F	methyl	H	H	4-chlorophenyl	3-chloro-2-pyridyl	N
9 F2	F	F	methyl	H	H	4-chlorophenyl	3-chloro-2-pyridyl	N
10	F	F	methyl	H	H	4-chlorophenyl	2-chloro-3-pyridyl	N
11	F	F	H	H	H	4-chlorophenyl	2-(trifluoromethyl)phenyl	N
12	H	H	H	H	H	4-fluorophenyl	2-chloro-3-pyridyl	N
13	F	F	H	H	H	4-chloro-2-fluoro-phenyl	2-(trifluoromethyl)phenyl	N
14	F	F	methyl	H	H	4-(trifluoromethyl)phenyl	2-(trifluoromethyl)phenyl	N
15	F	F	methyl	H	H	4-chlorophenyl	2-(trifluoromethyl)-3-pyridyl	N
16	H	H	methyl	H	H	4-fluorophenyl	2-chloro-3-pyridyl	N
17	F	F	methyl	H	H	6-fluoro-3-pyridyl	2-(trifluoromethyl)phenyl	N
18	F	F	H	H	H	4-chloro-3-fluoro-phenyl	2-(trifluoromethyl)phenyl	N
19	F	F	methyl	H	H	4-chloro-3-fluoro-phenyl	2-(trifluoromethyl)-3-pyridyl	N
20	F	F	methyl	H	H	4-chloro-3-fluoro-phenyl	3-(trifluoromethyl)-2-pyridyl	N
21	F	F	methyl	H	H	4-chloro-2-fluoro-phenyl	2-(trifluoromethyl)phenyl	N
22	F	F	methyl	H	H	4-chloro-3-fluoro-phenyl	2-(trifluoromethyl)phenyl	N
23	F	F	methyl	H	H	4-chloro-2-fluoro-phenyl	2-(trifluoromethyl)-3-pyridyl	N
24	F	F	methyl	H	H	4-chloro-2-fluoro-phenyl	3-(trifluoromethyl)-2-pyridyl	N
25	F	F	H	H	H	3,4-dichlorophenyl	2-(trifluoromethyl)-3-pyridyl	N
26	F	F	H	H	H	2-fluorophenyl	2-(trifluoromethyl)phenyl	N
27	F	F	H	H	H	3,4,5-trifluorophenyl	2-(trifluoromethyl)phenyl	N
28	F	F	H	H	H	2-fluoro-4-(trifluoromethyl)phenyl	2-(trifluoromethyl)phenyl	N
29	F	F	methyl	H	H	3,4-dichlorophenyl	2-(trifluoromethyl)-3-pyridyl	N
30	F	F	H	H	H	2,4,6-trifluorophenyl	2-(trifluoromethyl)phenyl	N
31	F	F	H	H	H	4-chloro-2,6-difluoro-	2-(trifluoromethyl)phenyl	N

						phenyl		
32	F	F	H	H	H	2,4,5-trifluorophenyl	2-(trifluoromethyl)phenyl	N
33	F	F	H	H	H	3-fluoro-4-(trifluoromethoxy)phenyl	2-(trifluoromethyl)phenyl	N
34	F	F	H	H	H	6-(trifluoromethyl)-3-pyridyl	2-(trifluoromethyl)phenyl	N
35	F	F	H	H	H	4-fluoro-3-(trifluoromethyl)phenyl	2-(trifluoromethyl)phenyl	N
36	F	F	H	H	H	2-fluoro-3-(trifluoromethyl)phenyl	2-(trifluoromethyl)phenyl	N
37	F	F	H	H	H	4-fluoro-2-(trifluoromethyl)phenyl	2-(trifluoromethyl)phenyl	N
38	F	F	methyl	H	H	4-chloro-2-methyl-phenyl	2-(trifluoromethyl)phenyl	N
39	F	F	H	H	H	2,2-difluoro-1,3-benzodioxol-5-yl	2-(trifluoromethyl)phenyl	N
40	F	F	H	H	H	2-fluoro-4-(trifluoromethoxy)phenyl	2-(trifluoromethyl)phenyl	N
41	F	F	H	H	H	4-chloro-3,5-difluoro-phenyl	2-(trifluoromethyl)phenyl	N
42	F	F	methyl	H	H	6-(trifluoromethyl)-3-pyridyl	2-(trifluoromethyl)phenyl	CH
43	F	F	methyl	H	H	6-(trifluoromethyl)-3-pyridyl	2-(trifluoromethyl)-3-pyridyl	CH
44	F	F	H	H	methyl formate	4-chlorophenyl	2-(trifluoromethyl)phenyl	N
45	F	F	methyl	H	H	2,2-difluoro-1,3-benzodioxol-5-yl	2-(trifluoromethyl)-3-pyridyl	N
46	F	F	methyl	H	H	4-(trifluoromethyl)phenyl	2-(trifluoromethyl)-3-pyridyl	N
47	F	F	H	H	H	4-chlorophenyl	3-(trifluoromethyl)-2-pyridyl	N

