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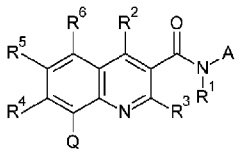

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(57) Abstract: The present invention covers new quinoline compounds of general formula (I), in which A, R^1, R^2, R^3, R^4, R^5, R^6, and Q are as defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds and the use of said compounds for manufacturing pharmaceutical compositions for the treatment, control and/or prevention of diseases, in particular of helminth infections, as a sole agent or in combination with other active ingredients.

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NEW QUINOLINE DERIVATIVES

The present invention covers new quinoline derivatives of general formula (I) as described and defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds, and the use of said compounds for manufacturing pharmaceutical compositions for the control, treatment and/or prevention of diseases, in particular for the control, treatment and/or prevention of infections with helminths, more particularly of infections with gastro-intestinal and extra-intestinal nematodes, in animals and humans, formulations containing such compounds and methods for the control, treatment and/or prevention of infections with helminths, more particularly of infections with gastro-intestinal and extra-intestinal nematodes, in animals and humans as a sole agent or in combination with other active ingredients.

BACKGROUND

The occurrence of resistances against all commercial anthelmintics seems to be a growing problem in the area of veterinary medicine. The extensive utilisation of anthelmintics to manage the control of nematodes resulted in significant selection of highly resistant worm populations. Therefore, the spread of resistance against all anthelmintic drug classes threatens effective worm control in cattle, goats, sheep and horses. Furthermore, successful prevention of heartworm disease in dogs, which currently solely relies on the utilisation of macrocyclic lactones, is in danger as loss of efficacy for multiple macrocyclic lactones has been described for some regions of the United States of America - especially in those areas where the heartworm challenge for infection is high. Finally, experimental infection studies with *Dirofilaria immitis* larvae from suspected field loss of efficacy cases in the Lower Mississippi Delta provided *in vivo* confirmation of the existence of macrocyclic lactone resistance.

Although resistance of human helminths against anthelmintics seems currently to be rare, the spread of anthelmintic resistance in the veterinary field as mentioned before needs to be considered in the treatment of human helminthosis as well. Persistent underdosed treatments against filariosis may lead to highly resistant genotypes and resistances have already been described for certain anthelmintics (e.g. praziquantel, benzimidazole and niclosamide).

Therefore, resistance-breaking anthelmintics with new molecular modes of action are urgently required.

It is an object of the present invention to provide compounds which can be used as anthelmintics in the medical, especially veterinary, field with a satisfactory or improved anthelmintic activity against a broad spectrum of helminths, particularly at relatively low dosages, for the control, treatment and/or prevention of infections with helminths in animals and humans, preferably without any adverse toxic effects to the treated organism.

Certain quinoline carboxamides are described in JP2008-214323A as agents suitable for treatment and/or prevention of skin diseases, like acne vulgaris, dermatitis or the like.

WO 2017/103851 A1 discloses quinoline-3-carboxamides as H-PGDS inhibitors, useful for treating atherosclerosis, psoriasis, sinusitis, and duchenne muscular dystrophy.

WO 2018/087036 A1 and WO 2019/215182 A1 disclose quinoline-3-carboxamides as anthelmintics in the medical especially veterinary field.

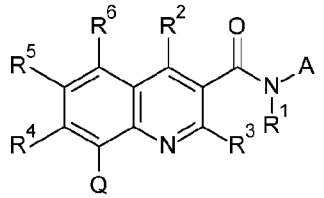
However, the state of the art does not describe the new quinoline derivatives of general formula (I) of the present invention as described and defined herein.

It has now been found, and this constitutes the basis of the present invention, that the compounds of the present invention have surprising and advantageous properties.

In particular, the compounds of the present invention have surprisingly been found to effectively interact with Slo-1 calcium-gated potassium channels of nematodes. This interaction is characterized by achieving paralysis/inhibition in particular of gastro-intestinal nematodes, of free-living nematodes, and of filariae, for which data are given in the biological experimental section. Therefore the compounds of the present invention may be used as anthelmintics for the control, treatment and/or prevention of gastro-intestinal and extra-intestinal helminth infections, in particular gastro-intestinal and extra-intestinal infections with nematodes, including filariae. The compounds of the present invention preferably possess a high chemical stability. Further, it is desirable that the compounds of the present invention have a suitable metabolic stability.

DESCRIPTION of the INVENTION

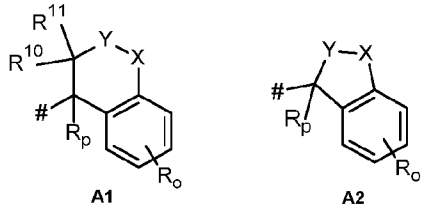
In accordance with a first aspect, the present invention covers compounds of general formula (I):



(I)

in which :

A is A1 or A2,



A1 A2

o is 0, 1, 2, 3 or 4,

R is selected from the group consisting of hydrogen, halogen, cyano, nitro, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl, –S(O)-C_1-C_4-halogenoalkyl and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, S, and N-R^9, wherein at least one of X and Y is CR^7R^8, or

X, Y form together a ring member selected from the group consisting of -C(O)-O-, -C(O)-NR^9-, -S(O)-NR^9-, $-SO_2$-NR^9- and $-SO_2$-O-,

R^1 is selected from the group consisting of hydrogen, cyano, -CHO, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, C_3-C_6-halogenocycloalkyl having 1 to 5 halogen atoms, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, cyano-C_1-C_4-alkyl, -NH-C_1-C_4-alkyl, -N(C_1-C_4-alkyl)$_2$, NH_2-C_1-C_4-alkyl-, C_1-C_4-alkyl-NH-C_1-C_4-alkyl-, (C_1-C_4-alkyl)$_2$N-C_1-C_4-alkyl-, C_1-C_4-alkyl-C(O)-, C_1-C_4-halogenoalkyl-C(O)- having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C(O)-, benzyloxy-C(O)-, C_1-C_4-alkoxy-C_1-C_4-alkyl-C(O)-, $-SO_2$-C_1-C_4-alkyl, and $–SO_2$-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

phenyl-C_1-C_4-alkyl, optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, –S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and $–SO_2$-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

heterocyclyl-C_1-C_4-alkyl, wherein the heterocyclyl substituent is selected from the group consisting of 4- to 10-membered heterocycloalkyl, 5-membered heteroaryl and 6-membered heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of halogen, -OH, -oxo, $-NO_2$, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, -S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and $–SO_2$-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 1,1-dioxido-1,2-thiazetidin-3-yl, 1,1-dioxido-1,2-

thiazetidin-4-yl, 1-oxido-1,2-thiazetidin-3-yl, 1-oxido-1,2-thiazetidin-4-yl, 2-oxido-1,2-oxathietan-3-yl, 2-oxido-1,2-oxathietan-4-yl, 2,2-dioxido-1,2-oxathietan-3-yl, 2,2-dioxido-1,2-oxathietan-4-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 4-thioxoazetidin-2-yl, 2-thioxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-mercaptocyclobutyl, 3-mercaptocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-chlorocyclobutyl, 3-chlorocyclobutyl, 2,2-dichlorocyclobutyl, 3,3-dichlorocyclobutyl, 2-bromocyclobutyl, 3-bromocyclobutyl, 2,2-dibromocyclobutyl, 3,3-dibromocyclobutyl, 2-iodocyclobutyl, 3-iodocyclobutyl, 2,2-diiodocyclobutyl, 3,3-diiodocyclobutyl, 3-methoxyiminocyclobutyl, 2-fluoro-3-(methoxyimino)cyclobutyl, 2,2-difluoro-3-(methoxyimino)cyclobutyl, 2-chloro-3-(methoxyimino)cyclobutyl, 2,2-dichloro-3-(methoxyimino)cyclobutyl, 2-bromo-3-(methoxyimino)cyclobutyl, 2,2-dibromo-3-(methoxyimino)cyclobutyl, 2-iodo-3-(methoxyimino)cyclobutyl, 2,2-diiodo-3-(methoxyimino)cyclobutyl, 3-(hydroxyimino)cyclobutyl, 2-fluoro-3-(hydroxyimino)cyclobutyl, 2,2-difluoro-3-(hydroxyimino)cyclobutyl, 2-chloro-3-(hydroxyimino)cyclobutyl, 2,2-dichloro-3-(hydroxyimino)cyclobutyl, 2-bromo-3-(hydroxyimino)cyclobutyl, 2,2-dibromo-3-(hydroxyimino)cyclobutyl, 2-iodo-3-(hydroxyimino)cyclobutyl, 2,2-diiodo-3-(hydroxyimino)cyclobutyl,

5- to 10-membered heterocycloalkyl, 5-membered heteroaryl and 6-membered heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of halogen, -OH, -oxo, $-NO_2$, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, -S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and $–SO_2$-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R^3 is hydrogen or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl,

R^7 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^8 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

or R^7 and R^8 together form an oxo group (=O),

or R^7 and R^8 form, together with the carbon atom to which they are attached, a 3- to 6-membered ring selected from the group consisting of C_3-C_6-cycloalkyl and 3- to 6-membered heterocycloalkyl,

R^9 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and C_1-C_4-alkoxy,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^{11} is selected from the group consisting of hydrogen, C_1-C_4-alkyl and C_1-C_4-alkoxy,

or R^{10} and R^{11} form, together with the carbon atom to which they are attached, a 3- to 6-membered ring selected from the group consisting of C_3-C_6-cycloalkyl and 3- to 6-membered heterocycloalkyl,

Q represents phenyl having 1 to 5 halogen atoms.

wherein when Y is O, S or N-R^9, none of R^7, R^8, R^{10} and R^{11} is –OH or C_1-C_4-alkoxy, and wherein when X is O, S or N-R^9, none of R^7 and R^8 is –OH or C_1-C_4-alkoxy;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

DEFINITIONS

The term “substituted” means that one or more hydrogen atoms on the designated atom or group are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded. Combinations of substituents and/or variables are permissible.

The term “optionally substituted” means that the number of substituents can be equal to or different from zero. Unless otherwise indicated, it is possible that optionally substituted groups are substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom. Commonly, it is possible for the number of optional substituents, when present, to be 1, 2, 3, 4 or 5, in particular 1, 2 or 3.

As used herein, the term "one or more", *e.g.* in the definition of the substituents of the compounds of general formula (I) of the present invention, means "1, 2, 3, 4 or 5, particularly 1, 2, 3 or 4, more particularly 1, 2 or 3, even more particularly 1 or 2".

As used herein, an oxo substituent represents an oxygen atom, which is bound to a carbon atom or to a sulfur atom via a double bond.

The term "ring substituent" means a substituent attached to an aromatic or nonaromatic ring which replaces an available hydrogen atom on the ring.

Should a composite substituent be composed of more than one parts, *e.g.* (C_1-C_4-alkoxy)-(C_1-C_4-alkyl)-, it is possible for the position of a given part to be at any suitable position of said composite substituent, *i.e.* the C_1-C_4-alkoxy part can be attached to any carbon atom of the C_1-C_4-alkyl part of said (C_1-C_4-alkoxy)-(C_1-C_4-alkyl)- group. A hyphen at the beginning or at the end of such a composite substituent indicates the point of attachment of said composite substituent to the rest of the molecule. Should a ring, comprising carbon atoms and optionally one or more heteroatoms, such as nitrogen, oxygen or sulfur atoms for example, be substituted with a substituent, it is possible for said substituent to be bound at any suitable position of said ring, be it bound to a suitable carbon atom and/or to a suitable heteroatom.

As used herein, the position via which a respective subsituent is connected to the rest of the molecule may in a drawn structure be depicted by a hash sign (#) or a dashed line in said substituent.

The term "comprising" when used in the specification includes "consisting of".

If within the present text any item is referred to as "as mentioned herein", it means that it may be mentioned anywhere in the present text.

The terms as mentioned in the present text have the following meanings:

The term "halogen atom" means a fluorine, chlorine, bromine or iodine atom, particularly a fluorine, chlorine or bromine atom.

The term "C_1-C_6-alkyl" means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms. The term "C_1-C_4-alkyl" means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, or 4 carbon atoms, *e.g.* a methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl or a *tert*-butyl group, or a further constitutional isomer thereof. Particularly, said group has 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), *e.g.* a methyl, ethyl, *n*-propyl or isopropyl group.

The term "C_1-C_4-hydroxyalkyl" means a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_4-alkyl" is defined *supra*, and in which 1 hydrogen atoms are replaced with a hydroxy group, *e.g.* a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-hydroxypropyl, 1-hydroxypropan-2-yl, 2-hydroxypropan-2-yl, 2,3-dihydroxypropyl, 1,3-dihydroxypropan-2-yl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl group.

The term "-NH(C_1-C_4-alkyl)" or "-N(C_1-C_4-alkyl)$_2$" means a linear or branched, saturated, monovalent group in which the term "C_1-C_4-alkyl" is as defined *supra*, *e.g.* a methylamino, ethylamino, *n*-propylamino, isopropylamino, *N,N*-dimethylamino, *N*-methyl-*N*-ethylamino or *N,N*-diethylamino group.

The term "-S-C_1-C_4-alkyl", "-S(O)-C_1-C_4-alkyl" or "-SO_2-C_1-C_4-alkyl" means a linear or branched, saturated group in which the term "C_1-C_4-alkyl" is as defined *supra*, *e.g.* a methylsulfanyl, ethylsulfanyl, *n*-propylsulfanyl, isopropylsulfanyl, *n*-butylsulfanyl, *sec*-butylsulfanyl, isobutylsulfanyl or *tert*-butylsulfanyl group, a methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, isopropylsulfinyl, *n*-butylsulfinyl, *sec*-butylsulfinyl, isobutylsulfinyl or *tert*-butylsulfinyl group, or a methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, isobutylsulfonyl or *tert*-butylsulfonyl group.

The term "C_1-C_4-halogenoalkyl" means a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_4-alkyl" is as defined *supra*, and in which one or more of the hydrogen atoms are replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine atom. More particularly, all said halogen atoms are fluorine atoms ("C_1-C_4-fluoroalkyl"). Said C_1-C_4-halogenoalkyl group is, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl or 1,3-difluoropropan-2-yl.

The term "C_1-C_4-alkoxy" means a linear or branched, saturated, monovalent group of formula (C_1-C_4-alkyl)-O-, in which the term "C_1-C_4-alkyl" is as defined *supra*, *e.g.* a methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy or *tert*-butoxy group, or a further constitutional isomer thereof.

The term "C_1-C_4-halogenoalkoxy" means a linear or branched, saturated, monovalent C_1-C_4-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine atom. Said C_1-C_4-halogenoalkoxy group is, for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy or pentafluoroethoxy.

The term "C_2-C_4-alkenyl" means a linear or branched, monovalent hydrocarbon group, which contains one double bond, and which has 2, 3 or 4 carbon atoms. Said C_2-C_4-alkenyl group is, for example, an ethenyl (or "vinyl"), a prop-2-en-1-yl (or "allyl"), prop-1-en-1-yl, but-3-enyl, but-2-enyl, but-1-enyl, prop-1-en-2-yl (or "isopropenyl"), 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl or a 1-methylprop-1-enyl, group. Particularly, said group is allyl.

The term "C_2-C_4-alkynyl" means a linear monovalent hydrocarbon group which contains one triple bond, and which contains 2, 3 or 4 carbon atoms. Said C_2-C_4-alkynyl group is, for example, an ethynyl, a prop-1-ynyl, prop-2-ynyl (or "propargyl"), but-1-ynyl, but-2-ynyl, but-3-ynyl or 1-methylprop-2-ynyl, group. Particularly, said alkynyl group is prop-1-ynyl or prop-2-ynyl.

The term "C_3-C_6-cycloalkyl" means a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms ("C_3-C_6-cycloalkyl"). Said C_3-C_6-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

The term "C_3-C_6-halogenocycloalkyl" means a saturated, monovalent, monocyclic hydrocarbon ring in which the term "C_3-C_6-cycloalkyl" is as defined *supra*, and in which one or more of the hydrogen atoms are replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine or chlorine atom. Said C_3-C_6-halogenocycloalkyl group is for example, a monocyclic hydrocarbon ring substituted with one or two fluorine or chlorine atoms, *e.g.* a 1-fluoro-cyclopropyl, 2-fluorocyclopropyl, 2,2-difluorocyclopropyl, 2,3-difluorocyclopropyl, 1-chlorocyclopropyl, 2-chlorocyclopropyl, 2,2-dichlorocyclopropyl, 2,3-dichlorocyclopropyl, 2-fluoro-2-chlorocyclopropyl and 2-fluoro-3-chlorocyclopropyl group.

The term "benzo-C_5-C_6-cycloalkyl" means a monovalent, bicyclic hydrocarbon ring wherein a saturated, monovalent, monocyclic hydrocarbon ring which contains 5 or 6 carbon atoms ("C_5-C_6-cycloalkyl") is annelated to a phenyl ring. Said benzo-C_5-C_6-cycloalkyl group is for example, a bicyclic hydrocarbon ring, *e.g.* an indane (i.e. 2,3-dihydro-1*H*-indene) or tetraline (i.e. 1,2,3,4-tetrahydronaphthalene) group.

The term "spirocycloalkyl" means a saturated, monovalent bicyclic hydrocarbon group in which the two rings share one common ring carbon atom, and wherein said bicyclic hydrocarbon group contains 5, 6, 7, 8, 9, 10 or 11 carbon atoms, it being possible for said spirocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms except the spiro carbon atom. Said spirocycloalkyl group is, for example, spiro[2.2]pentyl, spiro[2.3]hexyl, spiro[2.4]heptyl, spiro[2.5]octyl, spiro[2.6]nonyl, spiro[3.3]heptyl, spiro[3.4]octyl, spiro[3.5]nonyl, spiro[3.6]decyl, spiro[4.4]nonyl, spiro[4.5]decyl, spiro[4.6]undecyl or spiro[5.5]undecyl.

The term "heterocycloalkyl" means a monocyclic or bicyclic, saturated or partially saturated heterocycle with 4, 5, 6, 7, 8, 9 or 10 ring atoms in total (a "4- to 10-membered heterocycloalkyl" group), particularly 4, 5 or 6 ring atoms (a "4- to 6-membered heterocycloalkyl" group), which contains one or two identical or different ring heteroatoms from the series N, O and S, it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom.

Said heterocycloalkyl group, without being limited thereto, can be a 4-membered ring, such as azetidinyl, oxetanyl or thietanyl, for example; or a 5-membered ring, such as tetrahydrofuranyl, oxolanyl, 1,3-dioxolanyl, thiolanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, 1,1-dioxidothiolanyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, 1,3-thiazolidinyl or 1,2,4-triazolidinyl, for example; or a 6-membered ring, such as tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, oxanyl, 1,3-dioxanyl, 1,4-dioxanyl or 1,2-oxazinanyl, for example; or a 7-membered ring, such as azepanyl, 1,4-diazepanyl or 1,4-oxazepanyl, for example; or a bicyclic 7-membered ring, such as 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl or 6-oxa-3-azabicyclo[3.1.1]heptan, for example; or a bicyclic 8-membered ring, such as 5,6-dihydro-4H-furo[2,3-c]pyrrole or 8-oxa-3-azabicyclo[3.2.1]octan, for example; or a bicyclic 9-membered ring, such as octahydro-1H-pyrrolo[3,4-b]pyridine, 1,3-dihydro-

isoindol, 2,3-dihydro-indol, 3,7-dioxa-9-azabicyclo[3.3.1]nonan or 3,9-dioxa-7-azabicyclo[3.3.1]nonan, for example; or a bicyclic 10-membered ring, such as decahydroquinoline or 3,4-dihydroisoquinolin, for example.

The term "heterospirocycloalkyl" means a bicyclic, saturated heterocycle with 6, 7, 8, 9, 10 or 11 ring atoms in total, in which the two rings share one common ring carbon atom, which "heterospirocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said heterospirocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms, except the spiro carbon atom, or, if present, a nitrogen atom.

Said heterospirocycloalkyl group is, for example, azaspiro[2.3]hexyl, azaspiro[3.3]heptyl, oxaazaspiro[3.3]heptyl, thiaazaspiro[3.3]heptyl, oxaspiro[3.3]heptyl, oxazaspiro[5.3]nonyl, oxazaspiro[4.3]octyl, oxaazaspiro[2.5]octyl, azaspiro[4.5]decyl, oxazaspiro[5.5]undecyl, diazaspiro[3.3]heptyl, thiazaspiro[3.3]heptyl, thiazaspiro[4.3]octyl, azaspiro[5.5]undecyl, or one of the further homologous scaffolds such as spiro[3.4]-, spiro[4.4]-, spiro[2.4]-, spiro[2.5]-, spiro[2.6]-, spiro[3.5]-, spiro[3.6]-, spiro[4.5]- and spiro[4.6]-.

The term "6- or 10-membered aryl" means a monovalent, monocyclic or bicyclic aromatic ring having 6 or 10 carbon ring atoms, e.g. a phenyl or naphthyl group.

The term "heteroaryl" means a monovalent, monocyclic, bicyclic or tricyclic aromatic ring having 5, 6, 9 or 10 ring atoms (a "5- to 10-membered heteroaryl" group), particularly 5 or 6 ring atoms (a "5- to 6-membered heteroaryl" group), which contains at least one ring heteroatom and optionally one, two or three further ring heteroatoms from the series: N, O and/or S, and which is bound via a ring carbon atom or optionally via a ring nitrogen atom (if allowed by valency).

Said heteroaryl group can be a 5-membered heteroaryl group, such as, for example, thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl or tetrazolyl; or a 6-membered heteroaryl group, such as, for example, pyridinyl, dihydropyridinyl, pyridazinyl, pyrimidinyl, tetrahydropyrimidinyl, pyrazinyl or triazinyl.

The term "heterocyclyl" means a heterocycle selected from the group consisting of heterocycloalkyl and heteroaryl. Particularly, the term "4- to 6-membered heterocyclyl" means a heterocycle selected from the group consisting of 4- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl.

In general, and unless otherwise mentioned, the heteroaryl or heteroarylene groups include all possible constitutional isomeric forms thereof, *e.g.*: tautomers and positional isomers with respect to the point of linkage to the rest of the molecule. Thus, for some illustrative non-restricting examples, the term pyridinyl includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl; or the term thienyl includes thien-2-yl and thien-3-yl.

The term "C_1-C_4", as used in the present text, *e.g.* in the context of the definition of "C_1-C_4-alkyl", "C_1-C_4-halogenoalkyl", "C_1-C_4-hydroxyalkyl", "C_1-C_4-alkoxy" or "C_1-C_4-halogenoalkoxy" means an alkyl group having a finite number of carbon atoms of 1 to 4, *i.e.* 1, 2, 3 or 4 carbon atoms.

Further, as used herein, the term "C_3-C_6", as used in the present text, *e.g.* in the context of the definition of "C_3-C_6-cycloalkyl" or C_3-C_6-halogenocycloalkyl, means a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms.