48	F	F	H	H	H	4-chlorophenyl	2-(trifluoromethyl)-3-pyridyl	N
49	F	F	H	H	H	benzothiophen-5-yl	2-(trifluoromethyl)phenyl	N
50	F	F	methyl	H	H	3-quinolyl	3-(trifluoromethyl)-2-pyridyl	CH
51	F	F	methyl	H	H	1-methylpyrazol-4-yl	2-(trifluoromethyl)phenyl	CH
52	F	F	methyl	H	H	benzofuran-5-yl	2-(trifluoromethyl)-3-pyridyl	CH
53	F	F	methyl	H	H	benzofuran-6-yl	3-(trifluoromethyl)pyrazin-2-yl	CH
54	F	F	methyl	H	H	2,2-dimethyl-1,3-benzodioxol-5-yl	2-(trifluoromethyl)phenyl	CH
55	F	F	methyl	H	H	pyrazolo[1,5-a]pyridin-6-yl	2-(trifluoromethyl)phenyl	CH
56	F	F	methyl	H	H	6-quinolyl	3-(trifluoromethyl)-2-thienyl	CH
57	F	F	methyl	H	H	1,3-benzothiazol-6-yl	2-(trifluoromethyl)phenyl	CH

Example 2: **Determining activity against *Ascaridia galli* and *Oesophagostomum dentatum***

Anthelmintic effects of compounds of this invention were tested in vitro using gut-dwelling larval stages of two parasitic species: *A. galli* (intestinal round worm of chicken), larval stage 3 (L3); and *O. dentatum* (nodular worm of swine), larval stages 3 and 4 (L3 and L4). Various concentrations of the compounds were incubated in 96-well microtiter plates together with 20 larvae per well. The anthelmintic effects were classified by microscopic examination, assessing mortality, damage, motility, progression of development, and neutral red uptake by the larvae in comparison to a DMSO-control and standard anthelmintics. The anthelmintic effects were defined by the minimum effective concentration ("MEC").

The following compounds showed activity against one or both of the parasites with an MEC of 25 µM or less:

1-26, 28-49

Example 3: In vivo studies

Efficacy against *Haemonchus contortus* and *Trichostrongylus colubriformis* in jirds.

Compounds according to this invention were tested in vivo using *Haemonchus contortus* or *Trichostrongylus colubriformis* in jirds (Meriones unguiculatus). The jirds that have been orally infected with third·stage larvae of *Haemonchus contortus* or *Trichostrongylus colubriformis*, were treated once either orally or subcutaneously with compounds at a dose of 10 mg or 50 mg per kg bodyweight. No treatment related adverse·reactions in jirds were observed.. Three days after treatment, the jirds were necropsied, and the larvae burden in the stomach was determined. The efficacy was defined as the

reduction of the mean larvae count in the infected jirds of the treatment group in comparison to the infected jirds in an untreated control group (negative control).

All compounds that were tested showed activity against *Haemonchus contortus* and the following compounds showed a reduction in *Haemonchus contortus* count of 50% or more when administered orally at 10 mg/kg bodyweight :
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 42, 43, 44, 45.