When a range of values is given, said range encompasses each value and sub-range within said range.

For example:

"C_1-C_4" encompasses C_1, C_2, C_3, C_4, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_4, C_2-C_3, and C_3-C_4;

"C_2-C_6" encompasses C_2, C_3, C_4, C_5, C_6, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_3-C_4" encompasses C_3, C_4, and C_3-C_4;

"C_3-C_{10}" encompasses C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_3-C_{10}, C_3-C_9, C_3-C_8, C_3-C_7, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_{10}, C_4-C_9, C_4-C_8, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_{10}, C_5-C_9, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_{10}, C_6-C_9, C_6-C_8, C_6-C_7, C_7-C_{10}, C_7-C_9, C_7-C_8, C_8-C_{10}, C_8-C_9 and C_9-C_{10};

"C_3-C_8" encompasses C_3, C_4, C_5, C_6, C_7, C_8, C_3-C_8, C_3-C_7, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_8, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_8, C_6-C_7 and C_7-C_8;

"C_3-C_6" encompasses C_3, C_4, C_5, C_6, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_4-C_8" encompasses C_4, C_5, C_6, C_7, C_8, C_4-C_8, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_8, C_6-C_7 and C_7-C_8;

"C_4-C_7" encompasses C_4, C_5, C_6, C_7, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_7, C_5-C_6 and C_6-C_7;

"C_4-C_6" encompasses C_4, C_5, C_6, C_4-C_6, C_4-C_5 and C_5-C_6;

"C_5-C_{10}" encompasses C_5, C_6, C_7, C_8, C_9, C_{10}, C_5-C_{10}, C_5-C_9, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_{10}, C_6-C_9, C_6-C_8, C_6-C_7, C_7-C_{10}, C_7-C_9, C_7-C_8, C_8-C_{10}, C_8-C_9 and C_9-C_{10};

"C_6-C_{10}" encompasses C_6, C_7, C_8, C_9, C_{10}, C_6-C_{10}, C_6-C_9, C_6-C_8, C_6-C_7, C_7-C_{10}, C_7-C_9, C_7-C_8, C_8-C_{10}, C_8-C_9 and C_9-C_{10}.

As used herein, the term "leaving group" means an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. In particular, such a leaving group is selected from the group comprising: halide, in particular fluoride, chloride, bromide or iodide, (methylsulfonyl)oxy, [(trifluoromethyl)sulfonyl]oxy, [(nonafluorobutyl)sulfonyl]oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy, [(4-bromophenyl)sulfonyl]oxy, [(4-nitrophenyl)sulfonyl]oxy, [(2-nitrophenyl)sulfonyl]oxy, [(4-isopropylphenyl)sulfonyl]oxy, [(2,4,6-triisopropylphenyl)sulfonyl]oxy, [(2,4,6-trimethylphenyl)sulfonyl]oxy, [(4-*tert*-butylphenyl)sulfonyl]oxy and [(4-methoxyphenyl)sulfonyl]oxy.

As used herein, the term "saponification" means the hydrolysis of an ester performed in the presence of an aqueous solution of an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxides or mixtures thereof. The saponification may or may not be followed by a decarboxylation reaction.

It is possible for the compounds of general formula (I) to exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula (I), particularly deuterium-containing compounds of general formula (I).

The term "Isotopic variant" of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term "Isotopic variant of the compound of general formula (I)" is defined as a compound of general formula (I) exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression "unnatural proportion" means a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and ^{131}I, respectively.

With respect to the treatment and/or prevention of the disorders specified herein the isotopic variant(s) of the compounds of general formula (I) preferably contain deuterium ("deuterium-containing compounds of general formula (I)"). Isotopic variants of the compounds of general formula (I) in which one or more radioactive isotopes, such as ^{3}H or ^{14}C, are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula (I). These isotopic variants of the compounds of general formula (I) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of general formula (I) can be used in mass spectrometry analyses in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds. Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds and acetylenic bonds is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons. A variety of deuterated reagents and synthetic building blocks are

commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA.

The term "deuterium-containing compound of general formula (I)" is defined as a compound of general formula (I), in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula (I) the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., J. Am. Chem. Soc., 2007, 129, 4490], basicity [C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res. Toxicol., 2013, 26, 410; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208) and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. / Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of general formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium-containing compound(s) of general formula (I) is/are attached to a carbon atom and/or is/are located at those positions of the compound of general formula (I), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P_{450}.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, stereoisomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of the present invention optionally contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. It is possible that one or more asymmetric carbon atoms are present in the (R) or (S) configuration, which can result in racemic mixtures in the case of a single asymmetric centre, and in diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, it is possible that asymmetry also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. In certain instances, it is possible that asymmetry may also be present due to restricted rotation around a double bond or due to a ring structure, wherein the rotation of bonds is restricted or prevented. These geometric isomers may be indicated as cis- or trans-isomers or as (E)- and (Z)-isomers.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified constitutional isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of the present invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

Preferred stereoisomers are those which produce the more desirable biological activity. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical

isomers involves the use of chiral chromatography (*e.g.*, HPLC columns using a chiral phase), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable HPLC columns using a chiral phase are commercially available, such as those manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ, for example, among many others, which are all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of the present invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

In order to distinguish different types of stereoisomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* (R)- or (S)- stereoisomers, (E)- or (Z)-isomers, cis- or trans-isomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention is achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also covers useful forms of the compounds of the present invention, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and/or co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example, as structural element of the crystal lattice of the compounds. It is possible for the amount of polar solvents, in particular water, to exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, it is possible for the compounds of the present invention to exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or to exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, which is customarily used in pharmacy, or which is used, for example, for isolating or purifying the compounds of the present invention.

The term “pharmaceutically acceptable salt" refers to an inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* “Pharmaceutical Salts,” J. Pharm. Sci. 1977, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, or "mineral acid", such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, 3-phenylpropionic, pivalic, 2-hydroxyethanesulfonic, itaconic, trifluoromethanesulfonic, dodecylsulfuric, ethanesulfonic, benzenesulfonic, para-toluenesulfonic, methanesulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium, magnesium or strontium salt, or an aluminium or a zinc salt, or an ammonium salt derived from ammonia or from an organic primary, secondary or tertiary amine having 1 to 20 carbon atoms, such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, diethylaminoethanol, tris(hydroxymethyl)aminomethane, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, 1,2-ethylenediamine, *N*-methylpiperidine, *N*-methyl-glucamine, *N,N*-dimethyl-glucamine, *N*-ethyl-glucamine, 1,6-hexanediamine, glucosamine, sarcosine, serinol, 2-amino-1,3-propanediol, 3-amino-1,2-propanediol, 4-amino-1,2,3-butanetriol, or a salt with a quarternary ammonium ion having 1 to 20 carbon atoms, such as tetramethylammonium, tetraethylammonium, tetra(*n*-propyl)ammonium, tetra(*n*-butyl)ammonium, *N*-benzyl-*N,N,N*-trimethylammonium, choline or benzalkonium.

Those skilled in the art will further recognise that it is possible for acid addition salts of the claimed compounds to be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the present invention are prepared by reacting the compounds of the present invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae relating to salts, such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF_3COOH", "x Na^+", for example, mean a salt form, the stoichiometry of which salt form not being specified.

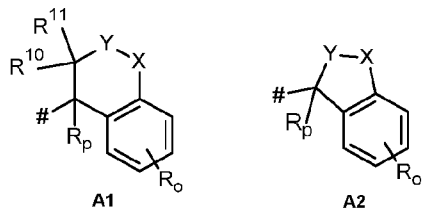
This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates, with (if defined) unknown stoichiometric composition.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

Moreover, the present invention also includes prodrugs of the compounds according to the invention. The term "prodrugs" here designates compounds which themselves can be biologically active or inactive, but are converted (for example metabolically or hydrolytically) into compounds according to the invention during their residence time in the body.

In accordance with a second embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

A is A1 or A2,



o is 0, 1, 2, 3 or 4,

R is selected from the group consisting of hydrogen, halogen, cyano, nitro, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl, –S(O)-C_1-C_4-halogenoalkyl and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, S, and N-R^9, wherein at least one of X and Y is CR^7R^8, or

X, Y form together a ring member selected from the group consisting of -C(O)-O-, -C(O)-NR^9-, -S(O)-NR^9-, $-SO_2$-NR^9- and $-SO_2$-O-,

R^1 is selected from the group consisting of hydrogen, cyano, -CHO, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, C_3-C_6-halogenocycloalkyl having 1 to 5 halogen atoms, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, cyano-C_1-C_4-alkyl, -NH-C_1-C_4-alkyl, -N(C_1-C_4-alkyl)$_2$, NH_2-C_1-C_4-alkyl-, C_1-C_4-alkyl-NH-C_1-C_4-alkyl-, (C_1-C_4-alkyl)$_2$N-C_1-C_4-alkyl-, C_1-C_4-alkyl-C(O)-, C_1-C_4-halogenoalkyl-C(O)- having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C(O)-, benzyloxy-C(O)-, C_1-C_4-alkoxy-C_1-C_4-alkyl-C(O)-, -SO_2-C_1-C_4-alkyl, and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

phenyl-C_1-C_4-alkyl, optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of halogen, -OH, -NO_2, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, –S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

heterocyclyl-C_1-C_4-alkyl, wherein the heterocyclyl substituent is selected from the group consisting of 4- to 10-membered heterocycloalkyl, 5-membered heteroaryl and 6-membered heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of halogen, -OH, -NO_2, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, –S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 1,1-dioxido-1,2-thiazetidin-3-yl, 1,1-dioxido-1,2-thiazetidin-4-yl, 1-oxido-1,2-thiazetidin-3-yl, 1-oxido-1,2-thiazetidin-4-yl, 2-oxido-1,2-oxathietan-3-yl, 2-oxido-1,2-oxathietan-4-yl, 2,2-dioxido-1,2-oxathietan-3-yl, 2,2-dioxido-1,2-oxathietan-4-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 4-thioxoazetidin-2-yl, 2-thioxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-mercaptocyclobutyl, 3-mercaptocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-chlorocyclobutyl, 3-chlorocyclobutyl, 2,2-dichlorocyclobutyl, 3,3-dichlorocyclobutyl, 2-bromocyclobutyl, 3-bromocyclobutyl, 2,2-dibromocyclobutyl, 3,3-dibromocyclobutyl, 2-iodocyclobutyl, 3-iodocyclobutyl, 2,2-diiodocyclobutyl, 3,3-diiodocyclobutyl, 3-methoxyiminocyclobutyl, 2-fluoro-3-(methoxyimino)cyclobutyl, 2,2-difluoro-3-(methoxyimino)cyclobutyl, 2-chloro-3-(methoxyimino)cyclobutyl, 2,2-dichloro-3-

(methoxyimino)cyclobutyl, 2-bromo-3-(methoxyimino)cyclobutyl, 2,2-dibromo-3-(methoxyimino)cyclobutyl, 2-iodo-3-(methoxyimino)cyclobutyl, 2,2-diiodo-3-(methoxyimino)cyclobutyl, 3-(hydroxyimino)cyclobutyl, 2-fluoro-3-(hydroxyimino)cyclobutyl, 2,2-difluoro-3-(hydroxyimino)cyclobutyl, 2-chloro-3-(hydroxyimino)cyclobutyl, 2,2-dichloro-3-(hydroxyimino)cyclobutyl, 2-bromo-3-(hydroxyimino)cyclobutyl, 2,2-dibromo-3-(hydroxyimino)cyclobutyl, 2-iodo-3-(hydroxyimino)cyclobutyl, 2,2-diiodo-3-(hydroxyimino)cyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2,5-dihydrofuran-3-yl, 2,3-dihydrofuran-3-yl, 4,5-dihydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 2,5-dihydrofuran-2-yl, 2,3-dihydrofuran-2-yl, furan-3-yl, furan-2-yl, tetrahydrothiophen-3-yl, tetrahydrothiophen-2-yl, 2,5-dihydrothiophen-3-yl, 2,3-dihydrothiophen-3-yl, 4,5-dihydrothiophen-3-yl, 4,5-dihydrothiophen-2-yl, 2,5-dihydrothiophen-2-yl, 2,3-dihydrothiophen-2-yl, thiophen-3-yl, thiophen-2-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 4,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, 4,5-dihydro-1H-pyrrol-3-yl, 3,4-dihydro-2H-pyrrol-4-yl, 3,4-dihydro-2H-pyrrol-3-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-3-yl, 2H-pyrrol-5-yl, 3H-pyrrol-2-yl, 2H-pyrrol-4-yl, 1H-pyrrol-3-yl, 5-oxopyrrolidin-3-yl, 2-oxopyrrolidin-3-yl, 5-oxopyrrolidin-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 4-alkyl-3-oxopiperazin-1-yl, 4-alkyl-2-oxopiperazin-1-yl, wherein the alkyl is C_1-C_6-alkyl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen, or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$,

R^7 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^8 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

or R^7 and R^8 together form an oxo group (=O),

R^9 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and C_1-C_4-alkoxy,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^{11} is selected from the group consisting of hydrogen, C_1-C_4-alkyl and C_1-C_4-alkoxy,

Q is represents phenyl having 1 to 5 halogen atoms,

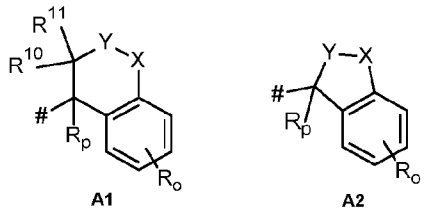
wherein when Y is O, S or N-R^9, none of R^7, R^8, R^{10} and R^{11} is –OH or C_1-C_4-alkoxy, and

wherein when X is O, S or N-R^9, none of R^7 and R^8 is –OH or C_1-C_4-alkoxy;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a third embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

A is A1 or A2,



o is 0, 1 or 2,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl and C_1-C_4-alkoxy, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, S, and N-R^9, wherein at least one of X and Y is CR^7R^8,

R^1 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, cyano-C_1-C_4-alkyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^9 is hydrogen or C_1-C_4-alkyl,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^{11} is hydrogen,

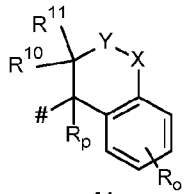
Q represents phenyl having 1 to 5 substituents independently selected from fluorine, chlorine, or bromine,

wherein when Y is O, S or N-R^9, R^{10} is not –OH or C_1-C_4-alkoxy;

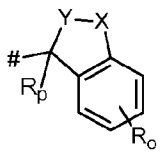
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a fourth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

A is A1 or A2,



A1



A2

o is 0, 1 or 2,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, and cyano,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X is selected from the group consisting of CR^7R^8, O, S, and N-R^9,

Y is CR^7R^8 or O,

R^1 is hydrogen or C_1-C_4-alkyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^9 is hydrogen or C_1-C_4-alkyl,

R^{10} is selected from the group consisting of hydrogen, -OH and C_1-C_4-alkyl,

R^{11} is hydrogen,

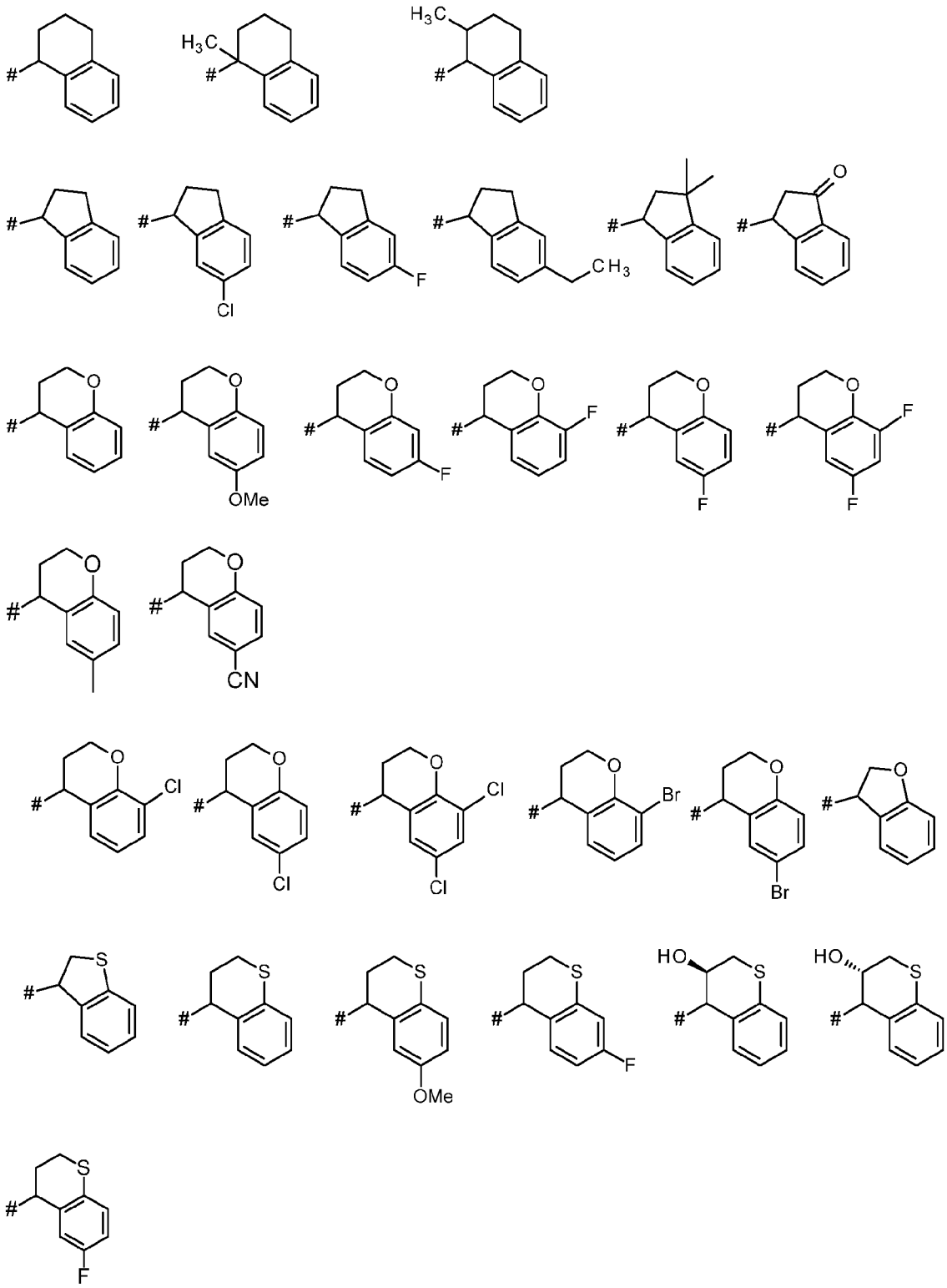
Q represents phenyl having 2 or 3 substituents independently selected from fluorine, chlorine, or bromine,

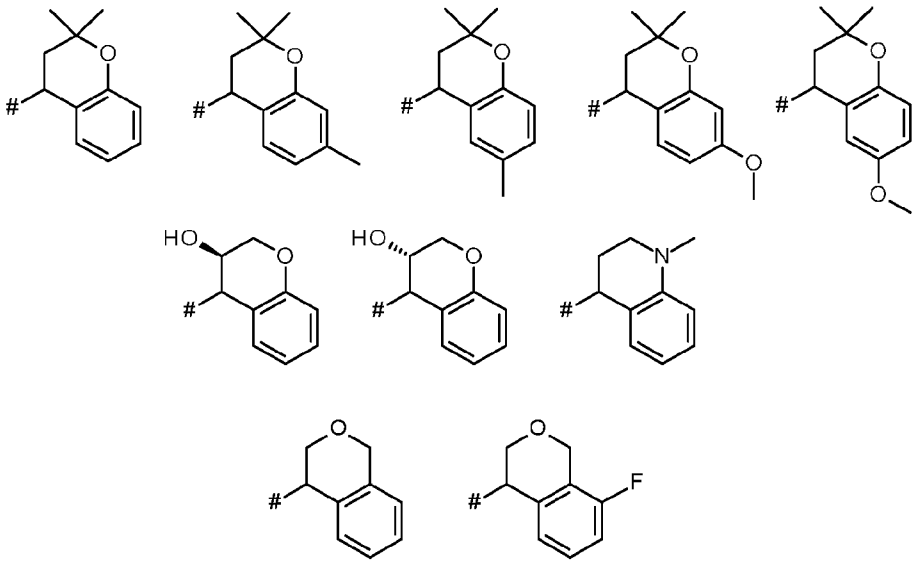
wherein when Y is O, R^{10} is not –OH,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a fifth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

A is selected from the group consisting of


H3C
CH3
O
Cl
F
OMe
CN
Br
HO
S



R^1 is hydrogen or methyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl 2-fluorocyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or methyl,

R^4 is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl, methoxy, isopropoxy, trifluoromethyl, and trifluoromethoxy, preferably hydrogen, fluorine, chlorine and C_1-C_4-alkoxy, more preferably hydrogen, fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, $-NH_2$, cyano, methyl, methoxy, trifluoromethoxy, and trifluoromethyl,