The following compounds showed a reduction in *Haemonchus contortus* count of 50% or more when administered subcutaneously at 10 mg/kg bodyweight:
1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 42, 43, 44

All compounds that were tested showed activity against *Trichostrongylus colubriformis* and the following compounds showed a reduction in *Trichostrongylus colubriformis* count of 50% or more when administered orally at 10 mg/kg bodyweight:
6, 8, 9, 10, 11, 13, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 31, 32, 33, 35, 38, 39, 40, 41, 45, 46, 50, 54, 56, 57

The following compound showed a reduction in *Trichostrongylus colubriformis* count of 50% or more when administered subcutaneously at 10 mg/kg bodyweight:
1, 2, 10, 13, 18, 26, 27, 20, 21, 22, 23, 29, 32, 34, 35, 39, 48, 50, 51, 53

The following compounds showed an inhibition of 80% or more of *Haemonchus contortus* when administered orally:
3, 4, 6, 7, 8, 9, 10, 11, 18, 13, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 45

The following compounds showed an inhibition of 80% or more of *Trichostrongylus colubriformis* when administered orally:
8, 11, 18, 13, 15, 21, 22, 23, 25, 46, 28, 35, 29, 40, 41

Efficacy against *Haemonchus contortus* and *Trichostrongylus colubriformis* in sheep

Compounds according to this invention were tested in vivo using *Haemonchus contortus* and *Trichostrongylus colubriformis* in a simultaneous infection. Healthy sheep were experimentally co-infested with third stage larvae from *H. contortus* and *T. colubriformis*. Following proved patency sheep were treated orally at a dose of 10 mg per kg bodyweight. No treatment related adverse reactions in sheep were observed. Seven days after treatment, the animals were necropsied, and the number of nematodes in the abomasum (*H. contortus*) and duodenum (*T. colubriformis*) was determined.. The efficacy was defined as the reduction of the mean worm count in the infected sheep of the treatment group in comparison to the mean worm count in an untreated control group (negative control).

The following compounds showed an inhibition of 50% or more of *Haemonchus contortus* when administered orally: 11, 15, 18 22, 23, 29, 39.

The following compounds showed an inhibition of 50% or more of *Trichostrongylus colubriformis* when administered orally: 11, 15, 18, 22, 23, 29, 34, 39.

Efficacy against field isolates containing *Haemonchus placei, Ostertagia ostertagi* and *Cooperia* spp. in cattle

Compounds according to this invention were tested in vivo using a mixed species field isolate containing *Haemonchus placei*, *Ostertagia ostertagi* and *Cooperia* spp. Healthy cattle were experimentally co-infested with third stage larvae from the mixed isolated and following proved potency cattle were treated orally at a dose of 10 mg per kg bodyweight. No treatment related adverse reactions in cattle were observed. Seven days after treatment, the animals were necropsied, and the number of nematodes in the gastro-intestinal tract was determined. The efficacy was defined as the reduction of the mean worm count in the infected cattle of the treatment group in comparison to the mean worm count in an untreated control group (negative control).

The following compounds showed an inhibition of 100% of *Haemonchus placei* when administered orally: 15, 18, 23.

The following compounds showed an inhibition of 50% or more of *Ostertagia ostertagi* when administered orally: 15, 23.

The following compounds showed an inhibition of 45% or more of *Cooperia* spp when administered orally: 15, 18, 23.

Example 4: In vitro ADME and toxicity assays

Cytotoxicity assay (AlamarBlue® assay)

Cytotoxicity was assessed by the AlamarBlue® assay in human HepG2 liver cells. Cells were incubated with different test compound concentrations for 24 h. After addition of AlamarBlue® assay reagent, viability of cells was determined via fluorescencespectroscopy. Finally, IC_{50} values were calculated. The following compounds showed an IC_{50} value of 70 µM or more: 1-11, 13-15, 17-18, 20-22, 24, 16-35, 37-48.

Genotoxicity assay (Greenscreen®)

Genotoxicity was assessed by the cell-based in vitro Greenscreen® HC assay (Gentronix, UK). Cells were incubated with different concentrations (1:2 titrations) of test compound for 48 h. Reporter gene induction by test compounds is defined biologically relevant if cellular GFP fluorescence is elevated by

more than the 1.5-fold (50% fluorescence increase) compared to control cells (Gentronix, UK). A positive Greenscreen indicates mutagenic, clastogenic or aneuploidy inducing compounds.

All compounds that were tested turned out not to be genotoxic. The following compounds were found to be negative in the GreenScreen® assay:
10, 11, 15, 18, 19, 20, 21, 22, 23, 24, 25, 29, 34, 39, 40, 41.