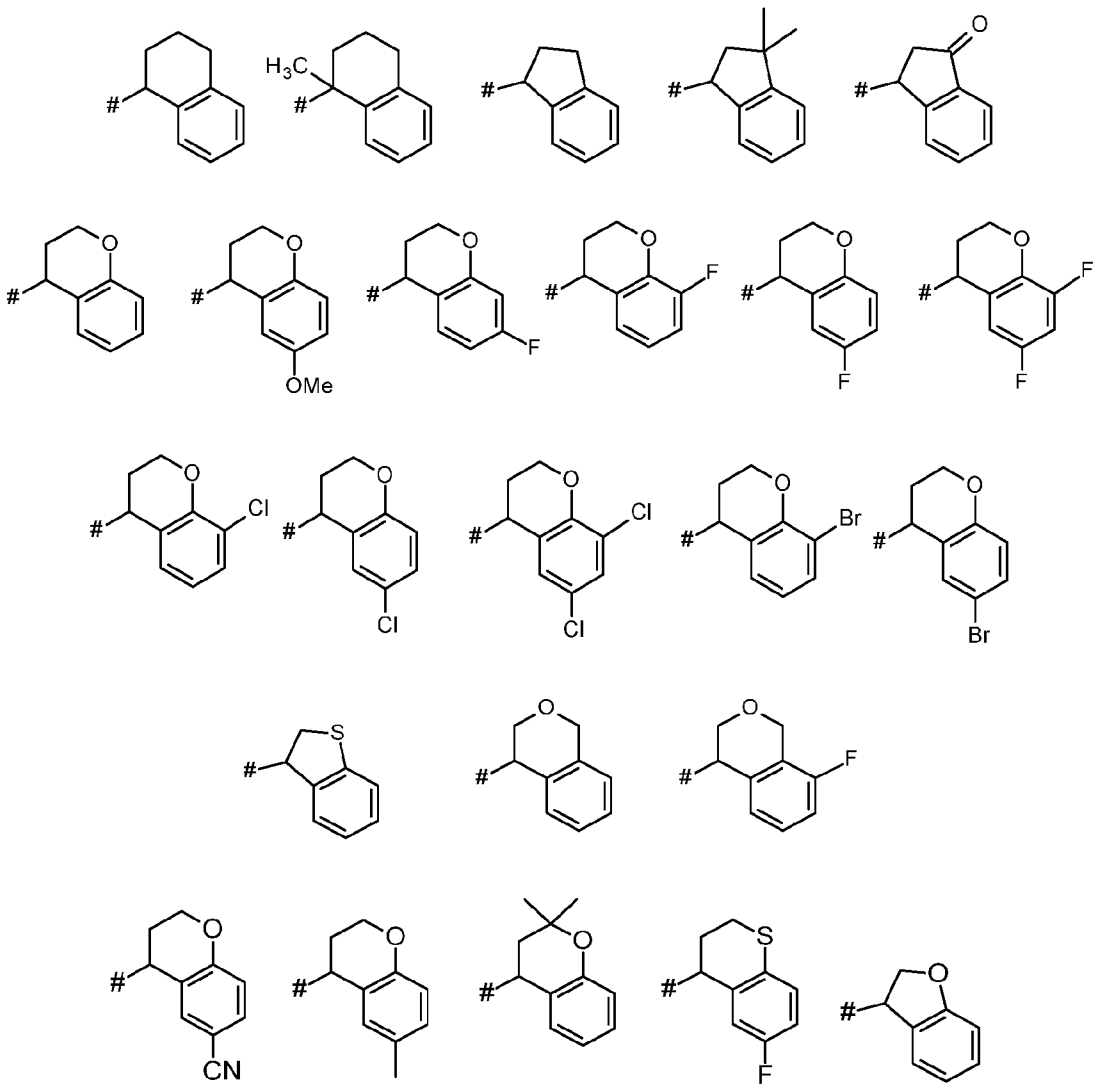
R^6 is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl and methoxy,

Q is selected from the group consisting of 2,3-dichlorophenyl, 3,5-dichlorophenyl, and 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a sixth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

A is selected from the group consisting of



R[1] is hydrogen or methyl,

R[2] is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R[3] is hydrogen or methyl,

R^4 is selected from the group consisting of hydrogen, chlorine, fluorine, methyl, methoxy, isopropoxy and trifluoromethyl, preferably hydrogen, fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, chlorine, fluorine, -OH, cyano, methyl, trifluoromethoxy and NH_2,

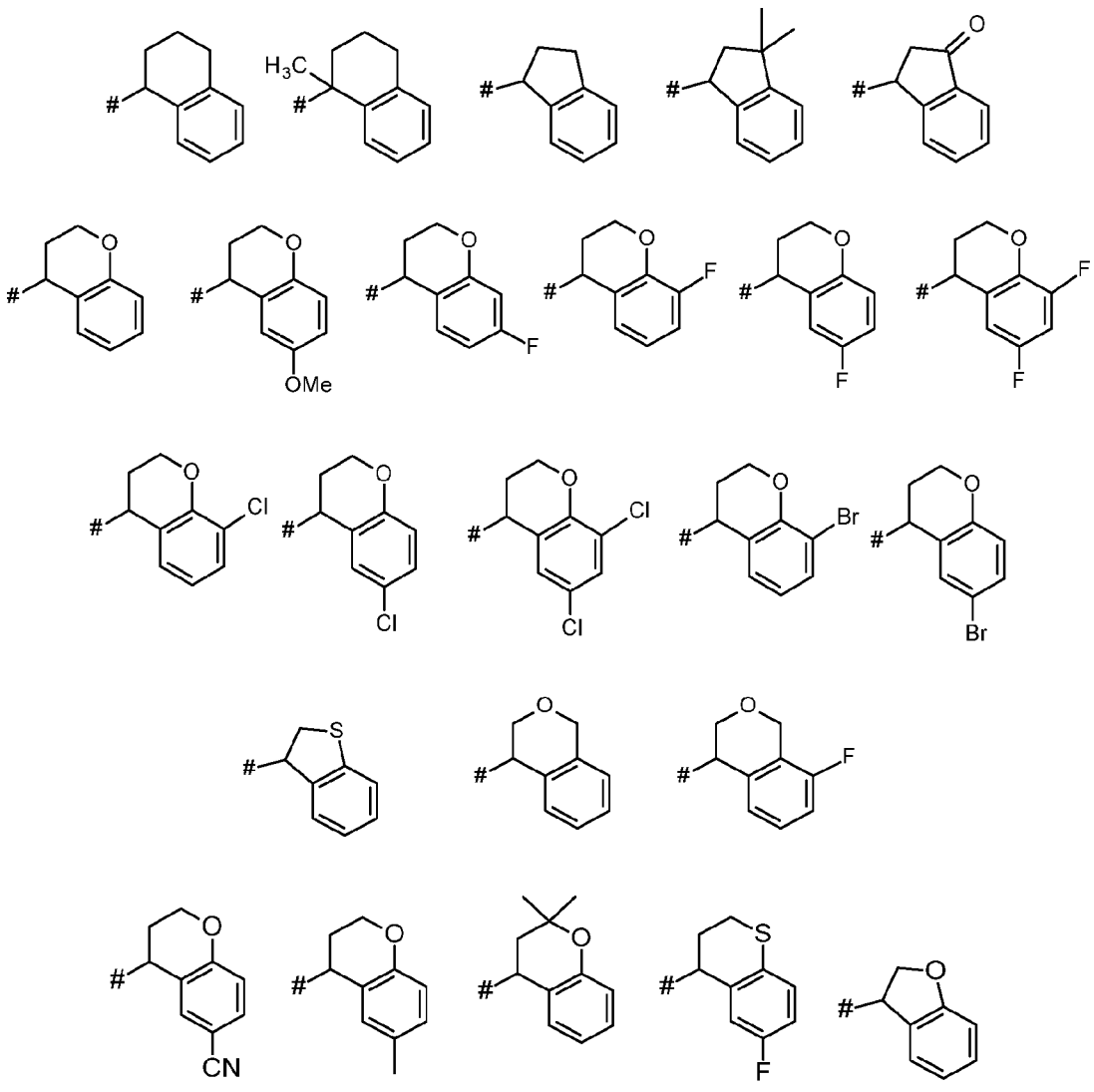
R^6 is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl and methoxy,

Q is selected from the group of 2,3-dichlorophenyl, 3,5-dichlorophenyl, and 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a further embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

A is selected from the group consisting of



,

R^1 is hydrogen or methyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 2-thietanyl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-hydroxycyclobutyl, 2-fluorocyclobutyl, tetrahydrofuran-2-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or methyl,

R^4 is selected from the group consisting of hydrogen, chlorine, fluorine, -OH, cyano, methyl, methoxy, trifluoromethyl, isopropoxy, and trifluoromethoxy, preferably hydrogen, fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, chlorine, fluorine, -OH, $-NH_2$, cyano, methyl, methoxy, trifluoromethoxy, and trifluoromethyl,

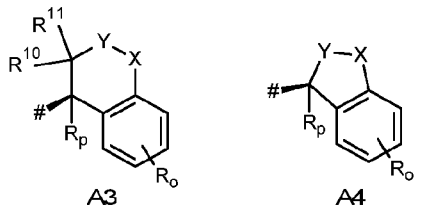
R^6 is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl and methoxy,

Q is selected from the group of 2,3-dichlorophenyl, 3,5-dichlorophenyl, and 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a further embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

A is A3 or A4



o is 0, 1 or 2,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy and cyano,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X is selected from the group consisting of CR^7R^8, O, S, and N-R^9,

Y is CR^7R^8 or O,

R^1 is hydrogen or C_1-C_4-alkyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-

oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^9 is hydrogen or C_1-C_4-alkyl,

R^{10} is selected from the group consisting of hydrogen, -OH and C_1-C_4-alkyl,

R^{11} is hydrogen,

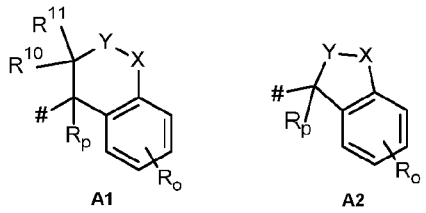
Q represents phenyl having 2 or 3 substituents independently selected from fluorine, chlorine or bromine,

wherein when Y is O, R^{10} is not –OH,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is A1 or A2,



o is 0, 1 or 2,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl and C_1-C_4-alkoxy, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, S, and N-R^9, wherein at least one of X and Y is CR^7R^8,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^9 is hydrogen or C_1-C_4-alkyl,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy, and

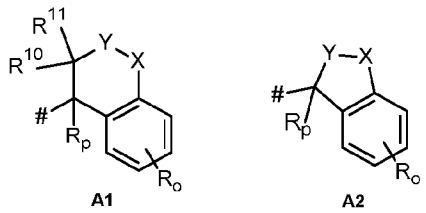
R^{11} is hydrogen,

wherein when Y is O, S or N-R^9, R^{10} is not –OH or C_1-C_4-alkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is A1 or A2,



o is 0, 1 or 2,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl and C_1-C_4-alkoxy, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is hydrogen or C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, and S,

wherein at least one of X and Y is CR^7R^8,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy, and

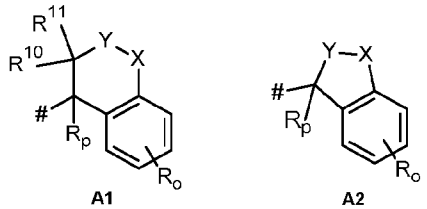
R^{11} is hydrogen,

wherein when Y is O, S or N-R^9, R^{10} is not –OH or C_1-C_4-alkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is A1 or A2,



o is 0 or 1,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X is selected from the group consisting of CR^7R^8, O, S, and N-R^9,

Y is CR^7R^8,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^9 is hydrogen or C_1-C_4-alkyl,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl, and C_1-C_4-alkoxy, and

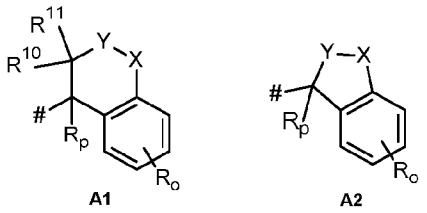
R^{11} is hydrogen,

wherein when Y is O, R^{10} is not –OH or C_1-C_4-alkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is A1 or A2,



o is 0 or 1,

R is selected from the group consisting of hydrogen, and halogen, ,

R_p is hydrogen,

X is selected from the group consisting of CR^7R^8, O and S,

Y is CR^7R^8,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^{10} is selected from the group consisting of hydrogen, , and

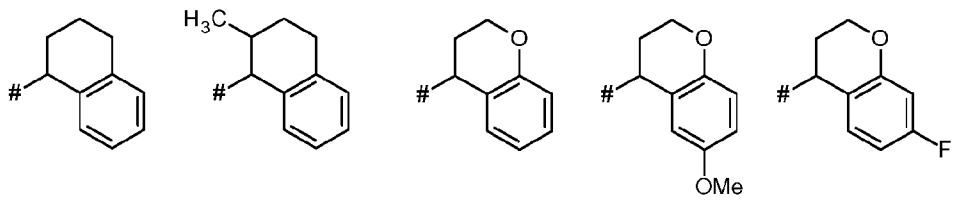
R^{11} is hydrogen,

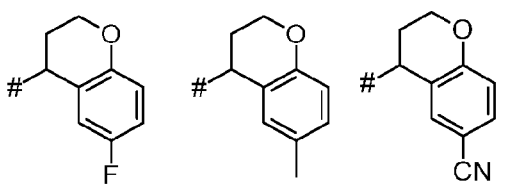
,

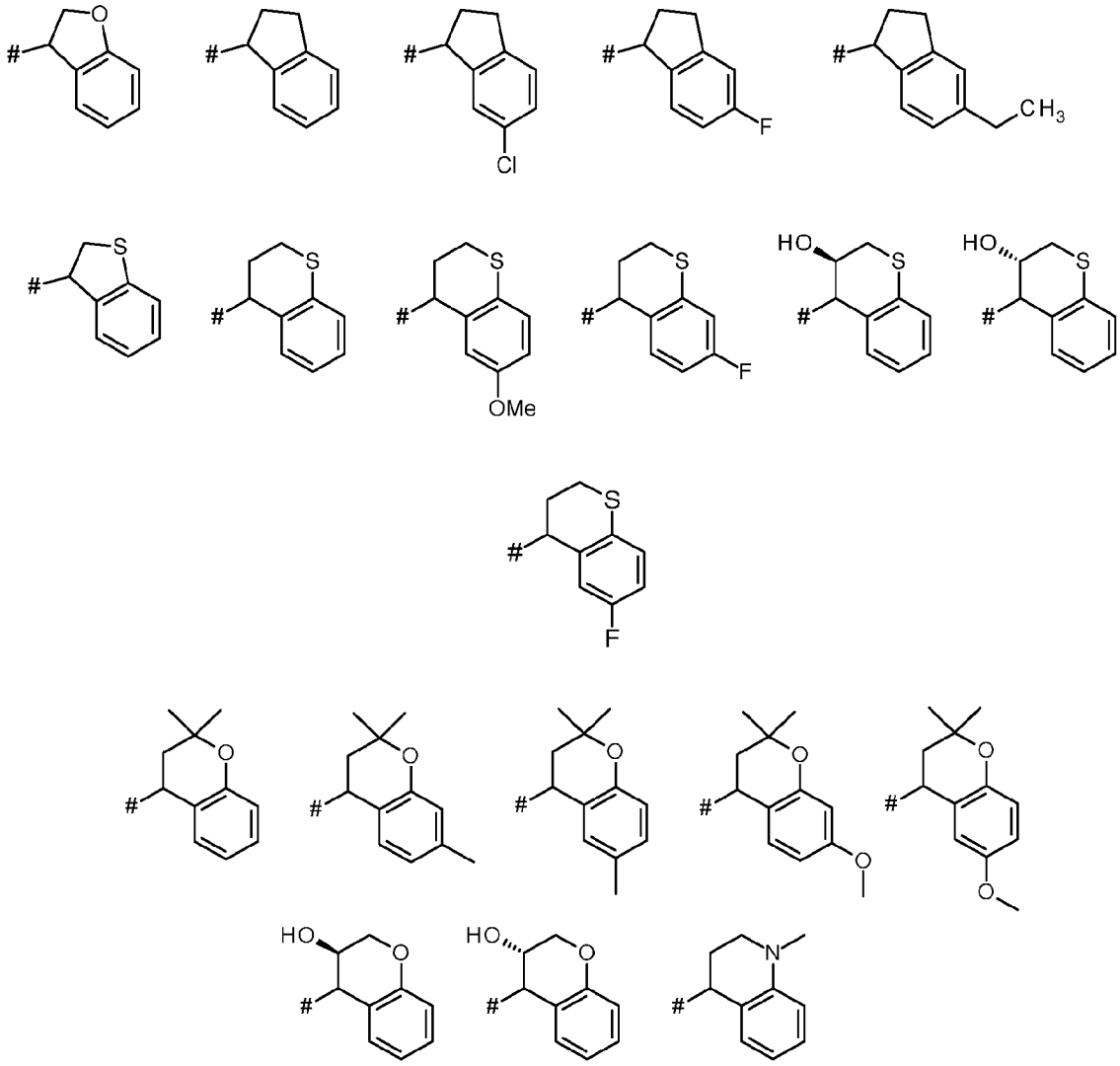
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is selected from the group consisting of



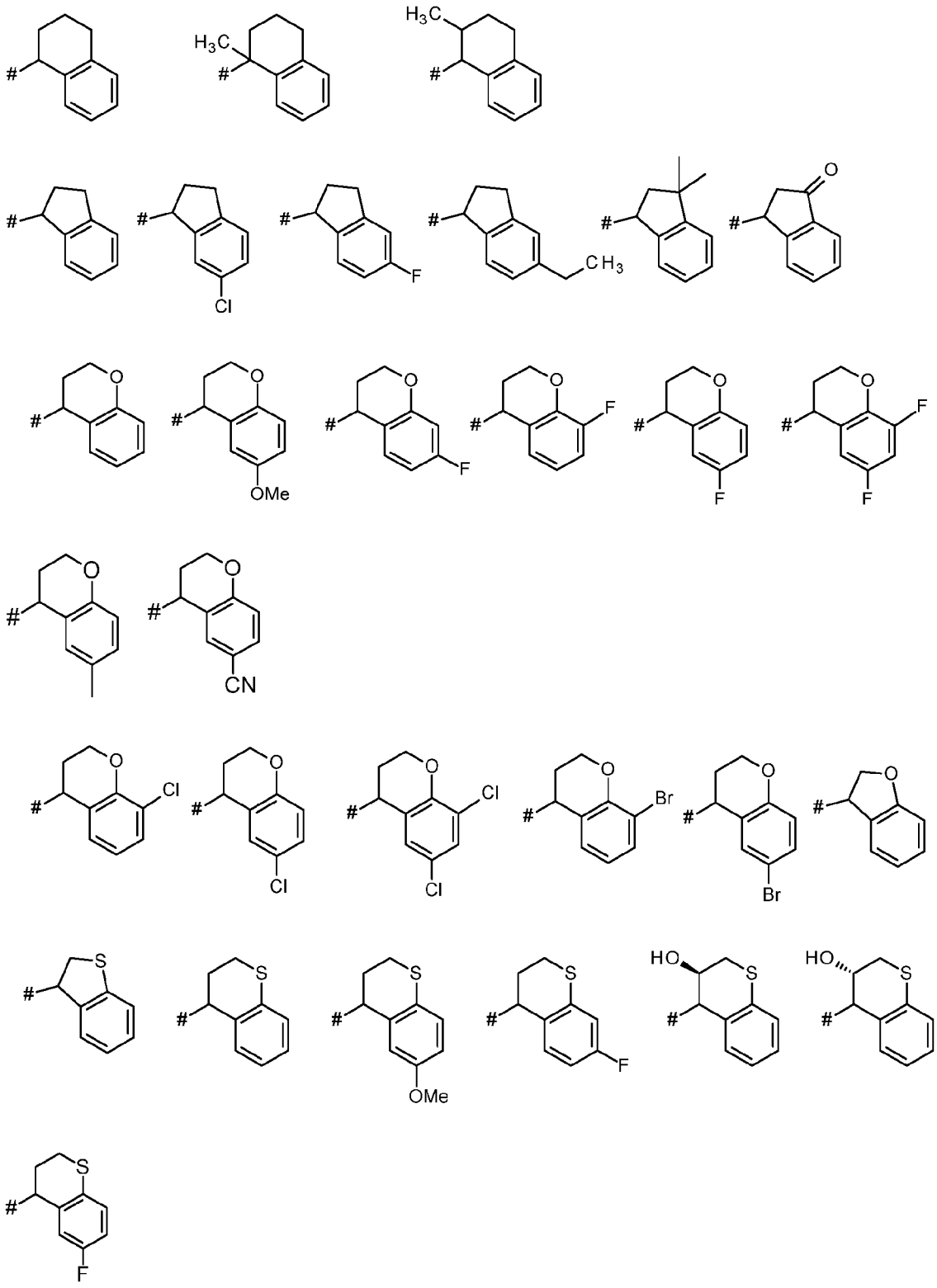




and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is selected from the group consisting of


H3C
H3C
CH3
Cl
F
O
OMe
F
F
F
F
CN
Cl
Cl
Cl
Br
Br
O
S
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S
S
OMe
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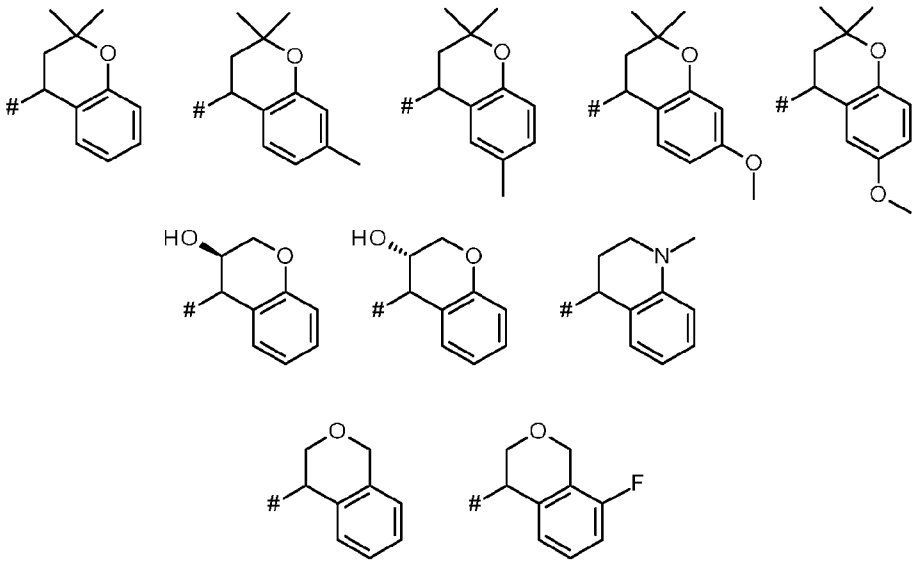
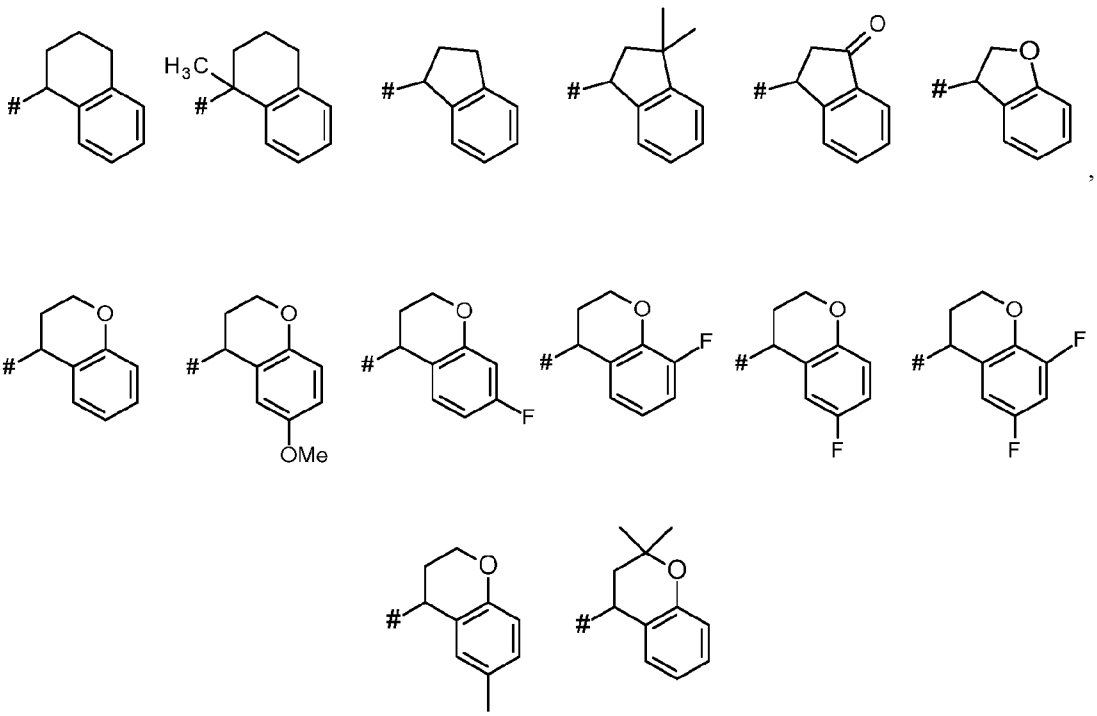
HO
HO
S
F