Cellular respiration toxicity assay (MitoXpress®)

The mitochondrial toxicity potential of test compounds (e.g., electron transport chain inhibitors or uncouplers) was assessed by the cellular respiration toxicity assay (MitoXpress®) in human liver HepG2 cells. Using an oxygen sensing fluorophore, cellular oxygen consumption at different test compound concentrations was measured and IC_{50} values were calculated. The assay may be predictive for mammalian mitochondria dysfunction in vivo in case of low IC_{50} values.
All compounds showed an IC_{50} higher than 34 µM.
The following compounds showed an IC_{50} of 70 µM or more:
1-17, 19-39, 41, 42, 44-46, 48-49.

Electron transport chain (ETC) enzyme assay

Potential mitochondrial toxicity of compounds of this invention was assessed by the ETC enzyme assay. Different test compound concentrations were added to ETC complex I/II (NADH fumarate oxidoreductase) from the metazoan parasite *Ascaridia galli* or to mammalian ETC complex I/III (NADH-cytochrome C oxidoreductase) from cattle (*Bos taurus*) or mice (*Mus musculus*). The ETC enzyme activity is proportional to the measured NADH absorbance (340 nm). Finally, compound-specific inhibition of ETC enzymes was determined by calculation of IC_{50} values. The values indicate specificity for parasitic Electron transport chain (ETC) enzymes over the mammalian Electron transport chain (ETC) enzymes.

The following compounds had an IC_{50} of more than 5 µM for the mammalian ETC:
1, 2, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 17, 26.

The following compounds had an IC_{50} of 0.1 µM or less for the parasitic ETC:
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 26.

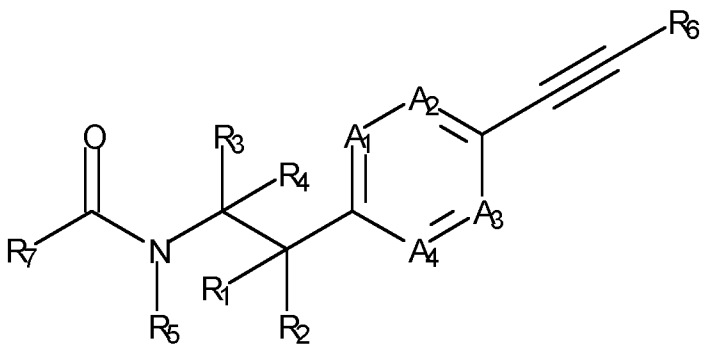
Metabolic Stability Screening

Metabolic stability of test compounds was assessed in bovine liver microsomes and in cryo-preserved sheep hepatocyte suspensions. Test compound (1 µM) was added to microsomes for up to 60 min or to hepatocytes for up to 90 min. Reactions were stopped by addition of 100% ethanol. For analysis, samples were prepared by centrifugation following semiquantitative determination of test compounds through triple TOF LC/MS/MS spectrometry. Metabolic stability was defined as the time-dependent depletion of compound in the test system. Finally, the in vitro half-life ($t_{1/2}$) of test items was calculated by regression analysis using the following equation: $t_{1/2} = \ln 2/k$, where k is the elimination rate constant.

The following compounds had $t_{1/2}$ >60 min in bovine liver microsomes and in cryo-preserved sheep hepatocyte suspensions:
6, 8, 9, 10, 18, 13, 15, 17, 19, 20, 21, 22, 23, 24, 25.

Claims

1. A compound of formula (I)



(I)

or a stereoisomer, pharmaceutically acceptable salt, ester, solvate, N-oxide, or prodrug thereof for use in the treatment of a helmintic infection, wherein

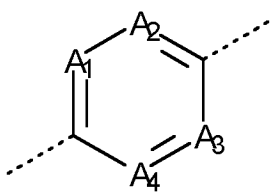
R^1 and R^2 are each independently a hydrogen atom, a halogen atom, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, cyano(C_1-C_4)alkoxy, C_3-C_6 alkenyloxy, C_3-C_6 haloalkenyloxy, C_3-C_6 alkynyloxy, C_3-C_6 haloalkynyloxy, C_1-C_4 alkylthio, C_1-C_4 alkoxyamino, C_1-C_4 alkoxycarbonyl, $-C(=O)NH_2$ or $-C(=S)NH_2$;

R^3 and R^4 are each independently a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxymethyl, or C_3-C_6 cycloalkyl, or R^3 and R^4 together can form C_3-C_6 cycloalkyl;

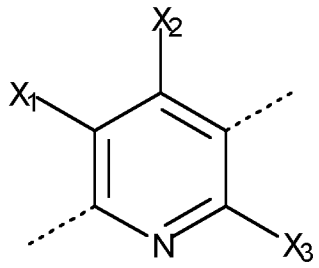
R^5 is a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, (C_1-C_2)alkyl substituted by R^8, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_3-C_4 alkynyl, -OH, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 haloalkylthio, $-C(=O)R^9$, $C(=O)OR^9$ or C_1-C_4 alkoxycarbonyl;

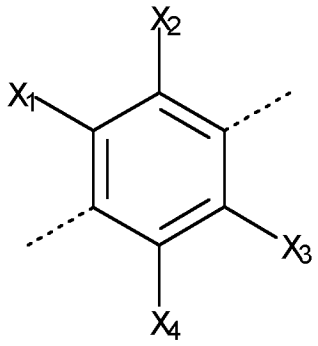
R^6 is aryl or aromatic heterocycle; wherein the aryl or aromatic heterocycle may be optionally substituted;

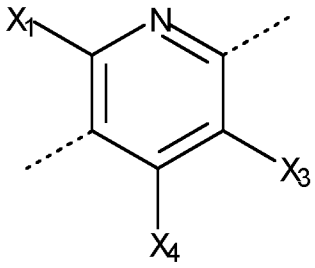
R^7 aryl or aromatic heterocycle; wherein the aryl and aromatic heterocycle may be optionally substituted;



is selected from the group consisting of



,


,


(x-1) (x-2) (x-3)

wherein X^1 and X^4 are each independently a hydrogen atom, a halogen atom, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy or C_1-C_4 alkylthio,

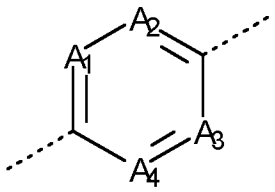
X^2 and X^3 are each independently a hydrogen atom, a halogen atom or methyl, halogenated methyl;

R^8 is cyano, -OR^{10}, C_1-C_4 alkylthio, C_1-C_4 alkoxycarbonyl, -C(=O)NH_2 or -C(S)NH_2,

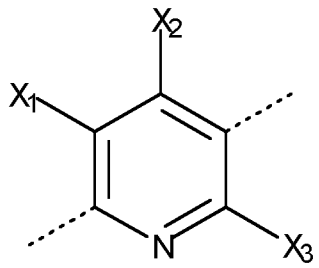
R^9 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, C_3-C_4 cycloalkyl or C_2-C_4 alkenyl, C_2-C_4 haloalkyl

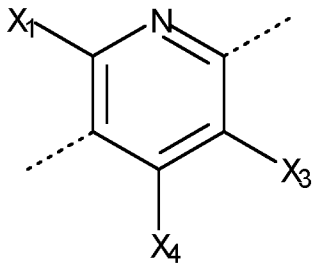
R^{10} is hydrogen, C_1-C_4 alkyl, C_2-C_4 haloalkyl, C_1-C_4 alkylcarbonyl, C_3-C_6 cycloalkylcarbonyl or C_1-C_4 alkoxycarbonyl.

2. A compound for use according to claim 1 wherein



is selected from the group consisting of

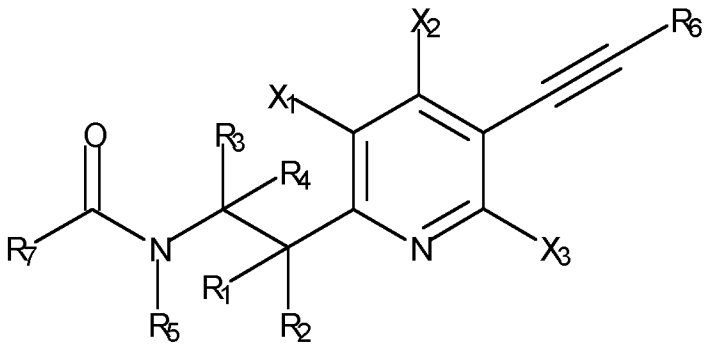




, and

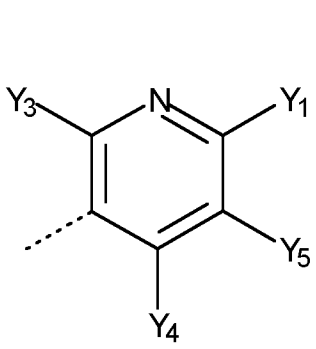
. (x-1) (x-3)