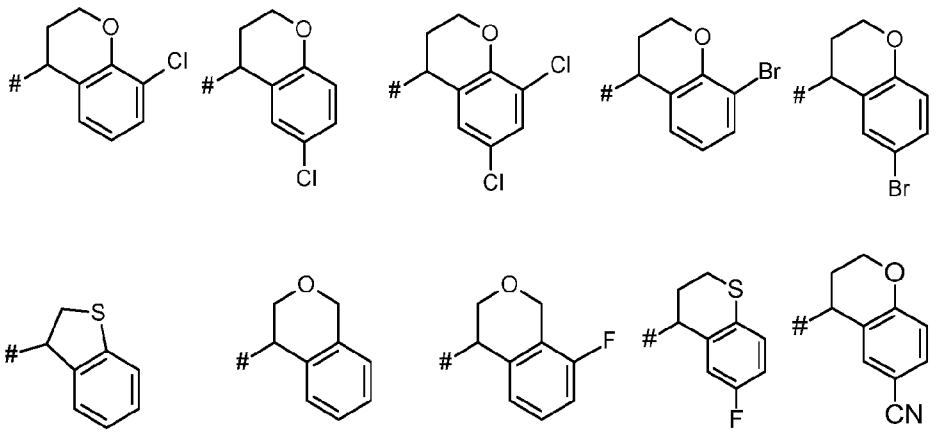


and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

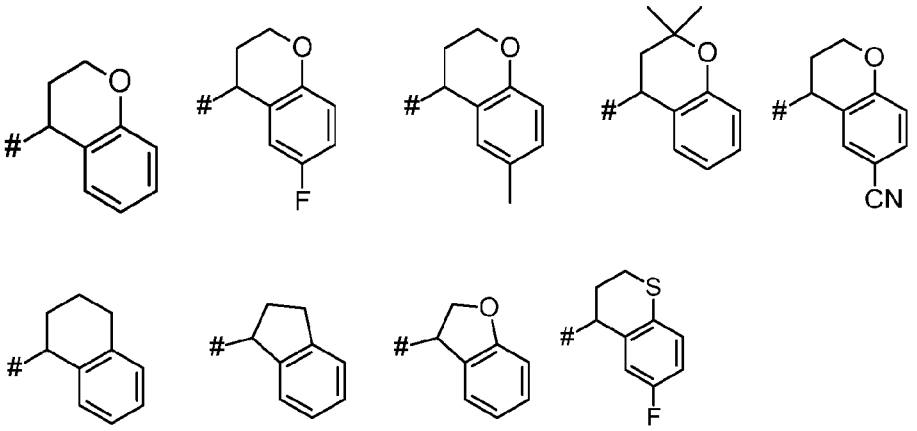
In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is selected from the group consisting of





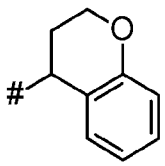
preferably



and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

A is selected from a group A1 as defined anywhere herein *supra*;

preferably, A is  .

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-

dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 1,1-dioxido-1,2-thiazetidin-3-yl, 1,1-dioxido-1,2-thiazetidin-4-yl, 1-oxido-1,2-thiazetidin-3-yl, 1-oxido-1,2-thiazetidin-4-yl, 2-oxido-1,2-oxathietan-3-yl, 2-oxido-1,2-oxathietan-4-yl, 2,2-dioxido-1,2-oxathietan-3-yl, 2,2-dioxido-1,2-oxathietan-4-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 4-thioxoazetidin-2-yl, 2-thioxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-mercaptocyclobutyl, 3-mercaptocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-chlorocyclobutyl, 3-chlorocyclobutyl, 2,2-dichlorocyclobutyl, 3,3-dichlorocyclobutyl, 2-bromocyclobutyl, 3-bromocyclobutyl, 2,2-dibromocyclobutyl, 3,3-dibromocyclobutyl, 2-iodocyclobutyl, 3-iodocyclobutyl, 2,2-diiodocyclobutyl, 3,3-diiodocyclobutyl, 3-methoxyiminocyclobutyl, 2-fluoro-3-(methoxyimino)cyclobutyl, 2,2-difluoro-3-(methoxyimino)cyclobutyl, 2-chloro-3-(methoxyimino)cyclobutyl, 2,2-dichloro-3-(methoxyimino)cyclobutyl, 2-bromo-3-(methoxyimino)cyclobutyl, 2,2-dibromo-3-(methoxyimino)cyclobutyl, 2-iodo-3-(methoxyimino)cyclobutyl, 2,2-diiodo-3-(methoxyimino)cyclobutyl, 3-(hydroxyimino)cyclobutyl, 2-fluoro-3-(hydroxyimino)cyclobutyl, 2,2-difluoro-3-(hydroxyimino)cyclobutyl, 2-chloro-3-(hydroxyimino)cyclobutyl, 2,2-dichloro-3-(hydroxyimino)cyclobutyl, 2-bromo-3-(hydroxyimino)cyclobutyl, 2,2-dibromo-3-(hydroxyimino)cyclobutyl, 2-iodo-3-(hydroxyimino)cyclobutyl, 2,2-diiodo-3-(hydroxyimino)cyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2,5-dihydrofuran-3-yl, 2,3-dihydrofuran-3-yl, 4,5-dihydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 2,5-dihydrofuran-2-yl, 2,3-dihydrofuran-2-yl, furan-3-yl, furan-2-yl, tetrahydrothiophen-3-yl, tetrahydrothiophen-2-yl, 2,5-dihydrothiophen-3-yl, 2,3-dihydrothiophen-3-yl, 4,5-dihydrothiophen-3-yl, 4,5-dihydrothiophen-2-yl, 2,5-dihydrothiophen-2-yl, 2,3-dihydrothiophen-2-yl, thiophen-3-yl, thiophen-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 4,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, 4,5-dihydro-1H-pyrrol-3-yl, 3,4-dihydro-2H-pyrrol-4-yl, 3,4-dihydro-2H-pyrrol-3-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-3-yl, 2H-pyrrol-5-yl, 3H-pyrrol-2-yl, 2H-pyrrol-4-yl, 1H-pyrrol-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 4-alkyl-3-oxopiperazin-1-yl, 4-alkyl-2-oxopiperazin-1-yl, wherein the alkyl is C_1-C_6-alkyl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R_p is hydrogen or C_1-C_4-alkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R_p is hydrogen or methyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^3 is hydrogen or C_1-C_4-alkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^3 is hydrogen or methyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, and C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 is selected from the group consisting of hydrogen, chlorine, fluorine, -OH, cyano, methyl, methoxy, isopropoxy, trifluoromethyl, and trifluoromethoxy, preferably hydrogen, fluorine, chlorine, methoxy and isopropoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 is selected from the group consisting of hydrogen, chlorine, fluorine, -OH, cyano, methyl, methoxy and trifluoromethyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^6 is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-oxocyclobutyl, 3-thietanyl, 1-oxidothietan-3-yl, 1-imino-1-oxido-1-thietan-3-yl, 1,1-dioxidothietan-3-yl, 2-oxoazetidin-3-yl, 3-hydroxycyclobutyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

Q is 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-oxocyclobutyl, 3-thietanyl, 1-oxidothietan-3-yl, 1-imino-1-oxido-1-thietan-3-yl, 1,1-dioxidothietan-3-yl, 2-oxoazetidin-3-yl, 3-hydroxycyclobutyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

Q is 3,5-dichlorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-oxocyclobutyl,

Q is 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-oxocyclobutyl,

Q is 3,5-dichlorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-thietanyl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 1-oxidothietan-3-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 1-imino-1-oxido-1-thietan-3-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 1,1-dioxidothietan-3-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 2-oxoazetidin-3-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-hydroxycyclobutyl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-fluorocyclobutyl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3,3-difluorocyclobutyl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is tetrahydrofuran-3-yl,

Q is 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is tetrahydrofuran-3-yl,

Q is 3,5-dichlorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 1-methylpyrrolidine-2-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 1-methylpyrrolidine-3-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 5-oxopyrrolidine-3-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 2-oxopyrrolidine-3-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 5-oxopyrrolidine-2-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is tetrahydropyran-4-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3-oxopiperazin-1-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-

alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 is selected from the group consisting of 3-oxocyclobutyl, 3-thietanyl, 1-oxidothietan-3-yl, 1-imino-1-oxido-1-thietan-3-yl, 1,1-dioxidothietan-3-yl, 2-oxoazetidin-3-yl, 3-hydroxycyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

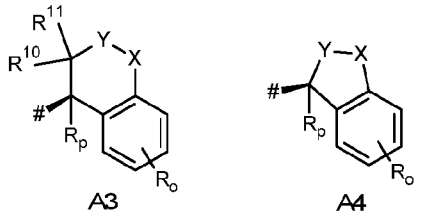
R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

Q is 2,3,5-trifluorophenyl or 3,5-dichlorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which

A is A3 or A4



wherein

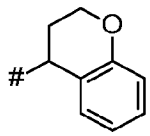
R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl; preferably hydrogen,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further aspect of the present invention in any or all of the embodiments described anywhere herein in the definition of X and/or Y "NR^9" as defined *supra* is excluded.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which

A is



R^1 is hydrogen

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 1,1-dioxido-1,2-thiazetidin-3-yl, 1,1-dioxido-1,2-thiazetidin-4-yl, 1-oxido-1,2-thiazetidin-3-yl, 1-oxido-1,2-thiazetidin-4-yl, 2-oxido-1,2-oxathietan-3-yl, 2-oxido-1,2-oxathietan-4-yl, 2,2-dioxido-1,2-oxathietan-3-yl, 2,2-dioxido-1,2-oxathietan-4-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 4-thioxoazetidin-2-yl, 2-thioxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-mercaptocyclobutyl, 3-mercaptocyclobutyl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-chlorocyclobutyl, 3-chlorocyclobutyl, 2,2-dichlorocyclobutyl, 3,3-dichlorocyclobutyl, 2-bromocyclobutyl, 3-bromocyclobutyl, 2,2-dibromocyclobutyl, 3,3-dibromocyclobutyl, 2-iodocyclobutyl, 3-iodocyclobutyl, 2,2-diiodocyclobutyl, 3,3-diiodocyclobutyl, 3-methoxyiminocyclobutyl, 2-fluoro-3-(methoxyimino)cyclobutyl, 2,2-difluoro-3-(methoxyimino)cyclobutyl, 2-chloro-3-(methoxyimino)cyclobutyl, 2,2-dichloro-3-(methoxyimino)cyclobutyl, 2-bromo-3-(methoxyimino)cyclobutyl, 2,2-dibromo-3-(methoxyimino)cyclobutyl, 2-iodo-3-(methoxyimino)cyclobutyl, 2,2-diiodo-3-(methoxyimino)cyclobutyl, 3-(hydroxyimino)cyclobutyl, 2-fluoro-3-(hydroxyimino)cyclobutyl, 2,2-difluoro-3-(hydroxyimino)cyclobutyl, 2-chloro-3-(hydroxyimino)cyclobutyl, 2,2-dichloro-3-(hydroxyimino)cyclobutyl, 2-bromo-3-(hydroxyimino)cyclobutyl, 2,2-dibromo-3-(hydroxyimino)cyclobutyl, 2-iodo-3-(hydroxyimino)cyclobutyl, 2,2-diiodo-3-(hydroxyimino)cyclobutyl,

5- to 10-membered heterocycloalkyl, 5-membered heteroaryl and 6-membered heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of halogen, -OH, -oxo, $-NO_2$, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, $-SO_2$-C_1-C_4-alkyl, –S-C_1-C_4-

halogenoalkyl having 1 to 5 halogen atoms, -S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, preferably the 5- to 10-membered heterocycloalkyl is tetrahydrofuran-3-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, or 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl

R^3 is hydrogen,

R^4 is halogen,

R^5 is hydrogen,

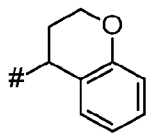
R^6 is hydrogen,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which

A is



R^1 is hydrogen

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 1,1-dioxido-1,2-thiazetidin-3-yl, 1,1-dioxido-1,2-thiazetidin-4-yl, 1-oxido-1,2-thiazetidin-3-yl, 1-oxido-1,2-thiazetidin-4-yl, 2-oxido-1,2-oxathietan-3-yl, 2-oxido-1,2-oxathietan-4-yl, 2,2-dioxido-1,2-oxathietan-3-yl, 2,2-dioxido-1,2-oxathietan-4-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 4-thioxoazetidin-2-yl, 2-thioxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-mercaptocyclobutyl, 3-mercaptocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-chlorocyclobutyl, 3-chlorocyclobutyl, 2,2-dichlorocyclobutyl, 3,3-dichlorocyclobutyl, 2-bromocyclobutyl, 3-bromocyclobutyl, 2,2-dibromocyclobutyl, 3,3-dibromocyclobutyl, 2-iodocyclobutyl, 3-iodocyclobutyl, 2,2-diiodocyclobutyl, 3,3-diiodocyclobutyl, 3-methoxyiminocyclobutyl, 2-fluoro-3-(methoxyimino)cyclobutyl, 2,2-difluoro-3-(methoxyimino)cyclobutyl, 2-chloro-3-(methoxyimino)cyclobutyl, 2,2-dichloro-3-(methoxyimino)cyclobutyl, 2-bromo-3-(methoxyimino)cyclobutyl, 2,2-dibromo-3-(methoxyimino)cyclobutyl, 2-iodo-3-(methoxyimino)cyclobutyl, 2,2-diiodo-3-(methoxyimino)cyclobutyl, 3-(hydroxyimino)cyclobutyl, 2-fluoro-3-(hydroxyimino)cyclobutyl,

2,2-difluoro-3-(hydroxyimino)cyclobutyl, 2-chloro-3-(hydroxyimino)cyclobutyl, 2,2-dichloro-3-(hydroxyimino)cyclobutyl, 2-bromo-3-(hydroxyimino)cyclobutyl, 2,2-dibromo-3-(hydroxyimino)cyclobutyl, 2-iodo-3-(hydroxyimino)cyclobutyl, 2,2-diiodo-3-(hydroxyimino)cyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2,5-dihydrofuran-3-yl, 2,3-dihydrofuran-3-yl, 4,5-dihydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 2,5-dihydrofuran-2-yl, 2,3-dihydrofuran-2-yl, furan-3-yl, furan-2-yl, tetrahydrothiophen-3-yl, tetrahydrothiophen-2-yl, 2,5-dihydrothiophen-3-yl, 2,3-dihydrothiophen-3-yl, 4,5-dihydrothiophen-3-yl, 4,5-dihydrothiophen-2-yl, 2,5-dihydrothiophen-2-yl, 2,3-dihydrothiophen-2-yl, thiophen-3-yl, thiophen-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 4,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, 4,5-dihydro-1H-pyrrol-3-yl, 3,4-dihydro-2H-pyrrol-4-yl, 3,4-dihydro-2H-pyrrol-3-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-3-yl, 2H-pyrrol-5-yl, 3H-pyrrol-2-yl, 2H-pyrrol-4-yl, 1H-pyrrol-3-yl, 5-oxopyrrolidin-3-yl, 2-oxopyrrolidin-3-yl, 5-oxopyrrolidin-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 4-methyl-3-oxopiperazin-1-yl, 4-ethyl-3-oxopiperazin-1-yl, 4-propyl-3-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen,

R^4 is fluor,

R^5 is hydrogen,

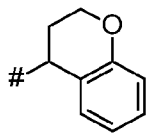
R^6 is hydrogen,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which

A is



R^1 is hydrogen

R^2 is selected from the group consisting of 3-oxocyclobutyl, 3-thietanyl, 1-oxidothietan-3-yl, 1,1-dioxidothietan-3-yl, 1-imino-1-oxido-1-thietan-3-yl, 3-hydroxycyclobutyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-3-yl, pyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, tetrahydrothiophen-3-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 4-methyl-3-oxopiperazin-1-yl, 4-ethyl-3-oxopiperazin-1-yl, 4-propyl-3-

oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen,

R^4 is fluor,

R^5 is hydrogen,

R^6 is hydrogen,

Q is 3,5-dichlorophenyl or 2,3,5-trifluorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In a particular further embodiment of the first aspect, the present invention covers combinations of two or more of the above mentioned embodiments under the heading "further embodiments of the first aspect of the present invention".

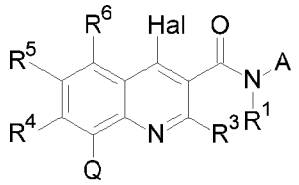
The present invention covers any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I), *supra*.

The present invention covers the compounds of general formula (I) which are disclosed in the Example Section of this text, *infra*.

The compounds according to the invention of general formula (I) can be prepared according to the procedures as shown in the Experimental Section to the present invention (General Procedures). The procedures described illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified can be modified in various ways. The order of transformations exemplified in these procedures is therefore not intended to be limiting. In addition, interconversion of any of the substituents, Q, A, R^1, R^2, R^3, R^4, R^5 or R^6 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, saponification, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

A saponification can be performed in the presence of an aqueous solution of an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxides or mixtures thereof. The saponification may or may not be followed by a decarboxylation reaction. Preferably, the saponification is followed by a decarboxylation reaction.

In accordance with a second aspect, the present invention covers methods of preparing compounds of general formula (I) as defined *supra*, said methods comprising the step of allowing an intermediate compound of general formula **1N**:



1N,

in which A, R^1, R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) as defined *supra*, and Hal is halogen, particularly chlorine and bromine, to react with a compound of general formula **1F** :

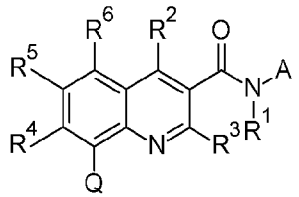
$R^{2\#}H$

1F,

in which $R^{2\#}$ is selected from the group consisting of methyl 2,2-dimethoxycyclobutane-1-carboxylate, methyl 3,3-dimethoxycyclobutane-1-carboxylate, methyl 2,2-bis(methylthio)cyclobutane-1-carboxylate, methyl 3,3-bis(methylthio)cyclobutane-1-carboxylate, ethyl thietane-3-carboxylate, ethyl thietane-2-carboxylate, ethyl oxetane-3-carboxylate, ethyl oxetane-2-carboxylate,
methyl 2-fluorocyclobutane-1-carboxylate, methyl 3-fluorocyclobutane-1-carboxylate, methyl 2,2-difluorocyclobutane-1-carboxylate, methyl 3,3-difluorocyclobutane-1-carboxylate,
methyl tetrahydrofuran-2-carboxylate, methyl tetrahydrofuran-3-carboxylate, methyl furan-3-carboxylate, methyl furan-2-carboxylate,
methyl tetrahydrothiophen-3-carboxylate, methyl tetrahydrothiophen-2-carboxylate, methyl thiophen-3-carboxylate, methyl thiophen-2-carboxylate, methyl 1-methylpyrrolidine-2-carboxylate, methyl 1-methylpyrrolidine-3-carboxylate, methyl 5-oxopyrrolidine-3-carboxylate, methyl 2-oxopyrrolidine-3-carboxylate, methyl 5-oxopyrrolidine-2-carboxylate, methyl tetrahydropyran-4-carboxylate,

followed by a saponification reaction in the presence of aqueous alkali metal hydroxide and optionally an oxidation step,

thereby giving a compound of general formula (I) :

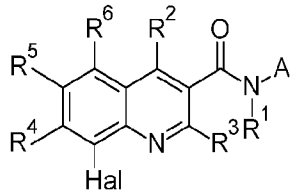


(I),

in which A, R^1, R^3, R^4, R^5, R^6, and Q are as defined *supra* and R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, furan-3-yl, furan-2-yl, tetrahydrothiophen-3-yl, tetrahydrothiophen-2-yl, thiophen-3-yl, thiophen-2-yl, 1-methylpyrrolidin-2-yl, 1-methylpyrrolidin-3-yl, 5-oxopyrrolidin-3-yl, 2-oxopyrrolidin-3-yl, 5-oxopyrrolidin-2-yl, and tetrahydropyran-4-yl.

then optionally converting said compound into solvates, salts and/or solvates of such salts using the corresponding (i) solvents and/or (ii) bases or acids.

In accordance with an alternative embodiment of the second aspect, the present invention covers methods of preparing compounds of general formula (I) as defined *supra*, said methods comprising the step of allowing an intermediate compound of general formula **1T**:



1T,

in which A, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for the compound of general formula (I) as defined *supra*, and in which Hal is halogen, particularly chlorine, bromine or iodine,

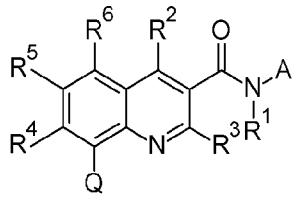
to react with a compound of general formula **1H** :

$$Q\text{-}B(OR)_2$$

1H,

in which Q is 2,3,5-trifluorophenyl, and each R may be individually H or Me or both R are pinacolate,

thereby giving a compound of general formula (I) :

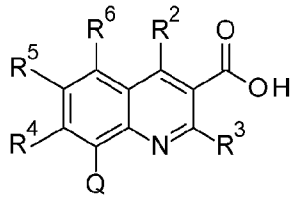


(I),

in which A, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined *supra* and Q is 2,3,5-trifluorophenyl,

then optionally converting said compound into solvates, salts and/or solvates of such salts using the corresponding (i) solvents and/or (ii) bases or acids.

In accordance with an alternative embodiment of the second aspect, the present invention covers methods of preparing compounds of general formula (I) as defined *supra*, said methods comprising the step of allowing an intermediate compound of general formula **1W**:



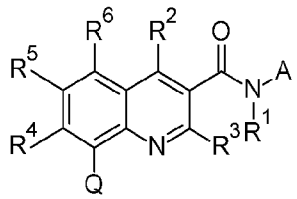
1W,

in which Q, R^2, R^3, R^4, R^5 and R^6 are as defined for the compound of general formula (I) as defined *supra*, to react with a compound of general formula **1M**:

1M,

in which R^1 and A are as defined for the compound of general formula (I) as defined *supra*,

thereby giving a compound of general formula (I):



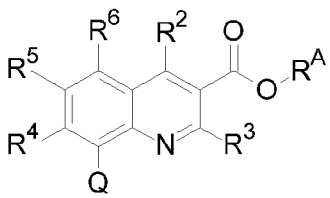
(I),

in which A, R^1, R^2, R^3, R^4, R^5, R^6, and Q are as defined *supra*,

then optionally converting said compound into solvates, salts and/or solvates of such salts using the corresponding (i) solvents and/or (ii) bases or acids.