3. A compound for use according to claim 1 or 2 of formula (II)



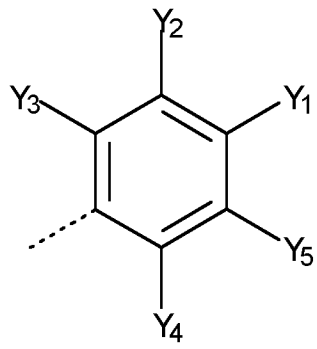
(II)

4. A compound for use according to any of claims 1 to 3 wherein R^6 is selected from the group consisting of



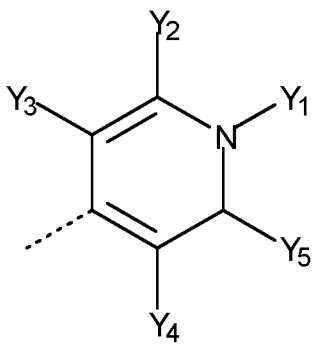
(y-1)

and

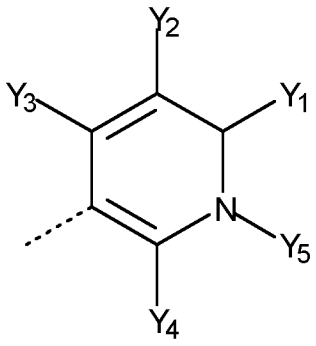


(y-2)

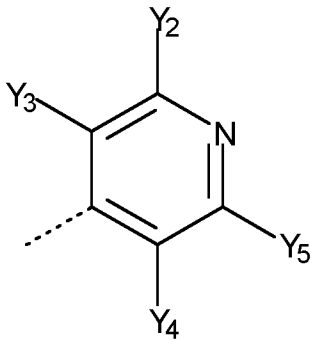
,



(y-3)



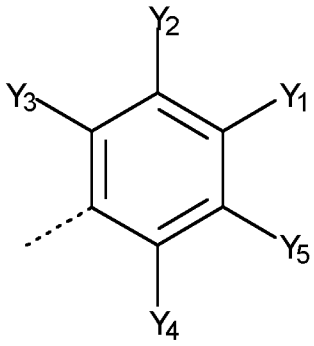
(y-4)



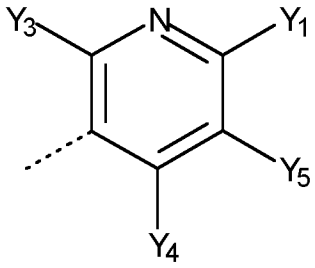
(y-5)

wherein Y^1, Y^2, Y^3, Y^4, Y^5 are each independently a hydrogen, halogen atom, cyano, nitro, C_1-C_4 alkyl, haloalkyloxy, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, trifluoromethylthio, trifluoromethylsulfinyl, trifluoromethylsulfonyl or phenyl wherein Y^1 and Y^5 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^5 and Y^4 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^1 and Y^2 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to, or Y^2 and Y^3 may form a ring so that they form a bicyclic ring system together with the aromatic ring they are attached to.

5. A compound for use according to any of claims 1 to 4 wherein R^6 is

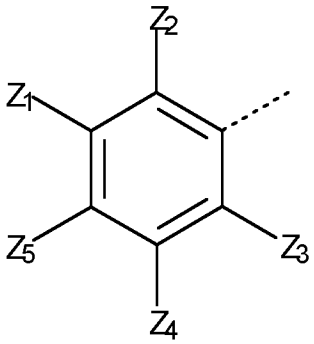


(y-2)

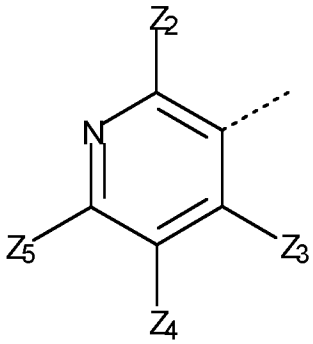


(y-1)

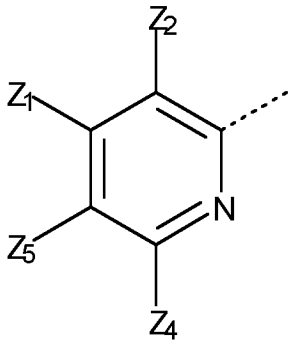
6. A compound for use according to any of claims 1 to 5 wherein R^7 is selected from the group consisting of;



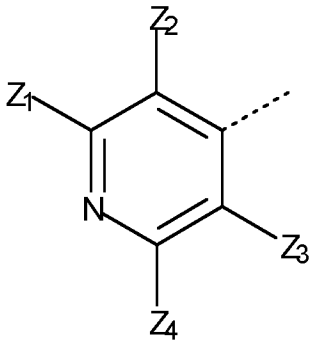
(z-1),



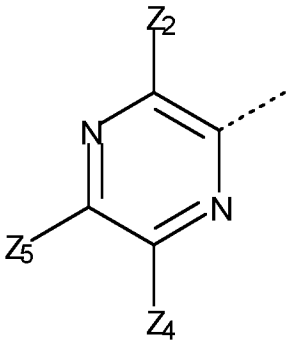
(z-2),



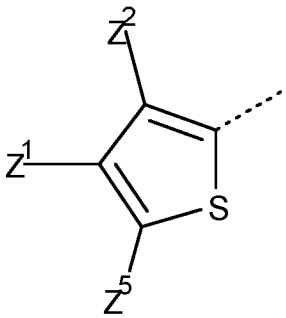
(z-3),



(z-4), and



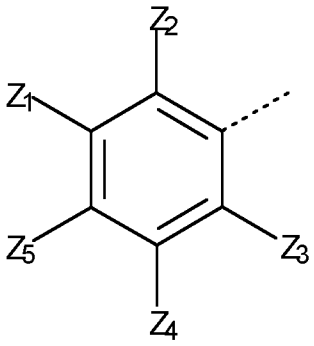
(z-5)



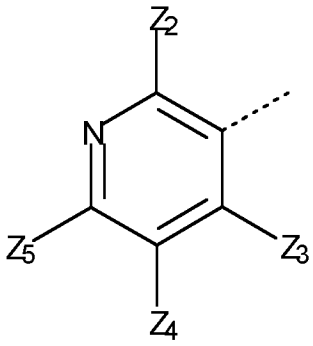
(z-6)

wherein $Z^{2,}$ Z^3 are each independently a hydrogen, halogen atom, nitro, C_1-C_4 alkyl or C_1-C_4 haloalkyl, Z^1, Z^4, Z^5 are each independently hydrogen, a halogen atom, or C_1-C_4 alkyl.

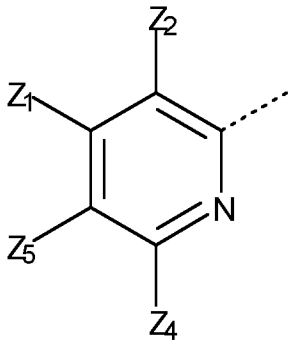
7. A compound for use according to any of claims 1 to 6 wherein R^7 is selected from the group consisting of;



(z-1)



(z-2)



(z-3)

8. A compound for use according to any of claims 1 to 7 wherein X^1 is a halogen atom, preferably a chloride.

9. A compound for use according to any of claims 1 to 8 wherein X^2 and X^3 are hydrogen.

10. A compound for use according to any of claims 1 to 9 whereinX^4 is hydrogen.

11. A compound for use according to any of claims 1 to 10 wherein Z^2 is a halogen atom or C_1-C_4 haloalkyl.

12. A compound for use according to any of claims 1 to 11 wherein Z^2 is chloride or CF_3, preferably CF_3.

13. A compound for use according to any of claims 1 to 11 wherein Z^1, Z^4, Z^5 are hydrogen.

14. A compound for use according to any of claims 1 to 13 wherein R^4 is hydrogen and R^3 is hydrogen or CH_3, preferably CH_3.