In accordance with a third aspect, the present invention covers intermediate compounds which are useful for the preparation of the compounds of general formula (I), *supra*.

Particularly, the inventions covers the intermediate compounds of general formula (II) :



(II),

in which

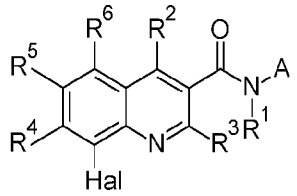
R^2 is –OH, Cl, Br or as defined for the compound of general formula (I) *supra,*

R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) *supra*, and

R^A is H or C_1-C_4-alkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

According to a further embodiment the invention covers compounds of formula (1T)

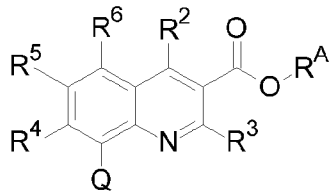


1T,

in which A, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for the compound of general formula (I) as defined *supra*, and in which Hal is halogen, particularly chlorine, bromine or iodine, more particularly bromine,

In accordance with a fourth aspect, the present invention covers the use of said intermediate compounds for the preparation of a compound of general formula (I) as defined *supra*.

Particularly, the inventions covers the use of intermediate compounds of general formula (II) :



(II),

in which

R^2 is –OH, Cl, Br or as defined for the compound of general formula (I) *supra,*

R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) *supra*, and

R^A is H or C_1-C_4-alkyl,

for the preparation of a compound of general formula (I) as defined *supra*.

According to a further embodiment the invention covers the use of compounds of formula (1T) as defined *supra* for the preparation of a compound of general formula (I) as defined *supra.*

The present invention covers the intermediate compounds which are disclosed in the Example Section of this text, *infra*.

The compounds of general formula (I) of the present invention can be converted to any salt, preferably pharmaceutically acceptable salts, as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of general formula (I) of the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

The compounds of the present invention have been found to possess a high chemical stability.

Compounds of general formula (I) of the present invention demonstrate a valuable pharmacological spectrum of action, which could not have been predicted. Compounds of the present invention have surprisingly been found to effectively interact with Slo-1 and it is possible therefore that said compounds be used for the treatment or prevention of diseases, preferably helminthic infections, particulary of gastro-intestinal and extra-intestinal helminth infections, more particulary of gastro-intestinal and extra-intestinal infections with nematodes in humans and animals.

Compounds of the present invention can be utilized to control, treat and/or prevent helminth infections, in particular gastro-intestinal and extra-intestinal helminth infections. This method comprises administering to a mammal in need thereof an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; which is effective to treat the disorder.

In an alternative aspect, this method comprises administering to birds, namely cage birds or in particular poultry, in need thereof an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; which is effective to treat the disorder.

Specifically in the field of veterinary medicine, compounds of the the present invention are suitable, with favourable toxicity in warm blooded animals, for controlling parasites, in particular helminths, which occur in animal breeding and animal husbandry in livestock, breeding, zoo, laboratory, experimental and domestic animals. They are active against all or specific stages of development of the parasites, in particular of the helminths.

Agricultural livestock include, for example, mammals, such as, sheep, goats, horses, donkeys, camels, buffaloes, rabbits, reindeers, fallow deers, and in particular cattle and pigs; or poultry, such as turkeys, ducks, geese, and in particular chickens; or fish or crustaceans, e.g. in aquaculture.

Domestic animals include, for example, mammals, such as hamsters, guinea pigs, rats, mice, chinchillas, ferrets or in particular dogs, cats; cage birds; reptiles; amphibians or aquarium fish.

The present invention also provides methods of treating helminth infections, particularly gastro-intestinal and extra-intestinal helminth infections, more particularly gastro-intestinal and extra-intestinal infections with nematodes.

These disorders have been well characterized in animals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as used in the present text is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of a disease or disorder, such as a nematode infection. In particular, and particularly in the animal health or veterinary field, the term "treating" or "treatment" includes prophylactic, metaphylactic or therapeutical treatment

Helminths pathogenic for humans or animals include, for example, acanthocephala, nematodes, pentastoma and platyhelmintha (e.g. monogenea, cestodes and trematodes).

Exemplary helminths include, without any limitation:

Monogenea: e.g.: Dactylogyrus spp., Gyrodactylus spp., Microbothrium spp., Polystoma spp., Troglocephalus spp.

Cestodes: from the order of the Pseudophyllidea, for example: Bothridium spp., Diphyllobothrium spp., Diplogonoporus spp., Ichthyobothrium spp., Ligula spp., Schistocephalus spp., Spirometra spp.

from the order of the Cyclophyllida, for example: Andyra spp., Anoplocephala spp., Avitellina spp., Bertiella spp., Cittotaenia spp., Davainea spp., Diorchis spp., Diplopylidium spp., Dipylidium spp., Echinococcus spp., Echinocotyle spp., Echinolepis spp., Hydatigera spp., Hymenolepis spp., Joyeuxiella spp., Mesocestoides spp., Moniezia spp., Paranoplocephala spp., Raillietina spp., Stilesia spp., Taenia spp., Thysaniezia spp., Thysanosoma spp.

Trematodes: from the class of the Digenea, for example: Austrobilharzia spp., Brachylaima spp., Calicophoron spp., Catatropis spp., Clonorchis spp. Collyriclum spp., Cotylophoron spp., Cyclocoelum spp., Dicrocoelium spp., Diplostomum spp., Echinochasmus spp., Echinoparyphium spp., Echinostoma spp., Eurytrema spp., Fasciola spp., Fasciolides spp., Fasciolopsis spp., Fischoederius spp., Gastrothylacus spp., Gigantobilharzia spp., Gigantocotyle spp., Heterophyes spp., Hypoderaeum spp., Leucochloridium spp., Metagonimus spp., Metorchis spp., Nanophyetus spp., Notocotylus spp., Opisthorchis spp., Ornithobilharzia spp., Paragonimus spp., Paramphistomum spp., Plagiorchis spp., Posthodiplostomum spp., Prosthogonimus spp., Schistosoma spp., Trichobilharzia spp., Troglotrema spp., Typhlocoelum spp.

Nematodes: from the order of the Trichinellida, for example: Capillaria spp., Eucoleus spp., Paracapillaria spp., Trichinella spp., Trichomosoides spp., Trichuris spp.

from the order of the Tylenchida, for example: Micronema spp., Parastrongyloides spp., Strongyloides spp.

from the order of the Rhabditina, for example: Aelurostrongylus spp., Amidostomum spp., Ancylostoma spp., Angiostrongylus spp., Bronchonema spp., Bunostomum spp., Chabertia spp., Cooperia spp., Cooperioides spp., Crenosoma spp., Cyathostomum spp., Cyclococercus spp., Cyclodontostomum spp., Cylicocyclus spp., Cylicostephanus spp., Cylindropharynx spp., Cystocaulus spp., Dictyocaulus spp.,

Elaphostrongylus spp., Filaroides spp., Globocephalus spp., Graphidium spp., Gyalocephalus spp., Haemonchus spp., Heligmosomoides spp., Hyostrongylus spp., Marshallagia spp., Metastrongylus spp., Muellerius spp., Necator spp., Nematodirus spp., Neostrongylus spp., Nippostrongylus spp., Obeliscoides spp., Oesophagodontus spp., Oesophagostomum spp., Ollulanus spp.; Ornithostrongylus spp., Oslerus spp., Ostertagia spp., Paracooperia spp., Paracrenosoma spp., Parafilaroides spp., Parelaphostrongylus spp., Pneumocaulus spp., Pneumostrongylus spp., Poteriostomum spp., Protostrongylus spp., Spicocaulus spp., Stephanurus spp., Strongylus spp., Syngamus spp., Teladorsagia spp., Trichonema spp., Trichostrongylus spp., Triodontophorus spp., Troglostrongylus spp., Uncinaria spp.

from the order of the Spirurida, for example: Acanthocheilonema spp., Anisakis spp., Ascaridia spp.; Ascaris spp., Ascarops spp., Aspiculuris spp., Baylisascaris spp., Brugia spp., Cercopithifilaria spp., Crassicauda spp., Dipetalonema spp., Dirofilaria spp., Dracunculus spp.; Draschia spp., Enterobius spp., Filaria spp., Gnathostoma spp., Gongylonema spp., Habronema spp., Heterakis spp.; Litomosoides spp., Loa spp., Onchocerca spp., Oxyuris spp., Parabronema spp., Parafilaria spp., Parascaris spp., Passalurus spp., Physaloptera spp., Probstmayria spp., Pseudofilaria spp., Setaria spp., Skjrabinema spp., Spirocerca spp., Stephanofilaria spp., Strongyluris spp., Syphacia spp., Thelazia spp., Toxascaris spp., Toxocara spp., Wuchereria spp.

Acantocephala: from the order of the Oligacanthorhynchida, for example: Macracanthorhynchus spp., Prosthenorchis spp.; from the order of the Moniliformida, for example: Moniliformis spp.

from the order of the Polymorphida, for example: Filicollis spp.; from the order of the Echinorhynchida, for example: Acanthocephalus spp., Echinorhynchus spp., Leptorhynchoides spp.

Pentastoma: from the order of the Porocephalida, for example: Linguatula spp.

The compounds of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of helminth infections, particularly gastro-intestinal and extra-intestinal helminth infections, more particularly gastro-intestinal and extra-intestinal infections with nematodes.

By using the compounds of the present invention to control animal parasites, in particular helminths, it is intended to reduce or prevent illness, cases of deaths and performance reductions (in the case of meat, milk, wool, hides, eggs, honey and the like), so that more economical and simpler animal keeping is made possible and better animal well-being is achievable.

The term “control” or "controlling", as used herein with regard to the animal health field, means that the compounds of the present invention are effective in reducing the incidence of the respective parasite in an animal infected with such parasites to innocuous levels. More specifically, "controlling", as used herein, means that the compounds of the present invention are effective in killing the respective parasite, inhibiting its growth, or inhibiting its proliferation.

In accordance with a further aspect, the present invention covers compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for use in the treatment or prevention of

diseases, in particular of helminth infections, particulary of gastro-intestinal and extra-intestinal helminth infections, more particulary of gastro-intestinal and extra-intestinal infections with nematodes.

The pharmaceutical activity of the compounds according to the invention can be explained by their interaction with the Slo-1 ion channel.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the treatment or prevention of diseases, in particular of helminth infections, particulary of gastro-intestinal and extra-intestinal helminth infections, more particulary of gastro-intestinal and extra-intestinal infections with nematodes.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, in a method of treatment or prevention of diseases, in particular of helminth infections, particulary of gastro-intestinal and extra-intestinal helminth infections, more particulary of gastro-intestinal and extra-intestinal infections with nematodes.

In accordance with a further aspect, the present invention covers use of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the preparation of a pharmaceutical composition, preferably a medicament, for the prevention or treatment of diseases, in particular of helminth infections, particulary of gastro-intestinal and extra-intestinal helminth infections, more particulary of gastro-intestinal and extra-intestinal infections with nematodes.

In accordance with a further aspect, the present invention covers a method of treatment or prevention of diseases, in particular of helminth infections, particularly of gastro-intestinal and extra-intestinal helminth infections, more particulary of gastro-intestinal and extra-intestinal infections with nematodes, using an effective amount of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

In accordance with a further aspect, the present invention covers compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for use as an antiendoparasitical agent.

In accordance with a further aspect, the present invention covers compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for use as a anthelmintic agent, in particular for use as a nematicidal agent, a platyhelminthicidal agent, an acanthocephalicidal agent, or a pentastomicidal agent.

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular a veterinary formulation, comprising a compound of general formula (I), as described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, a salt thereof, particularly a pharmaceutically acceptable salt, or a mixture of same, and one or more excipients), in particular one or more pharmaceutically acceptable excipient(s). Conventional procedures for preparing such pharmaceutical compositions in appropriate dosage forms can be utilized.

In accordance with a further aspect, the present invention covers a method for preparing a pharmaceutical composition, in particular a veterinary formulation, comprising the step of mixing a compound of general formula (I), as described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, a salt thereof, particularly a pharmaceutically acceptable salt, or a mixture of same, with one or more excipients), in particular one or more pharmaceutically acceptable excipient(s).

In accordance with a further aspect, the present invention covers a method of treatment or prevention of diseases, in particular of helminth infections, particularly of gastro-intestinal and extra-intestinal helminth infections, more particulary of gastro-intestinal and extra-intestinal infections with nematodes, using a pharmaceutical composition, in particular a veterinary formulation, comprising an effective amount of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

The present invention furthermore covers pharmaceutical compositions, in particular veterinary formulations, which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipients, and to their use for the above mentioned purposes.

It is possible for the compounds according to the invention to have systemic and/or local activity. For this purpose, they can be administered in a suitable manner, such as, for example, via the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, vaginal, dermal, transdermal, conjunctival, otic route or as an implant or stent. Such administration can be carried out prophylactically, methaphylactically or therapeutically.

For these administration routes, it is possible for the compounds according to the invention to be administered in suitable administration forms.

For oral administration, it is possible to formulate the compounds according to the invention to dosage forms known in the art that deliver the compounds of the invention rapidly and/or in a modified manner, such as, for example, tablets (uncoated or coated tablets, for example with enteric or controlled release coatings that dissolve with a delay or are insoluble), orally-disintegrating tablets, films/wafers, films/lyophylisates, capsules (for example hard or soft gelatine capsules), sugar-coated tablets, granules, pellets, chewables (for example soft chewables), powders, emulsions, suspensions, aerosols or solutions. It is possible to incorporate the compounds according to the invention in crystalline and/or amorphised and/or dissolved form into said dosage forms.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms which are suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophylisates or sterile powders.

Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia powder inhalers, nebulizers], nasal drops, nasal solutions, nasal sprays; tablets/films/wafers/capsules for lingual, sublingual or buccal administration; suppositories; eye drops, eye ointments, eye baths, ocular inserts, ear drops, ear sprays, ear powders, ear-rinses, ear tampons; vaginal capsules, aqueous suspensions (lotions, mixturae agitandae), lipophilic suspensions, emulsions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, spot-ons, dusting powders, implants or stents.

The compounds according to the invention can be incorporated into the stated administration forms. This can be effected in a manner known per se by mixing with pharmaceutically suitable excipients. Pharmaceutically suitable excipients include, inter alia,

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- solvents (for example water, ethanol, isopropanol, glycerol, propylene glycol, medium chain-length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example, Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),
- buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),
- isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas),
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose,

carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),

- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross- linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®)),
- flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),
- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropylmethylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),
- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to a pharmaceutical composition which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipient(s), and to their use according to the present invention.

In accordance with another aspect, the present invention covers pharmaceutical combinations, in particular medicaments, comprising at least one compound of general formula (I) of the present invention and at least one or more further active ingredients, in particular for the treatment and/or prevention of an endo- and/or ectoparasiticidal infection.

The term "endoparasite" in the present invention is used as known to persons skilled in the art, and refers in particular to helminths. The term "ectoparasite" in the present invention is used as known to persons skilled in the art, and refers in particular to arthropods, particularly insects or acarids.

Particularly, the present invention covers a pharmaceutical combination, in particular a veterinary combination, which comprises:

- one or more first active ingredients, in particular compounds of general formula (I) as defined *supra,* and
- one or more further active ingredients, in particular one or more endo- and/or ectoparasiticides.

The term "combination" in the present invention is used as known to persons skilled in the art, it being possible for said combination to be a fixed combination, a non-fixed combination or a kit-of-parts.

A "fixed combination" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein, for example, a first active ingredient, such as one or more compounds of general formula (I) of the present invention, and a further active ingredient are present together in one unit dosage or in one single entity. One example of a "fixed combination" is a pharmaceutical composition wherein a first active ingredient and a further active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein a first active ingredient and a further active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein a first active ingredient and a further active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the first active ingredient and the further active ingredient are present separately. It is possible for the components of the non-fixed combination or kit-of-parts to be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also covers such pharmaceutical combinations. For example, the compounds of the present invention can be combined with known ectoparasiticides and/or endoparasiticides.

The other or further active ingredients specified herein by their common names are known and described, for example, in the Pesticide Manual ("The Pesticide Manual" 16th Ed., British Crop Protection Council 2012) or can be searched in the internet (e.g. http://www.alanwood.net/pesticides). The classification is based on the current IRAC Mode of Action Classification Scheme at the time of filing of this patent application.

Examples of ectoparasiticides and/or endoparasiticides are insecticides, acaricides and nematicides, and include in particular:

(1) Acetylcholinesterase (AChE) inhibitors, such as, for example, carbamates, for example alanycarb, aldicarb, bendiocarb, benfuracarb, butocarboxim, butoxycarboxim, carbaryl, carbofuran, carbosulfan, ethiofencarb, fenobucarb, formetanate, furathiocarb, isoprocarb, methiocarb, methomyl, metolcarb, oxamyl, pirimicarb, propoxur, thiodicarb, thiofanox, triazamate, trimethacarb, XMC and xylylcarb; or organophosphates, for example acephate, azamethiphos, azinphos-ethyl, azinphos-methyl, cadusafos, chlorethoxyfos, chlorfenvinphos, chlormephos, chlorpyrifos-methyl, coumaphos, cyanophos, demeton-S-methyl, diazinon, dichlorvos/DDVP, dicrotophos, dimethoate, dimethylvinphos, disulfoton, EPN, ethion, ethoprophos, famphur, fenamiphos, fenitrothion, fenthion, fosthiazate, heptenophos, imicyafos, isofenphos, isopropyl O-(methoxyaminothiophosphoryl) salicylate, isoxathion, malathion, mecarbam, methamidophos, methidathion, mevinphos, monocrotophos, naled, omethoate, oxydemeton-methyl, parathion-methyl, phenthoate, phorate, phosalone, phosmet, phosphamidon, phoxim, pirimiphos-methyl, profenofos, propetamphos, prothiofos, pyraclofos, pyridaphenthion, quinalphos, sulfotep, tebupirimfos, temephos, terbufos, tetrachlorvinphos, thiometon, triazophos, triclorfon and vamidothion.

(2) GABA-gated chloride channel blockers, such as, for example, cyclodiene-organochlorines, for example chlordane and endosulfan or phenylpyrazoles (fiproles), for example ethiprole and fipronil.

(3) Sodium channel modulators, such as, for example, pyrethroids, e.g. acrinathrin, allethrin, d-cis-trans allethrin, d-trans allethrin, bifenthrin, bioallethrin, bioallethrin s-cyclopentenyl isomer, bioresmethrin, cycloprothrin, cyfluthrin, beta-cyfluthrin, cyhalothrin, lambda-cyhalothrin, gamma-cyhalothrin, cypermethrin, alpha-cypermethrin, beta-cypermethrin, theta-cypermethrin, zeta-cypermethrin, cyphenothrin [(1R)-trans-isomer], deltamethrin, empenthrin [(EZ)-(1R)-isomer], esfenvalerate, etofenprox, fenpropathrin, fenvalerate, flucythrinate, flumethrin, tau-fluvalinate, halfenprox, imiprothrin, kadethrin, momfluorothrin, permethrin, phenothrin [(1R)-trans-isomer], prallethrin, pyrethrins (pyrethrum), resmethrin, silafluofen, tefluthrin, tetramethrin, tetramethrin [(1R)- isomer)], tralomethrin and transfluthrin or DDT or methoxychlor.

(4) Nicotinic acetylcholine receptor (nAChR) competitive modulators, such as, for example, neonicotinoids, e.g. acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid and thiamethoxam or nicotine or sulfoxaflor or flupyradifurone.

(5) Nicotinic acetylcholine receptor (nAChR) allosteric modulators, such as, for example, spinosyns, e.g. spinetoram and spinosad.

(6) Glutamate-gated chloride channel (GluCl) allosteric modulators, such as, for example, avermectins/milbemycins, for example abamectin, emamectin benzoate, lepimectin and milbemectin.

(7) Juvenile hormone mimics, such as, for example, juvenile hormone analogues, e.g. hydroprene, kinoprene and methoprene or fenoxycarb or pyriproxyfen.

(9) Modulators of Chordotonal Organs, such as, for example pymetrozine or flonicamid.

(10) Mite growth inhibitors, such as, for example clofentezine, hexythiazox and diflovidazin or etoxazole.

(12) Inhibitors of mitochondrial ATP synthase, such as, ATP disruptors such as, for example, diafenthiuron or organotin compounds, for example azocyclotin, cyhexatin and fenbutatin oxide or propargite or tetradifon.

(13) Uncouplers of oxidative phosphorylation via disruption of the proton gradient, such as, for example, chlorfenapyr, DNOC and sulfluramid.

(14) Nicotinic acetylcholine receptor channel blockers, such as, for example, bensultap, cartap hydrochloride, thiocylam, and thiosultap-sodium.

(15) Inhibitors of chitin biosynthesis, type 0, such as, for example, bistrifluron, chlorfluazuron, diflubenzuron, flucycloxuron, flufenoxuron, hexaflumuron, lufenuron, novaluron, noviflumuron, teflubenzuron and triflumuron.

(16) Inhibitors of chitin biosynthesis, type 1, for example buprofezin.

(17) Moulting disruptor (in particular for Diptera, i.e. dipterans), such as, for example, cyromazine.

(18) Ecdysone receptor agonists, such as, for example, chromafenozide, halofenozide, methoxyfenozide and tebufenozide.

(19) Octopamine receptor agonists, such as, for example, amitraz.

(20) Mitochondrial complex III electron transport inhibitors, such as, for example, hydramethylnone or acequinocyl or fluacrypyrim.

(21) Mitochondrial complex I electron transport inhibitors, such as, for example from the group of the METI acaricides, e.g. fenazaquin, fenpyroximate, pyrimidifen, pyridaben, tebufenpyrad and tolfenpyrad or rotenone (Derris).

(22) Voltage-dependent sodium channel blockers, such as, for example indoxacarb or metaflumizone.

(23) Inhibitors of acetyl CoA carboxylase, such as, for example, tetronic and tetramic acid derivatives, e.g. spirodiclofen, spiromesifen and spirotetramat.

(25) Mitochondrial complex II electron transport inhibitors, such as, for example, *beta*-ketonitrile derivatives, e.g. cyenopyrafen and cyflumetofen and carboxanilides, such as, for example, pyflubumide.

(28) Ryanodine receptor modulators, such as, for example, diamides, e.g. chlorantraniliprole, cyantraniliprole and flubendiamide,

further active ingredients such as, for example, Afidopyropen, Afoxolaner, Azadirachtin, Benclothiaz, Benzoximate, Bifenazate, Broflanilide, Bromopropylate, Chinomethionat, Chloroprallethrin, Cryolite, Cyclaniliprole, Cycloxaprid, Cyhalodiamide, Dicloromezotiaz, Dicofol, epsilon-Metofluthrin, epsilon-Momfluthrin, Flometoquin, Fluazaindolizine, Fluensulfone, Flufenerim, Flufenoxystrobin, Flufiprole, Fluhexafon, Fluopyram, Fluralaner, Fluxametamide, Fufenozide, Guadipyr, Heptafluthrin, Imidaclothiz,

Iprodione, kappa-Bifenthrin, kappa-Tefluthrin, Lotilaner, Meperfluthrin, Paichongding, Pyridalyl, Pyrifluquinazon, Pyriminostrobin, Spirobudiclofen, Tetramethylfluthrin, Tetraniliprole, Tetrachlorantraniliprole, Tioxazafen, Thiofluoximate, Triflumezopyrim and iodomethane; furthermore preparations based on *Bacillus firmus* (I-1582, BioNeem, Votivo), and also the following compounds: 1-{2-fluoro-4-methyl-5-[(2,2,2-trifluoroethyl)sulphinyl]phenyl}-3-(trifluoromethyl)-1H-1,2,4-triazole-5-amine (known from WO2006/043635) (CAS 885026-50-6), {1'-[(2E)-3-(4-chlorophenyl)prop-2-en-1-yl]-5-fluorospiro[indol-3,4'-piperidin]-1(2H)-yl}(2-chloropyridin-4-yl)methanone (known from WO2003/106457) (CAS 637360-23-7), 2-chloro-N-[2-{1-[(2E)-3-(4-chlorophenyl)prop-2-en-1-yl]piperidin-4-yl}-4-(trifluoromethyl)phenyl]isonicotinamide (known from WO2006/003494) (CAS 872999-66-1), 3-(4-chloro-2,6-dimethylphenyl)-4-hydroxy-8-methoxy-1,8-diazaspiro[4.5]dec-3-en-2-one (known from WO 2010052161) (CAS 1225292-17-0), 3-(4-chloro-2,6-dimethylphenyl)-8-methoxy-2-oxo-1,8-diazaspiro[4.5]dec-3-en-4-yl ethyl carbonate (known from EP2647626) (CAS 1440516-42-6) , 4-(but-2-yn-1-yloxy)-6-(3,5-dimethylpiperidin-1-yl)-5-fluoropyrimidine (known from WO2004/099160) (CAS 792914-58-0), PF1364 (known from JP2010/018586) (CAS 1204776-60-2), N-[(2E)-1-[(6-chloropyridin-3-yl)methyl]pyridin-2(1H)-ylidene]-2,2,2-trifluoroacetamide (known from WO2012/029672) (CAS 1363400-41-2), (3*E*)-3-[1-[(6-chloro-3-pyridyl)methyl]-2-pyridylidene]-1,1,1-trifluoro-propan-2-one (known from WO2013/144213) (CAS 1461743-15-6), , *N*-[3-(benzylcarbamoyl)-4-chlorophenyl]-1-methyl-3-(pentafluoroethyl)-4-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (known from WO2010/051926) (CAS 1226889-14-0), 5-bromo-4-chloro-*N*-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide (known from CN103232431) (CAS 1449220-44-3), 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-2-methyl-*N*-(*cis*-1-oxido-3-thietanyl)-benzamide, 4-[5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-2-methyl-*N*-(*trans*-1-oxido-3-thietanyl)-benzamide and 4-[(5*S*)-5-(3,5-dichlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-2-methyl-*N*-(*cis*-1-oxido-3-thietanyl) benzamide (known from WO 2013/050317 A1) (CAS 1332628-83-7), *N*-[3-chloro-1-(3-pyridinyl)-1*H*-pyrazol-4-yl]-*N*-ethyl-3-[(3,3,3-trifluoropropyl)sulfinyl]-propanamide, (+)-*N*-[3-chloro-1-(3-pyridinyl)-1*H*-pyrazol-4-yl]-*N*-ethyl-3-[(3,3,3-trifluoropropyl)sulfinyl]-propanamide and (-)-*N*-[3-chloro-1-(3-pyridinyl)-1*H*-pyrazol-4-yl]-*N*-ethyl-3-[(3,3,3-trifluoropropyl)sulfinyl]-propanamide (known from WO 2013/162715 A2, WO 2013/162716 A2, US 2014/0213448 A1) (CAS 1477923-37-7), 5-[[(2*E*)-3-chloro-2-propen-1-yl]amino]-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1*H*-pyrazole-3-carbonitrile (known from CN 101337937 A) (CAS 1105672-77-2), 3-bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)thioxomethyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide, (Liudaibenjiaxuanan, known from CN 103109816 A) (CAS 1232543-85-9); *N*-[4-chloro-2-[[(1,1-dimethylethyl)amino]carbonyl]-6-methylphenyl]-1-(3-chloro-2-pyridinyl)-3-(fluoromethoxy)-1*H*-Pyrazole-5-carboxamide (known from WO 2012/034403 A1) (CAS 1268277-22-0), *N*-[2-(5-amino-1,3,4-thiadiazol-2-yl)-4-chloro-6-methylphenyl]-3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide (known from WO 2011/085575 A1) (CAS 1233882-22-8), 4-[3-[2,6-dichloro-4-[(3,3-dichloro-2-propen-1-yl)oxy]phenoxy]propoxy]-2-methoxy-6-(trifluoromethyl)-pyrimidine (known from

CN 101337940 A) (CAS 1108184-52-6); (2*E*)- and 2(*Z*)-2-[2-(4-cyanophenyl)-1-[3-(trifluoromethyl) phenyl]ethylidene]-*N*-[4-(difluoromethoxy)phenyl]-hydrazinecarboxamide (known from CN 101715774 A) (CAS 1232543-85-9); 3-(2,2-dichloroethenyl)-2,2-dimethyl-4-(1*H*-benzimidazol-2-yl)phenyl-cyclopropanecarboxylic acid ester (known from CN 103524422 A) (CAS 1542271-46-4); (4a*S*) -7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-[(trifluoromethyl)thio]phenyl]amino]carbonyl]-indeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylic acid methyl ester (known from CN 102391261 A) (CAS 1370358-69-2); 6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-, 1-[*N*-[4-[1-[4-(1,1,2,2,2-pentafluoroethoxy) phenyl]-1*H*-1,2,4-triazol-3-yl]phenyl]carbamate]-α-L-mannopyranose (known from US 2014/0275503 A1) (CAS 1181213-14-8); 8-(2-cyclopropylmethoxy-4-trifluoromethyl-phenoxy)-3-(6-trifluoromethyl-pyridazin-3-yl)-3-aza-bicyclo[3.2.1]octane (CAS 1253850-56-4), (8-*anti*)-8-(2-cyclopropylmethoxy-4-trifluoromethyl-phenoxy)-3-(6-trifluoromethyl-pyridazin-3-yl)-3-aza-bicyclo[3.2.1]octane (CAS 933798-27-7), (8-*syn*)-8-(2-cyclopropylmethoxy-4-trifluoromethyl-phenoxy) -3-(6-trifluoromethyl-pyridazin-3-yl)-3-aza-bicyclo[3.2.1]octane (known from WO 2007040280 A1, WO 2007040282 A1) (CAS 934001-66-8), N-[3-chloro-1-(3-pyridinyl)-1H-pyrazol-4-yl]-N-ethyl-3-[(3,3,3-trifluoropropyl)thio]-propanamide (known from WO 2015/058021 A1, WO 2015/058028 A1) (CAS 1477919-27-9), N-[4-(aminothioxomethyl)-2-methyl-6-[(methylamino)carbonyl]phenyl]-3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide (known from CN 103265527 A) (CAS 1452877-50-7), 5-(1,3-dioxan-2-yl)-4-[[4-(trifluoromethyl)phenyl]methoxy]-pyrimidine (known from WO 2013/115391 A1) (CAS 1449021-97-9), 3-(4-chloro-2,6-dimethylphenyl)-4-hydroxy-8-methoxy-1-methyl-1,8-diazaspiro[4.5]dec-3-en-2-one (known from WO 2010/066780 A1, WO 2011/151146 A1) (CAS 1229023-34-0), 3-(4-chloro-2,6-dimethylphenyl)-8-methoxy-1-methyl-1,8-diazaspiro[4.5]decane-2,4-dione (known from WO 2014/187846 A1) (CAS 1638765-58-8), 3-(4-chloro-2,6-dimethylphenyl)-8-methoxy-1-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-en-4-yl-carbonic acid ethyl ester (known from WO 2010/066780 A1, WO 2011151146 A1) (CAS 1229023-00-0), N-[1-[(6-chloro-3-pyridinyl)methyl]-2(1*H*)-pyridinylidene]-2,2,2-trifluoro-acetamide (known from DE 3639877 A1, WO 2012029672 A1) (CAS 1363400-41-2), [N(*E*)]-N-[1-[(6-chloro-3-pyridinyl)methyl]-2(1H)-pyridinylidene]-2,2,2-trifluoro-acetamide, (known from WO 2016005276 A1) (CAS 1689566-03-7), [N(*Z*)]-N-[1-[(6-chloro-3-pyridinyl)methyl]-2(1H)-pyridinylidene]-2,2,2-trifluoro-acetamide, (CAS 1702305-40-5), 3-*endo*-3-[2-propoxy-4-(trifluoromethyl)phenoxy]-9-[[5-(trifluoromethyl)-2-pyridinyl]oxy]-9-azabicyclo[3.3.1]nonane (known from WO 2011/105506 A1, WO 2016/133011 A1) (CAS 1332838-17-1).

Active ingredients with unknown or non-specific mode of action, e.g., fentrifanil, fenoxacrim, cycloprene, chlorobenzilate, chlordimeform, flubenzimine, dicyclanil, amidoflumet, quinomethionate, triarathene, clothiazoben, tetrasul, potassium oleate, petroleum, metoxadiazone, gossyplure, flutenzin, bromopropylate, cryolite;

Active ingredients from other classes, e.g. butacarb, dimetilan, cloethocarb, phosphocarb, pirimiphos (-ethyl), parathion (-ethyl), methacrifos, isopropyl o-salicylate, trichlorfon, sulprofos, propaphos, sebufos,

pyridathion, prothoate, dichlofenthion, demeton-S-methylsulphone, isazofos, cyanofenphos, dialifos, carbophenothion, autathiofos, aromfenvinfos (-methyl), azinphos (-ethyl), chlorpyrifos (-ethyl), fosmethilan, iodofenphos, dioxabenzofos, formothion, fonofos, flupyrazofos, fensulfothion, etrimfos;

organochlorines, e.g. camphechlor, lindane, heptachlor; or phenylpyrazoles, e.g. acetoprole, pyrafluprole, pyriprole, vaniliprole, sisapronil; or isoxazolines, e.g. sarolaner, afoxolaner, lotilaner, fluralaner;

pyrethroids, e.g. (cis-, trans-), metofluthrin, profluthrin, flufenprox, flubrocythrinate, fubfenprox, fenfluthrin, protrifenbute, pyresmethrin, RU15525, terallethrin, cis-resmethrin, heptafluthrin, , bioethanomethrin, biopermethrin, fenpyrithrin, cis-cypermethrin, cis-permethrin, clocythrin, cyhalothrin (lambda-), chlovaporthrin, or halogenated carbonhydrogen compounds (HCHs);

neonicotinoids, e.g. nithiazine;

dicloromezotiaz, triflumezopyrim;

macrocyclic lactones, e.g. nemadectin, ivermectin, latidectin, moxidectin, selamectin, eprinomectin, doramectin, emamectin benzoate; milbemycin oxime;

triprene, epofenonane, diofenolan;

Biologicals, hormones or pheromones, for example natural products, e.g. thuringiensin, codlemone or neem components;

dinitrophenols, e.g. dinocap, dinobuton, binapacryl;

benzoylureas, e.g. fluazuron, penfluron;

amidine derivatives, e.g. chlormebuform, cymiazole, demiditraz;

Bee hive varroa acaricides, for example organic acids, e.g. formic acid, oxalic acid.

Non-limiting examples of insecticides and acaricides of particular interest for use in animal health are and include in particular [i.e. Mehlhorn et al Encyclpaedic Reference of Parasitology 4th edition (ISBN 978-3-662-43978-4)]:

Effectors at arthropod ligand gated chloride channels: chlordane, heptachlor, endoculfan. Dieldrin, bromocyclen, toxaphene, lindane, fipronil, pyriprole, sisapronil, afoxolaner, fluralaner, sarolaner, lotilaner, fluxametamide, broflanilide, avermectin, doramectin, eprinomectin, ivermectin, milbemycin, moxidectin, selamectin;

Modulators of arthropod octopaminergic receptors: amitraz, BTS27271, cymiazole, demiditraz;

Effectors at arthropod voltage-gated sodium channels: DDT, methoxychlor, metaflumizone, indoxacarb, cinerin I, cinerin II, jasmolin I, jasmolin II, pyrethrin I, pyrethrin II, allethrin, alphacypermethrin, bioallethrin, betacyfluthrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, etofenprox, fenvalerate, flucythrinate, flumethrin, halfenprox, permethrin, phenothrin, resmethrin, tau-fluvalinate, tetramethrin;

Effectors at arthropod nicotinic cholinergic synapses (acetylcholine esterase, acetylcholine receptors): bromoprypylate, bendiocarb, carbaryl, methomyl, promacyl, propoxur, azamethiphos, chlorfenvinphos, chlorpyrifos, coumaphos, cythioate, diazinon, diclorvos, dicrotophos, dimethoate, ethion, famphur, fenitrothion, fenthion, heptenophos, malathion, naled, phosmet, phoxim, phtalofos, propetamphos, temephos, tetrachlorvinphos, trichlorfon, imidacloprid, nitenpyram, dinotefuran, spinosad, spinetoram;

Effectors on arthropod development processes: cyromazine, dicyclanil, diflubenzuron, fluazuron, lufenuron, triflumuron, fenoxycarb, hydroprene, methoprene, pyriproxyfen, fenoxycarb, hydroprene, S-methoprene, pyriproxyfen.

Exemplary active ingredients from the group of endoparasiticides, as a further or other active ingredient in the present invention, include, without limitation, anthelmintically active compounds and antiprotozoal active compounds.

Anthelmintically active compounds, including, without limitation, the following nematicidally, trematicidally and/or cestocidally active compounds:

from the class of macrocyclic lactones, for example: eprinomectin, abamectin, nemadectin, moxidectin, doramectin, selamectin, lepimectin, latidectin, milbemectin, ivermectin, emamectin, milbemycin;

from the class of benzimidazoles and probenzimidazoles, for example: oxibendazole, mebendazole, triclabendazole, thiophanate, parbendazole, oxfendazole, netobimin, fenbendazole, febantel, thiabendazole, cyclobendazole, cambendazole, albendazole-sulphoxide, albendazole, flubendazole;

from the class of depsipeptides, preferably cyclic depsipetides, in particular 24-membered cyclic depsipeptides, for example: emodepside, PF1022A;

from the class of tetrahydropyrimidines, for example: morantel, pyrantel, oxantel;

from the class of imidazothiazoles, for example: butamisole, levamisole, tetramisole;

from the class of aminophenylamidines, for example: amidantel, deacylated amidantel (dAMD), tribendimidine;

from the class of aminoacetonitriles, for example: monepantel;

from the class of paraherquamides, for example: paraherquamide, derquantel;

from the class of salicylanilides, for example: tribromsalan, bromoxanide, brotianide, clioxanide, closantel, niclosamide, oxyclozanide, rafoxanide;

from the class of substituted phenols, for example: nitroxynil, bithionol, disophenol, hexachlorophene, niclofolan, meniclopholan;

from the class of organophosphates, for example: trichlorfon, naphthalofos, dichlorvos/DDVP, crufomate, coumaphos, haloxon;

from the class of piperazinones / quinolines, for example: praziquantel, epsiprantel;

from the class of piperazines, for example: piperazine, hydroxyzine;

from the class of tetracyclines, for example: tetracyclin, chlorotetracycline, doxycyclin, oxytetracyclin, rolitetracyclin;

from diverse other classes, for example: bunamidine, niridazole, resorantel, omphalotin, oltipraz, nitroscanate, nitroxynile, oxamniquine, mirasan, miracil, lucanthone, hycanthone, hetolin, emetine, diethylcarbamazine, dichlorophen, diamfenetide, clonazepam, bephenium, amoscanate, clorsulon.

Antiprotozoal active ingredients in the present invention, including, without limitation, the following active ingredients:

from the class of triazines, for example: diclazuril, ponazuril, letrazuril, toltrazuril;

from the class of polylether ionophore, for example: monensin, salinomycin, maduramicin, narasin;

from the class of macrocyclic lactones, for example: milbemycin, erythromycin;

from the class of quinolones, for example: enrofloxacin, pradofloxacin;

from the class of quinines, for example: chloroquine;

from the class of pyrimidines, for example: pyrimethamine;

from the class of sulfonamides, for example: sulfaquinoxaline, trimethoprim, sulfaclozin;

from the class of thiamines, for example: amprolium;

from the class of lincosamides, for example: clindamycin;

from the class of carbanilides, for example: imidocarb;

from the class of nitrofuranes, for example: nifurtimox;

from the class of quinazolinone alkaloids, for example: halofuginon;

from diverse other classes, for example: oxamniquin, paromomycin;

from the class of vaccines or antigenes from microorganisms, for example: Babesia canis rossi, Eimeria tenella, Eimeria praecox, Eimeria necatrix, Eimeria mitis, Eimeria maxima, Eimeria brunetti, Eimeria acervulina, Babesia canis vogeli, Leishmania infantum, Babesia canis canis, Dictyocaulus viviparus.

All named other or further active ingredients in the present invention can, if their functional groups enable this, optionally form salts with suitable bases or acids.

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of helminth infections, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in animals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the compounds of the present invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of

these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the subject treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, it is possible for "drug holidays", in which a subject is not dosed with a drug for a certain period of time, to be beneficial to the overall balance between pharmacological effect and tolerability. Furthermore, it is possible to have long-acting treatments, wherein the subject gets treated once for more than four weeks. It is possible for a unit dosage to contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each subject will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the subject, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

EXPERIMENTAL SECTION

Abbreviations and Acronyms

aq.	aqueous
atm	standard atmosphere
DAD	diode array detector
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ELSD	evaporative light scattering detector

ESI	electrospray ionization
h	hour(s)
LC-MS	liquid chromatography-coupled mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
min	minute(s)
MCPBA	meta-chloroperoxybenzoic acid
MTBE	methyl-t.-butylether
NMR	nuclear magnetic resonance spectrometry
p.	page(s)
R_t	retention time
RT	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

GENERAL EXPERIMENTAL PART

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art.

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

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartridges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or dichloromethane/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

ANALYTICAL AND CHROMATOGRAPHY METHODS

Analytical and preparative liquid chromatography

Analytical (UP)LC-MS was performed by means of different equipments as described below. The masses (m/z) are reported from the positive mode electrospray ionisation unless the negative mode is indicated (ESI-).

M+1 (or M+H) means the molecular ion peak, plus or minus 1 a.m.u. (atomic mass unit) respectively, as observed in mass spectroscopy by electrospray ionization (ESI + or -).

LC-MS, Analytical Method A1:

System MS: Thermo Scientific FT-MS; System UHPLC+: Thermo Scientific UltiMate 3000; Column: Waters, HSST3, 2.1 x 75 mm, C18 1.8 µm; Eluent A: 1 l Water + 0.01% Formic acid; Eluent B: 1 l Acetonitrile + 0.01% Formic acid; Gradient: 0.0 min 10% B → 2.5 min 95% B → 3.5 min 95% B; Oven: 50°C; Flow: 0.90 ml/min; UV-Detection: 210 nm/ Optimum Integration Path 210-300 nm.

LC-MS, Analytical Method B1:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Gemini NX-C18 3.0 µm, 50 x 3.0 mm; eluent A: water + 0.05 vol % ammonium hydrogencarbonate, eluent B: acetonitrile; gradient: assigned for each compound; flow 1.2 mL/min; temperature: 40 °C; PDA scan: 190 - 400 nm.

LC-MS, Analytical Method C1:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Luna Omega 3.0 µm, 50 x 3.0 mm; eluent A: water + 0.09 vol % formic acid, eluent B: acetonitrile +0.1 vol % formic acid; gradient: assigned for each compound; flow 1.5 mL/min; temperature: 40 °C; PDA scan: 190 - 400 nm.

LC-MS, Analytical Method A2:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: CORTECS C18 2.7 µm, 50 x 2.1 mm; eluent A: water + 0.1 vol % formic acid, eluent B: acetonitrile + 0.10 vol %

formic acid; gradient: assigned for each compound; flow 1.2 mL/min; temperature: 40 °C; PDA scan: 190 - 400 nm.

LC-MS, Analytical Method B2:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Infinity Lab Poroshell HPH-C18 2.7 µm, 50 x 3.0 mm; eluent A: water + 0.04 vol % ammonium hydroxide, eluent B: acetonitrile; gradient: assigned for each compound; flow 1.2 mL/min; temperature: 40 °C; PDA scan: 190 - 400 nm.

LC-MS, Analytical Method A3:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Kinetex EVO C18 2.6 µm, 50 x 3.0 mm; eluent A: water + 0.05 vol % ammonium hydrogencarbonate, eluent B: acetonitrile; gradient: assigned for each compound; flow 1.5 mL/min; temperature: 40°C; PDA scan: 190 - 400 nm.

LC-MS, Analytical Method B3:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Kinetex EVO C18 2.6 µm, 50 x 3.0 mm; eluent A: water + 0.03 vol % ammonium hydroxide, eluent B: acetonitrile; gradient: assigned for each compound; flow 1.5 mL/min; temperature: 40°C; PDA scan: 190 - 400 nm.

LC-MS, Analytical Method C3:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Kinetex XB-C18 2.6 µm, 50 x 3.0 mm; eluent A: water + 0.1 vol % Formic acid, eluent B: acetonitrile + 0.1 vol % Formic acid; gradient: assigned for each compound; flow 1.2 mL/min; temperature: 40°C; PDA scan: 190 - 400 nm.

Preparative HPLC

Preparative reverse-phase HPLC was performed using Varian HPLC system. The column used was XBridge Prep C18 OBD Column, 5 um, 19 x 150 mm. The instrument using reverse-phase conditions (acetonitrile / water, containing 0.1% Ammonium hydrogen carbonate or formic acid).

^{1}H-NMR Data

Proton NMR spectra were recorded using a Bruker plus 400 NMR Spectrometer unless stated otherwise. All deuterated solvents such as CD_3CN, $CDCl_3$ or D_6-DMSO contained typically 0.03% to 0.05% v/v tetramethylsilane, in case tetramethylsilane was used as the reference signal (set at d 0.00 for both ^{1}H and ^{13}C).