15. A compound for use according to any of claims 1 to 14 wherein Y^1, is a halogen atom, trifluoromethyl, methoxy, difluoromethoxy, or trifluoromethoxy.

16. A compound for use according to any of claims 1 to 15 wherein Y^1, is a halogen atom,or methoxy, or trifluoromethyl, preferably a chloride,

17. A compound for use according to any of claims 1 to 16 wherein, Y^2, Y^3, Y^4, Y^5 are each independently a hydrogen, or a halogen atom.

18. A compound for use according to any of claims 1 to 17 wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, C_1-C_4 alkyl, or C_1-C_4 haloalkyl.

19. A compound for use according to any of claims 1 to 18 wherein R^1 and R^2 are each independently a hydrogen atom, or a halogen atom preferably R^1 and R^2 are fluor.

20. A compound for use according to any of claims 1 to 19 wherein R^5 is a hydrogen atom, C_1-C_4 alkyl, C_1-C_4 haloalkyl, preferably hydrogen.

21. A compound for use according to any of claims 1 to 20 wherein, Y^3, Y^5 are each independently a halogen atom.

22. A compound for use according to any of claims 1-21 wherein the compounds are administered orally subcutaneously, or topically.

23. A compound for use according to any of claims 1-22 for use against a nematode, cestode or trematatode, preferably against *Haemonchus contortus* and/or *Trichostrongylus colubriformis, Dirofilaria,* and/or *Fasciola hepatica*.

24. A compound for use according to any one of claim 1 to 23 wherein the compound is used for the treatment of non-human animals, preferably for the treatment of an animal selected from the group consisting of ruminant, equine, companion animal, swine, poultry, fish, preferable selected from the group consisting of sheep, bovine, horse.

25. A compound for use according to any one of claim 1 to 24 wherein the compound is administered in a composition comprising a pharmaceutically acceptable carrier.

26. A compound for use according to any one of claim 1 to 25 wherein the compound is administered in an effective dose between about 0.01 and about 50 mg/kg bodyweight.

27. A compound for use according to any one of claim 1 to 26 wherein the compound is administered in combination with another antiparasitic agent, preferably an anthelminthic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/067317

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/44 A61K31/36 A61K31/415 A61K31/428 A61K31/437
A61K31/443 A61K31/4436 A61K31/4439 A61K31/444 A61K31/4709
A61K31/497 A61K45/06 A61P33/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/003924 A1 (NISSAN CHEMICAL IND LTD [JP]) 4 January 2018 (2018-01-04) cited in the application paragraph [0158] - paragraph [0160] paragraph [0166] paragraph [0443] - paragraph [0476]; examples 12,14	1-27
X	JP 2017 036275 A (NISSAN CHEMICAL IND LTD) 16 February 2017 (2017-02-16) paragraphs [0175], [0184] paragraph [0508] - paragraph [0519] paragraph [0575] - paragraph [0576]	1-14, 17-20, 22-27

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

[X] See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2019	10/09/2019

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

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 3 109 234 A1 (NISSAN CHEMICAL IND LTD [JP]) 28 December 2016 (2016-12-28) abstract paragraphs [0139], [0149] claims; example 12	1-14, 17-20, 22-27
X	JP 2017 039722 A (NISSAN CHEMICAL IND LTD) 23 February 2017 (2017-02-23) paragraphs [0135], [0144] paragraph [0377] - paragraph [0378] paragraph [0414]	1-5, 8-10, 14-20, 22-27
X,P	WO 2018/124088 A1 (NISSAN CHEMICAL IND LTD [JP]) 5 July 2018 (2018-07-05) cited in the application paragraphs [0086], [0088], [0089] paragraph [0188] paragraph [0259] - paragraph [0275] paragraphs [0295], [0297]; examples 12,14	1,4-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/067317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018003924 A1	04-01-2018	NONE	
JP 2017036275 A	16-02-2017	NONE	
EP 3109234 A1	28-12-2016	AU 2015219902 A1	01-09-2016
		EP 3109234 A1	28-12-2016
		JP WO2015125824 A1	30-03-2017
		US 2017008847 A1	12-01-2017
		WO 2015125824 A1	27-08-2015
JP 2017039722 A	23-02-2017	NONE	
WO 2018124088 A1	05-07-2018	NONE	