Chemical shifts (δ) are displayed in parts per million [ppm]; the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad; coupling constants are displayed in Hertz [Hz].

NMR peak lists

NMR peak forms are stated as they appear in the spectra, possible higher order effects have not been considered.

^{1}H-NMR data of selected examples are written in form of ^{1}H-NMR peak lists. To each signal peak are listed the δ-value in ppm and the signal intensity in round brackets. Between the δ-value – signal intensity pairs are semicolons or commas as delimiters.

The peak list of an example has therefore the form:

δ_1 (intensity$_1$); δ_2 (intensity$_2$);……..; δ_i (intensity$_i$);……; δ_n (intensity$_n$) or

δ_1 (intensity$_1$), δ_2 (intensity$_2$),……..; δ_i (intensity$_i$),……, δ_n (intensity$_n$)

Intensity of sharp signals correlates with the height of the signals in a printed example of a NMR spectrum in cm and shows the real relations of signal intensities. From broad signals several peaks or the middle of the signal and their relative intensity in comparison to the most intensive signal in the spectrum can be shown.

For calibrating chemical shift for ^{1}H spectra, we use tetramethylsilane and/or the chemical shift of the solvent used, especially in the case of spectra measured in DMSO. Therefore in NMR peak lists, tetramethylsilane peak can occur but not necessarily.

The ^{1}H-NMR peak lists are similar to classical ^{1}H-NMR prints and contains therefore usually all peaks, which are listed at classical NMR-interpretation.

Additionally they can show like classical ^{1}H-NMR prints signals of solvents, stereoisomers of the target compounds, which are also object of the invention, and/or peaks of impurities.

To show compound signals in the delta-range of solvents and/or water the usual peaks of solvents, for example peaks of DMSO in DMSO-D_6 and the peak of water are shown in our ^{1}H-NMR peak lists and have usually on average a high intensity .

The peaks of stereoisomers of the target compounds and/or peaks of impurities have usually on average a lower intensity than the peaks of target compounds (for example with a purity >90%).

Such stereoisomers and/or impurities can be typical for the specific preparation process. Therefore their peaks can help to recognize the reproduction of our preparation process via “side-products-fingerprints”.

An expert, who calculates the peaks of the target compounds with known methods (MestreC, ACD-simulation, but also with empirically evaluated expectation values) can isolate the peaks of the target compounds as needed optionally using additional intensity filters. This isolation would be similar to relevant peak picking at classical ^{1}H-NMR interpretation.

Further details of NMR-data description with peak lists you find in the publication "Citation of NMR Peaklist Data within Patent Applications" of the Research Disclosure Database Number 564025.

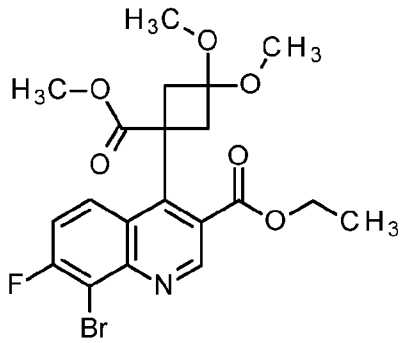
SYNTHETIC PROCEDURES

The general synthesis of the compounds of the formula (I) can be performed according to or in analogy to the schemes described in WO 2018/087036 A1 and WO 2019/215182 A1.

INTERMEDIATES

Intermediate 1

Ethyl 8-bromo-4-[3,3-dimethoxy-1-(methoxycarbonyl)cyclobutyl]-7-fluoroquinoline-3-carboxylate



To a solution of methyl-3,3-dimethoxycyclobutane-carboxylate (8.05 g, 46.2 mmol) in dry THF (60 ml) was added dropwise at -78 to -68°C bis-(trimethylsilyl)-lithiumamide (LiHMDS) (50 ml, 1M solution in THF, 50 mmol) and stirring continued for 5 min at this temperature. Then a solution of ethyl 8-bromo-4-chloro-7-fluoroquinoline-3-carboxylate (for example described in WO 2019/215182 A1 as intermediate 8A, 11.0 g, 33.0 mmol) in THF (40 ml) was added during 7 min keeping a temperature range of -72 to -65°C. A precipitate formed and the suspension was diluted with THF (20 ml) to enable stirring again for 20 min. The mixture was allowed to warm up to 0°C and was then slowly added to a stirred mixture of ice water (800 ml) and acetic acid (5.7 ml, 99 mmol). The mixture was warmed to 50°C and stirred for 40 min. The precipitate formed was filtered off, washed with water and dried in vacuo.

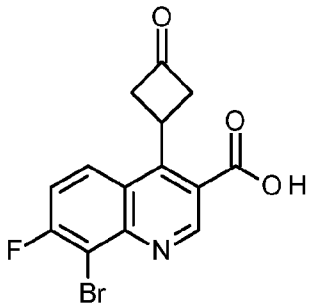
Yield: 14.0 g (90% of theory)

LC-MS (Analytical Method A1): R_t = 2.09 min; MS (ESIpos): m/z = 470 $[M+H]^+$

^{1}H-NMR (600MHz, DMSO-d_6): δ [ppm]= 9.10 (s, 1H), 8.10 (dd, 1H), 7.72 (t, 1H), 4.36 (q, 2H), 3.63 (s, 3H), 3.31 - 3.44 (m, 2H), 3.11 (s, 3H), 2.88 (s, 3H), 2.50 - 2.63 (m, 2H, overlayed by DMSO signal), 1.32 (t, 3H).

Intermediate 2

8-bromo-7-fluoro-4-(3-oxocyclobutyl)quinoline-3-carboxylic acid



A suspension of ethyl 8-bromo-4-[3,3-dimethoxy-1-(methoxycarbonyl)cyclobutyl]-7-fluoroquinoline-3-carboxylate (14.0 g, 29.8 mmol) in 1,2-dimethoxyethan (100 ml) was treated with sodium hydroxide (24 ml, 5.0 M aq. solution, 120 mmol) and stirred at 60°C over night. At the same temperature hydrochloric acid (36 ml, 5.0 M, 180 mmol) was added dropwise and stirring continued for 1,5 h leading to the formation of a precipitate. Water (160 ml) was added at 60°C causing more precipitation, stirring continued for 5 min and the heating removed. The precipitate was filtered off, washed with water and dried in vacuo.

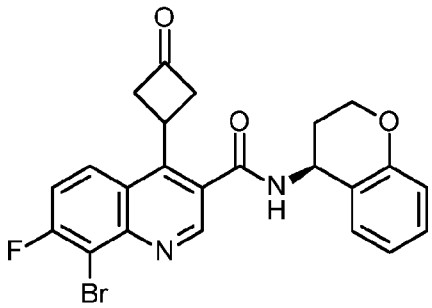
Yield: 8.59 g (100 %, 85 % of theory)

LC-MS (Analytical Method A1): R_t = 1.25 min; MS (ESIneg): m/z = 336 $[M-H]^-$

^{1}H-NMR (600MHz, DMSO-d_6): δ [ppm]= 13.93 (b, 1H), 9.10 (s, 1H), 8.29 - 8.39 (m, 1H), 7.71 - 7.82 (m, 1H), 4.62 - 4.75 (m, 1H), 3.59 - 3.72 (m, 2H), 3.39 - 3.50 (m, 2H).

Intermediate 3

8-bromo-N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(3-oxocyclobutyl)quinoline-3-carboxamide



8-bromo-7-fluoro-4-(3-oxocyclobutyl)quinoline-3-carboxylic acid (2.74 g, 8.10 mmol) in THF (32 ml) was treated with DIPEA (4.2 ml, 24 mmol) and 1-[bis(dimethylamino)methylene]-1H-[1,2,3]triazolo[4,5-b]pyridin-1-ium 3-oxide hexafluorophosphate(1-) (4.62 g, 12.2 mmol) and stirred at RT for 20 min. (4S)-chroman-4-amine hydrochloride (CAS registry number: 1035093-81-2; 1:1; 2.11 g, 11.3 mmol) was added to the solution and stirring continued over night at RT. Warm water (150 ml) was added under stirring and most of the THF evaporated at 50°C under diminished pressure. The mixture was sonicated for 30 min, the precipitate filtered off and washed with water. The solid was taken up in boiling ethanol, water (250 ml) added in the heat under stirring and the mixture allowed to cool to RT. The precipitate was filtered off, washed with water and dried in vacuo.

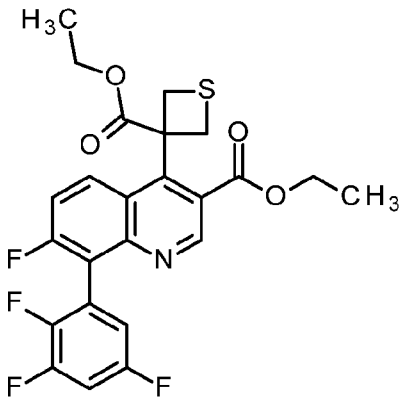
Yield: 2.75 g (67 % of theory, 92 % purity)

LC-MS (Analytical Method A1): R_t = 1.82 min; MS (ESIpos): m/z = 469 $[M+H]^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 9.31 (d, 1H), 8.96 (s, 1H), 8.33 (dd, 1H), 7.76 (dd, 1H), 7.36 (d, 1H), 7.18 (t, 1H), 6.93 (t, 1H), 6.80 (dd, 1H), 5.20 - 5.26 (m, 1H), 4.61 (quin, 1H), 4.19 - 4.32 (m, 2H), 3.49 - 3.68 (m, 4H), 2.17 - 2.25 (m, 1H), 2.01 - 2.09 (m, 1H).

Intermediate 4

Ethyl 4-[3-(ethoxycarbonyl)thietan-3-yl]-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate



Ethyl thietane-3-carboxylate (CAS registry number: 1379028-98-4; 1.07 g, 7.30 mmol) in dry THF (30 ml) was treated at -78°C with LiHMDS (7.8 ml, 1.0 M, 7.8 mmol) and stirred at -75 to -68°C for 4 min. A solution of ethyl 4-chloro-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (for example described in WO 2019/215182 as example IR-2) in THF (10 ml) was added dropwise, stirred for 3 min at this temperature range before removing the cooling bath. When the reaction mixture warmed up to room temperature, it was added slowly to a stirred mixture of acetic acid (0.9 ml, 16 mmol) and water (120 ml). The aqueous mixture was extracted several times with DCM, the combined organic phases dried and evaporated under diminished pressure. The residue was purified by flash chromatography on silica (100 g) with with cyclohexane / ethylacetate (9 to 14 %).

Yield: 2.22 g (86 % of theory)

LC-MS (Analytical Method A1): Rt = 2.46 min; MS (ESIpos): m/z = 494 [M+H]+

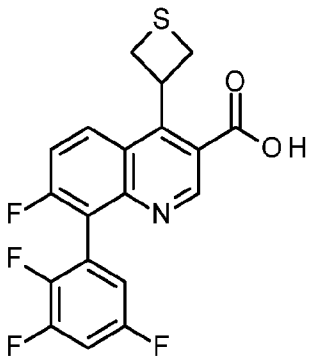
^{1}H NMR (DMSO-d_6) δ: 8.98 (s, 1H), 8.18 (m, 1H), 7.66-7.80 (m, 2H), 7.31-7.37 (m, 1H), 4.21-4.36 (m, 4H), 3.92-4.08 (m, 4H), 1.30 (m, 3H), 1.17 (m, 3H).

Peak list

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.153 (7.45), 1.171 (16.00), 1.189 (7.72), 1.287 (7.01), 1.304 (15.16), 1.322 (7.26), 3.930 (2.25), 3.955 (3.57), 3.969 (1.82), 3.994 (3.26), 4.030 (6.42), 4.055 (3.59), 4.218 (2.39), 4.235 (7.29), 4.253 (7.25), 4.271 (2.31), 4.298 (2.14), 4.316 (6.73), 4.333 (6.65), 4.352 (2.08), 5.753 (2.98), 7.327 (1.20), 7.339 (1.21), 7.349 (1.21), 7.662 (0.44), 7.670 (0.53), 7.678 (0.62), 7.685 (1.01), 7.698 (0.99), 7.706 (1.01), 7.712 (1.01), 7.718 (0.63), 7.726 (0.56), 7.734 (0.52), 7.752 (1.95), 7.775 (3.46), 7.798 (2.15), 8.159 (1.97), 8.174 (2.09), 8.184 (1.99), 8.199 (1.86), 8.984 (9.08).

Intermediate 5

7-fluoro-4-(thietan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid



A suspension of ethyl 4-[3-(ethoxycarbonyl)thietan-3-yl]-7-fluoro-8-(2,3,5-trifluorophenyl)-quinoline-3-carboxylate (1.60 g, 3.24 mmol) in 1,2-dimethoxyethane (100 ml) was treated with sodium hydroxide (2.6 ml, 5.0 M aq. solution, 13 mmol) and stirred 8 h at 70°C and 2 d at RT. At 70°C water (20 ml) was added, the heating removed and hydrochloric acid (3.9 ml, 5.0 M, 19 mmol) added dropwise under stirring. After cooling to RT a precipitate has formed. At 60°C more water (50 ml) was added and the organic solvent removed under dimished pressure leading to the formation of more precipitate. At RT the precipitate was filtered off, washed with water and dried in vacuo.

Yield: 1.10 g (86 % of theory)

LC-MS (Analytical Method A1): Rt = 2.04 min; MS (ESIpos): m/z = 394 [M+H]+

^{1}H NMR (DMSO-d_6) δ: 9.17 (m, 1H), 8.99 (s, 1H), 7.97 (t, 1H), 7.65-7.73 (m, 1H), 7.30-7.35 (m, 1H), 5.81 (m, 1H), 3.69-3.93 (m, 2H), 3.47-3.64 (m, 2H).

Peak list

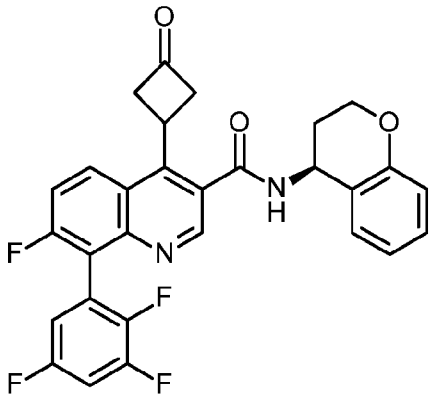
^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.150 (0.41), 1.169 (0.60), 2.368 (0.64), 2.712 (0.69), 2.999 (0.45), 3.236 (10.41), 3.427 (8.73), 3.507 (1.48), 3.540 (7.44), 3.564 (15.58), 3.588 (8.62), 3.778 (4.29),

3.802 (8.63), 3.828 (8.63), 3.851 (3.66), 5.765 (0.88), 5.789 (3.23), 5.813 (4.68), 5.837 (3.09), 5.860 (0.79), 7.312 (2.60), 7.323 (2.72), 7.334 (2.70), 7.654 (0.95), 7.661 (1.11), 7.681 (2.24), 7.689 (2.19), 7.702 (2.31), 7.718 (1.24), 7.726 (1.13), 7.944 (3.96), 7.967 (7.59), 7.989 (4.06), 8.988 (16.00), 9.147 (3.93), 9.161 (4.18), 9.170 (4.19), 9.185 (3.91).

EXAMPLES

Example 1

N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(3-oxocyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



Under argon a thickwalled microwave vessel was charged with 8-bromo-N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(3-oxocyclobutyl)quinoline-3-carboxamide (1.37 g, 2.92 mmol), 2,3,5-trifluorobenzene boronic acid (1.03 g, 5.84 mmol), cesiumfluoride (1.32 g, 8.76 mmol) and (2'-amino[biphenyl]-2-yl)(methanesulfonato-kappaO)palladium - dicyclohexyl(2',6'-dimethoxy[biphenyl]-2-yl)phosphine (1:1), (SPhos Pd G3), (228 mg, 292 µmol). Degassed dioxan/water (5:1), (11 ml) was added, the vessel capped and stirred 5 h at 60°. More 2,3,5-trifluorobenzene boronic acid (0.51 g, 2.92 mmol) and SPhos Pd G3 (114 mg, 146 µmol) was added and stirred for 3 h. The mixture was partitioned between water (80 ml) and ethylacetate (80 ml) and the water phase extracted with ethylacetate. The combined organic phases were dried over sodium sulfate and evaporated under diminished pressure. The residue was purified by flash chromatography on silica (100 g) with with cyclohexane/ethylacetate (23 to 33 %).

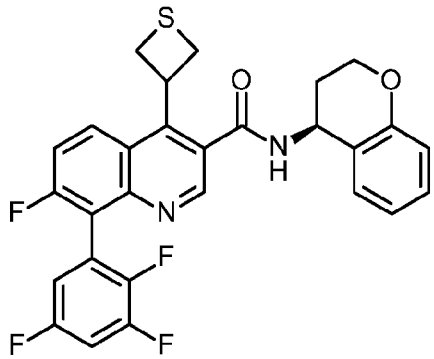
Yield: 820 mg (54 % of theory)

LC-MS (Analytical Method A1): R_t = 2.12 min; MS (ESIpos): m/z = 521 $[M+H]^+$

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm] = 9.29 (d, 1H), 8.83 (d, 1H), 8.46 (dd, 1H), 7.81 (t, 1H), 7.65 - 7.73 (m, 1H), 7.25 - 7.37 (m, 2H), 7.17 (t, 1H), 6.91 (t, 1H), 6.79 (d, 1H), 5.22 (br dd, 1H), 4.64 (q, 1H), 4.17 - 4.31 (m, 2H), 3.50 - 3.72 (m, 4H), 2.15 - 2.23 (m, 1H), 1.98 - 2.08 (m, 1H).

Example 2

N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(thietan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



7-fluoro-4-(thietan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid (950 mg, 2.42 mmol) in THF (4 ml) was treated with DIPEA (1.1 ml, 6.0 mmol) and 1-[bis(dimethylamino)methylene]-1H-[1,2,3]triazolo[4,5-b]pyridin-1-ium 3-oxide hexafluorophosphate(1-) (1.19 g, 3.14 mmol) and stirred at RT for 15 min. (4S)-chroman-4-amine hydrochloride (1:1) (538 mg, 2.90 mmol) was added to the turbid solution and stirring continued over night at RT. The reaction mixture was poured into 50°C warm water, stirred for 30 min at 50°C and the cooled to RT. The precipitate was filtered off, washed with water and dried in vacuo.

Yield: 1.19 g (94% of theory)

This product was 100% pure by LC-MS and used in the next steps.

LC-MS (Analytical Method A1): R_t = 2.33 min; MS (ESIpos): m/z = 525 $[M+H]^+$

For NMR a sample was repurified by preparative HPLC (RP 18, gradient with 0.1% aqueous formic acid and acetonitrile).

^{1}H NMR (DMSO-d_6) δ: 9.22 (d, 1H), 9.00 (m, 1H), 8.81 (d, 1H), 7.91 (m, 1H), 7.65-7.73 (m, 1H), 7.39 (br d, 1H), 7.30 (br m, 1H), 7.17 (m, 1H), 6.93 (m, 1H), 6.79 (d, 1H), 5.48 (m, 1H), 5.26-5.32 (m, 1H), 4.20-4.32 (m, 2H), 3.87 (m, 2H), 3.36-3.57 (m, 2H), 2.53-2.55 (m, 3H), 2.25 (m, 1H), 2.05-2.13 (m, 1H).

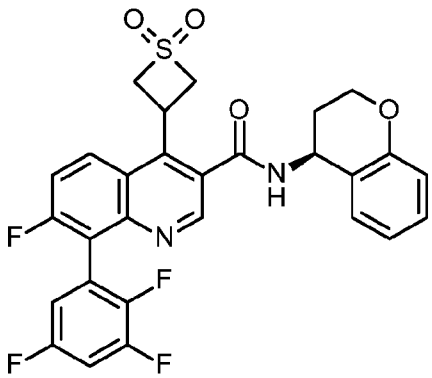
Peak list

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 2.063 (1.06), 2.069 (1.37), 2.075 (2.07), 2.081 (2.25), 2.091 (2.46), 2.103 (3.08), 2.109 (2.67), 2.115 (1.78), 2.121 (1.30), 2.213 (0.74), 2.224 (1.60), 2.231 (2.53), 2.241 (3.06), 2.248 (2.63), 2.251 (2.40), 2.258 (2.65), 2.269 (1.83), 2.276 (1.20), 2.286 (0.56), 3.482 (2.06), 3.496 (2.91), 3.500 (4.87), 3.515 (5.69), 3.519 (6.74), 3.539 (9.53), 3.558 (4.62), 3.844 (3.91), 3.847 (4.08), 3.858 (6.06), 3.863 (8.01), 3.865 (7.93), 3.876 (9.96), 3.881 (4.78), 3.883 (4.29), 3.895 (4.70), 4.209 (1.69), 4.215 (2.00), 4.227 (2.35), 4.232 (5.09), 4.237 (3.41), 4.249 (3.88), 4.254 (3.02),

4.278 (3.12), 4.283 (3.43), 4.290 (3.26), 4.295 (3.03), 4.306 (1.73), 4.312 (1.58), 5.267 (1.22), 5.278 (2.79), 5.284 (3.70), 5.288 (3.05), 5.294 (3.62), 5.299 (2.76), 5.311 (1.15), 5.438 (0.73), 5.446 (0.78), 5.457 (2.68), 5.465 (2.64), 5.476 (3.94), 5.484 (3.73), 5.495 (2.63), 5.503 (2.37), 5.514 (0.70), 5.522 (0.60), 5.756 (0.50), 6.787 (8.30), 6.804 (8.97), 6.910 (2.60), 6.913 (3.40), 6.916 (2.51), 6.925 (5.18), 6.928 (7.08), 6.931 (4.65), 6.940 (3.15), 6.943 (3.96), 6.946 (2.68), 7.157 (4.25), 7.172 (6.38), 7.173 (6.38), 7.188 (3.42), 7.279 (1.66), 7.297 (2.67), 7.302 (2.78), 7.306 (2.19), 7.316 (1.54), 7.320 (1.70), 7.329 (0.83), 7.386 (3.95), 7.391 (3.93), 7.393 (3.92), 7.399 (3.93), 7.407 (3.57), 7.662 (1.21), 7.668 (1.47), 7.675 (1.73), 7.680 (2.69), 7.684 (2.57), 7.690 (2.68), 7.697 (2.64), 7.701 (2.62), 7.707 (1.67), 7.713 (1.47), 7.719 (1.35), 7.891 (5.14), 7.909 (9.32), 7.927 (5.15), 8.808 (15.44), 8.817 (16.00), 8.987 (3.04), 8.994 (3.37), 8.999 (3.61), 9.006 (5.77), 9.013 (3.40), 9.018 (3.29), 9.025 (2.77), 9.217 (5.41), 9.220 (5.54), 9.233 (5.30), 9.236 (5.22).

Example 3

N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-4-(1,1-dioxidothietan-3-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(thietan-3-yl)-8-(2,3,5-trifluorophenyl)-quinoline-3-carboxamide (400 mg, 0.76 mmol) was supended in DCM (9 ml). MCPBA (359 mg, 77 % purity, 1.60 mmol) was added and the solution formed stirred over night at RT. The precipitatet reaction mixture was diluted with DCM (15 ml) and aq. potassiumcarbonate solution (15 ml, 0.5 M) and vigourously stirred. The remaining precipitate was filtered off. More DCM was added to the filtrat and the phases separated. The aqueous phase was extracted two times with DCM and the combined organic phases were dried and evaporated. The residue was combined with the first precipitate and purified by preparative HPLC (RP 18, gradient with 0.1% aqueous formic acid and acetonitrile).

Yield: 380 mg (90 % of theory)

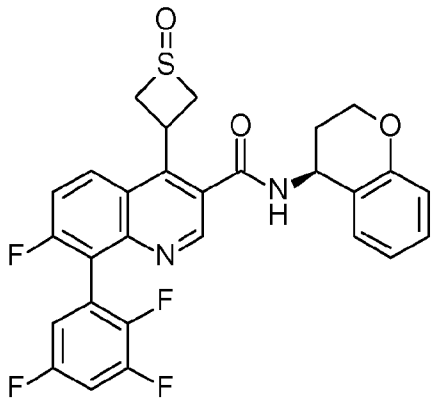
LC-MS (Analytical Method A1): R_t = 2.08 min; MS (ESIpos): m/z = 557 $[M+H]^+$

^{1}H NMR (DMSO-d_6) δ: 9.38 (m, 1H), 8.86 (d, 1H), 8.65 (m, 1H), 7.85 (m, 1H), 7.65-7.71 (m, 1H), 7.43 (d, 1H), 7.27 (m, 1H), 7.18 (m, 1H), 6.92 (m, 1H), 6.80 (d, 1H), 5.23-5.30 (m, 1H), 4.74-4.87 (m, 3H), 4.64-4.72 (m, 2H), 4.20-4.31 (m, 2H), 2.22-2.29 (m, 1H), 2.10-2.16 (m, 1H).

Example 4, Example 5, Example 6

N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(1-oxidothietan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide

Mixture of diastereomers (Example 4)



N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(thietan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (400 mg, 0.76 mmol) was supended in DCM (8 ml). MCPBA (137 mg, 77 % purity, 0.61 mmol) was added and the solution formed stirred 20 min at RT. Water was added, the phases separated and the aq. phase extracted with DCM. The combined organic phases were dried and evaporated. The residue (410 mg) purified by preparative HPLC (RP 18, gradient with 0.1% aqueous formic acid and acetonitrile) yielding 217 mg mixed fractions. This material was repurified by preparative LC (methode 1) yielding the two separated isomers.

Isomer 1 (Example 5): Yield: 26 mg (6 % of theory)

LC-MS (Analytical Method A1): R_t = 1.89 min; MS (ESIpos): m/z = 541 $[M+H]^+$

^{1}H NMR (DMSO-d_6) δ: 9.33 (br d, 1H), 8.82 (d, 1H), 8.45 (m, 1H), 7.65-7.81 (m, 2H), 7.39 (d, 1H), 7.24-7.32 (m, 1H), 7.18 (m, 1H), 6.92 (m, 1H), 6.80 (d, 1H), 5.91 (m, 1H), 5.26 (br m, 1H), 4.20-4.32 (m, 2H), 3.88-3.99 (m, 2H), 3.47-3.58 (m, 2H), 2.23 (m, 1H), 2.04-2.13 (m, 1H)

Peak list

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (1.62), 0.146 (1.64), 1.056 (0.53), 2.072 (3.49), 2.103 (3.61), 2.218 (3.04), 2.229 (3.36), 2.241 (3.59), 2.250 (2.55), 2.263 (2.13), 2.367 (2.09), 2.407 (0.51), 2.712 (2.08), 3.242 (1.87), 3.509 (5.61), 3.516 (4.16), 3.539 (9.78), 3.563 (6.74), 3.568 (5.92), 3.908 (5.06), 3.925 (6.95), 3.942 (5.90), 3.958 (4.82), 4.208 (1.85), 4.235 (4.98), 4.264 (5.56), 4.274 (5.40), 4.289 (4.78), 4.308 (2.10), 5.249 (3.77), 5.267 (4.73), 5.280 (3.97), 5.293 (1.39), 5.752 (13.70), 5.863 (1.33), 5.886 (4.96), 5.909 (7.31), 5.933 (4.73), 5.956 (1.21), 6.788 (9.95), 6.809 (11.07), 6.898 (4.22), 6.917 (8.80), 6.935 (5.07), 7.160 (5.33), 7.177 (8.64), 7.195 (4.13), 7.284 (3.76), 7.383 (8.99), 7.402 (8.33), 7.658 (1.77), 7.673 (3.38), 7.686 (3.36), 7.699 (3.45), 7.714 (1.82), 7.722 (1.58), 7.760 (5.73),

7.783 (10.89), 7.805 (6.10), 8.427 (6.26), 8.442 (6.66), 8.451 (6.62), 8.466 (6.15), 8.816 (15.13), 8.823 (16.00), 9.317 (7.21), 9.336 (6.84).

Isomer 2 (Example 6): Yield: 109 mg (26 % of theory)

LC-MS (Analytical Method A1): R_t = 1.90 min; MS (ESIpos): m/z = 541 $[M+H]^+$

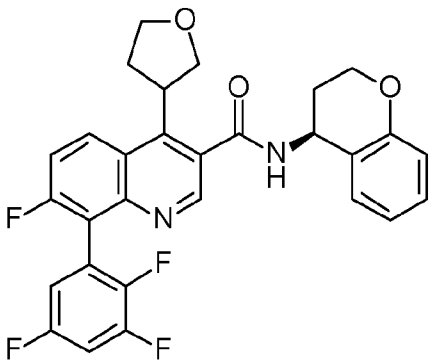
^{1}H NMR (DMSO-d_6) δ: 9.37 (d, 1H), 8.81 (d, 1H), 8.52 (m, 1H), 7.80 (m, 1H), 7.65-7.72 (m, 1H), 7.42 (d, 1H), 7.25-7.33 (m, 1H), 7.18 (m, 1H), 6.91 (m, 1H), 6.80 (d, 1H), 5.27 (br m, 1H), 4.38-4.48 (m, 1H), 4.17-4.31 (m, 4H), 3.50-3.59 (m, 2H), 2.21-2.30 (m, 1H), 2.13 (m, 1H).

Peak list

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.054 (0.66), 1.231 (0.71), 2.105 (2.73), 2.125 (3.29), 2.140 (4.26), 2.233 (3.52), 2.243 (3.80), 2.255 (3.82), 2.277 (2.24), 2.366 (1.32), 2.430 (0.47), 2.709 (1.24), 3.190 (0.52), 3.272 (2.57), 3.441 (3.26), 3.481 (1.76), 3.506 (5.14), 3.529 (9.30), 3.560 (10.10), 3.584 (5.48), 4.185 (5.09), 4.202 (12.56), 4.220 (13.98), 4.228 (11.12), 4.236 (10.66), 4.255 (9.63), 4.279 (5.41), 4.299 (2.33), 4.379 (2.04), 4.397 (3.40), 4.411 (4.26), 4.429 (6.16), 4.447 (3.37), 4.461 (2.96), 4.480 (1.29), 5.239 (1.34), 5.253 (4.15), 5.269 (6.16), 5.286 (4.28), 5.301 (1.55), 6.784 (10.78), 6.804 (12.11), 6.894 (3.47), 6.913 (7.15), 6.925 (4.04), 6.931 (4.12), 7.155 (5.80), 7.174 (9.65), 7.192 (4.67), 7.286 (3.27), 7.408 (10.27), 7.426 (9.67), 7.673 (3.77), 7.681 (3.76), 7.690 (3.90), 7.710 (2.03), 7.717 (1.77), 7.771 (6.30), 7.794 (12.17), 7.817 (6.79), 8.492 (6.47), 8.507 (7.11), 8.516 (7.14), 8.531 (6.52), 8.801 (14.53), 8.812 (16.00), 9.361 (10.25), 9.381 (10.18).

Example 7

N-[(4S)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolanyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



Synthesis according to steps described for intermediates 4 and 5 and example 2 starting from methyl tetrahydrofuran-3-carboxylate and ethyl 4-chloro-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate.

LC-MS (Analytical Method A1): R_t = 2.16 min; MS (ESIpos): m/z = 523 $[M+H]^+$

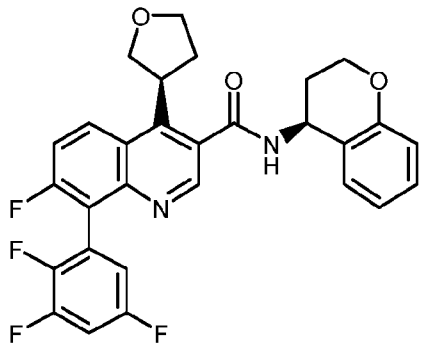
^{1}H NMR (CHLOROFORM-d) δ: 8.79 (m, 1H), 8.57-8.62 (m, 1H), 7.51 (t, 1H), 7.25-7.29 (m, 2H), 7.20 (m, 1H), 6.99-7.07 (m, 1H), 6.89-6.94 (m, 2H), 6.85 (d, 1H), 6.15-6.24 (m, 1H), 5.40 (br m, 1H), 4.50 (m, 1H), 4.28-4.41 (m, 3H), 4.10-4.23 (m, 2H), 3.81-3.89 (m, 1H), 2.46-2.57 (m, 1H), 2.31-2.46 (m, 2H), 2.21 (m, 1H).

Peak list NMR:

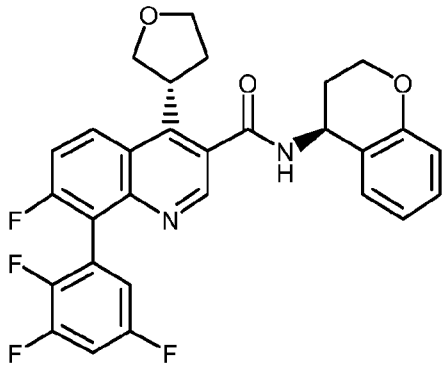
^{1}H-NMR (600 MHz, DMSO-d6) δ [ppm]: 2.060 (0.68), 2.224 (1.03), 2.424 (0.41), 3.289 (16.00), 3.783 (0.71), 4.054 (0.45), 4.063 (0.50), 4.128 (0.56), 4.224 (1.58), 4.236 (1.44), 4.263 (1.17), 4.339 (1.00), 4.352 (0.99), 5.279 (0.94), 6.778 (1.23), 6.792 (1.38), 6.905 (0.65), 6.918 (1.28), 6.930 (0.79), 7.150 (0.68), 7.162 (1.17), 7.175 (0.68), 7.268 (0.80), 7.353 (1.16), 7.364 (1.02), 7.669 (0.70), 7.785 (0.64), 7.800 (1.24), 7.815 (0.72), 8.579 (0.94), 8.767 (1.45), 8.774 (1.45), 9.139 (0.83), 9.151 (1.09).

Example 8 and 9

N-[(4S)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolan-(3S)-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (example 8) and N-[(4S)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolan-(3R)-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (example 9)

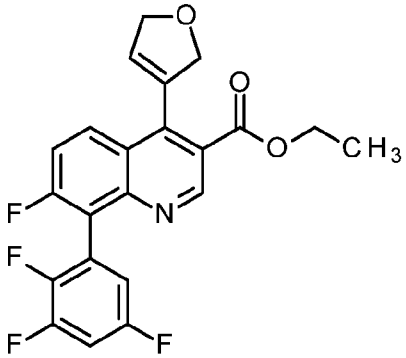


Example 8



Example 9

Step 1:
Ethyl 4-(2,5-dihydrofuran-3-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate.



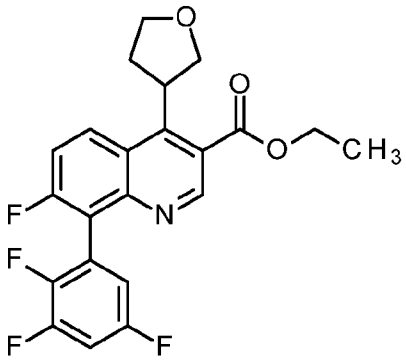
To a solution of ethyl 4-chloro-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (800 mg, 2.1 mmol) in dioxane (10 mL) and H_2O (2 mL), was added 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (450 mg, 2.3 mmol), $Pd(dppf)Cl_2$ (153 mg, 0.2 mmol and K_2CO_3 (576 mg, 4.2 mmol).

The reaction mixture was stirred overnight at 80 °C under nitrogen atmosphere. After cooling to room temperature, the resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether = 0-20%) to afford ethyl 4-(2,5-dihydrofuran-3-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (619 mg, 1.48 mmol) as yellow oil.

LC-MS (Analytical Method B2): R_t = 1.283 min; MS (ESIpos): m/z = 418 $(M+H)^+$.

Step 2:

Ethyl 7-fluoro-4-(oxolan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate.

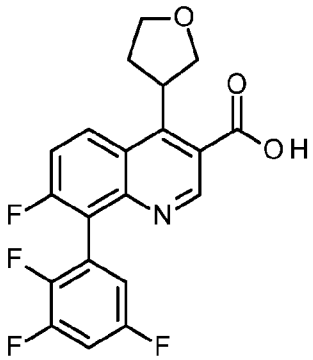


To a solution of ethyl 4-(2,5-dihydrofuran-3-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (619 mg, 1.5 mmol) in EtOH (10 mL) was added Pd/C (80 mg, 0.8 mmol) at rt. The reaction mixture was stirred overnight at rt under hydrogen atmosphere (1.5 atm). After completing of the reaction, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether = 0-20%) to afford ethyl 7-fluoro-4-(oxolan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (592 mg, 1.4 mmol) as yellow oil.

LC-MS (Analytical Method B2): R_t = 1.336 min; MS (ESIpos): m/z = 420 $(M+H)^+$.

Step 3:

7-Fluoro-4-(oxolan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid.

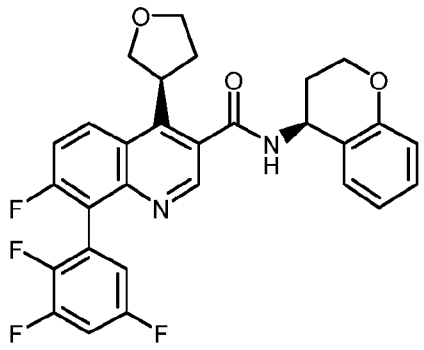


To a solution of ethyl 7-fluoro-4-(oxolan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (592 mg, 1.4 mmol) in a mixed solvent THF/MeOH/H_2O (V:V:V = 1:1:1, 6 mL) was added LiOH (169 mg, 7.1 mmol). The mixture was stirred overnight at rt. The solvent was removed in vacuum and then water was added. The solution was adjusted to pH = 4 with HCl (2 N) and then extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 7-fluoro-4-(oxolan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid (590 mg, 1.4 mmol) as yellow oil.

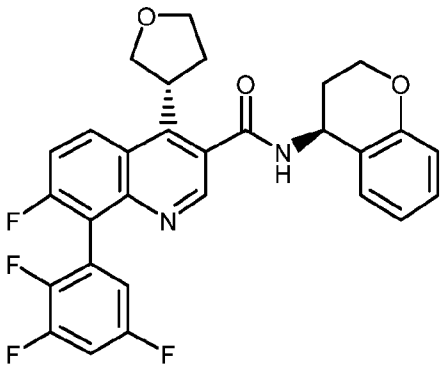
LC-MS (Analytical Method B2): R_t = 0.715 min; MS (ESIpos): m/z = 392 $(M+H)^+$.

Step 4:

N-[(4S)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolan-(3S)-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (example 8) and N-[(4S)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolan-(3R)-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (example 9)



Example 8



Example 9

To a solution of 7-fluoro-4-(oxolan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid (590 mg, 1.41 mmol) in DMF (10 mL) were added HATU (806.28 mg, 2.12 mmol), DIEA (365.41 mg, 2.83 mmol) and (4*S*)-3,4-dihydro-2H-1-benzopyran-4-amine (608.51 mg, 1.56 mmol). The resulting mixture was stirred overnight at rt. Then water was added and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with silica gel chromatography (petroleum ether: ethyl acetate = 0-20%) to afford *N*-[(4*S*)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (582 mg, 1.1 mmol) as a yellow oil.

The two isomers were separated by Chiral Prep-HPLC (Column: Lux 5μm Cellulose-2, 2.12*25 cm, 5 μm; Mobile Phase A: Hexane (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 31 min; Wave Length: 220/254 nm; RT1(min): 16.40; RT2(min): 26.04; Sample Solvent: EtOH) to afford *N*-[(4*S*)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolan-(3*S*)-

yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide **(Example 8)** (69.7 mg, 133.40 mmol, 13.44% yield, 98.7% purity) as a white solid.

1H NMR (400 MHz, DMSO-d6): 9.19 (d, 1H), 8.78 (s, 1H), 8.59 (t, 1H), 7.82 (t, 1H), 7.80-7.79 (m, 1H), 7.36 (t, 1H), 7.33-7.26 (m, 1H), 7.16 (t, 1H), 6.92 (t, 1H), 6.79 (d, 1H), 5.29-5.28 (m, 1H), 4.36 (t, 1H), 4.32-4.20 (m, 3H), 4.24-4.07 (m, 1H), 4.04-3.92 (m, 1H), 3.84-3.75 (m, 1H), 2.50-2.49 (m, 1H), 2.26-2.23 (m, 2H), 2.21-2.01 (m, 1H).

LC-MS (Analytical Method A2): R_t = 1.408min; MS (ESIpos): m/z = 523 $(M+H)^+$.

and

N-[(4*S*)-3,4-dihydro-2H-1-benzopyran-4-yl]-7-fluoro-4-(oxolan-(3*R*)-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide **(Example 9)** (97.2 mg, 186.03 µmol, 13.44% yield, 99.3% purity) as a white solid, whose absolute structure was confirmed by single crystal spectra.

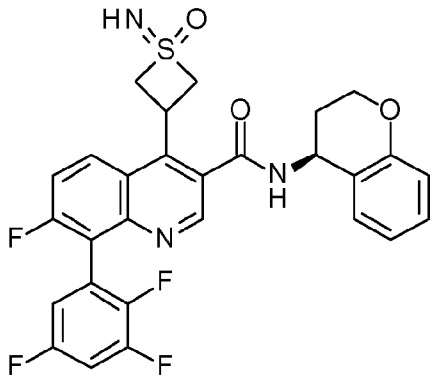
1H NMR (400 MHz, DMSO-d6): 9.19 (d, 1H), 8.78 (s, 1H), 8.59 (t, 1H), 7.82 (t, 1H), 7.80-7.79 (m, 1H), 7.36 (t, 1H), 7.33-7.26 (m, 1H), 7.16 (t, 1H), 6.92 (t, 1H), 6.79 (d, 1H), 5.29-5.28 (m, 1H), 4.36 (t, 1H), 4.32-4.20 (m, 3H), 4.24-4.07 (m, 1H), 4.04-3.92 (m, 1H), 3.84-3.75 (m, 1H), 2.50-2.49 (m, 1H), 2.26-2.23 (m, 2H), 2.21-2.01 (m, 1H).

LC-MS (Analytical Method A2): R_t = 1.269 min; MS (ESIpos): m/z = 523 $(M+H)^+$.

The absolute configurations of the stereogenic carbon atoms (4S; 3S, and 3R) of the examples 8 and 9 were confirmed by single crystal X-ray analysis.

Example 10

N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(1-imino-1-oxido-1lambda^4-thietan-3-yl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (mixture of diasteromers)



A suspension of N-[(4S)-3,4-dihydro-2H-chromen-4-yl]-7-fluoro-4-(thietan-3-yl)-8-(2,3,5-trifluorophenyl)-quinoline-3-carboxamide (75 mg, 0.14 mmol) in methanol (2 ml) and DCM (0.4 ml) was treated with diacetoxy(phenyl)-lambda^3-iodane (115 mg, 0.36) and ammonium carbamate (22.3 mg, 0.29 mmol). The mixture dissolved and was stirred at RT for 30 min. Then saturated aq. sodiumhydrogencarbonate solution was added and extracted 3 times with ethylacetate. The combined organic phases were dried over sodiumsulfate, evaporated under diminished pressure and the residue purified by flash chromatography on silica (25 g) with cyclohexane/ethylacetate (12 to 55 %).

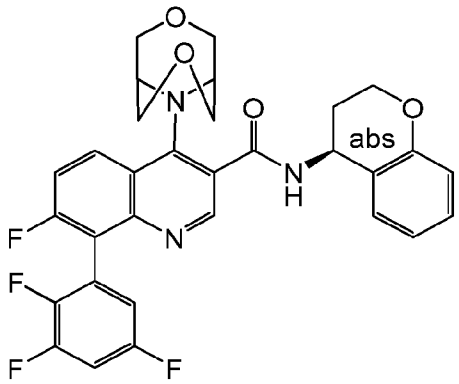
Yield: 39 mg (49 % of theory)

LC-MS (Analytical Method A1): R_t = 1.90 min; MS (ESIpos): m/z = 556 $[M+H]^+$

1H NMR (DMSO-d6) δ: 9.33-9.43 (m, 1H), 8.82-8.89 (m, 1H), 8.72-8.80 (m, 1H), 7.79-7.88 (m, 1H), 7.64-7.75 (m, 1H), 7.24-7.34 (m, 1H), 7.13-7.23 (m, 1H), 6.86-6.96 (m, 1H), 6.75-6.84 (m, 1H), 5.22-5.34 (m, 1H), 4.97-5.07 (m, 1H), 4.69-4.85 (m, 1H), 4.42-4.66 (m, 4H), 4.14-4.36 (m, 2H), 2.18-2.31 (m, 1H), 2.05-2.18 (m, 1H).

Example 11

4-((1R,5R)-3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl)-*N*-((*S*)-chroman-4-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



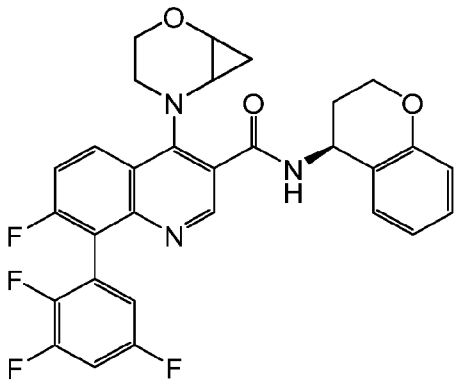
Into a 20-mL round-bottom flask was placed 4-chloro-*N*-((*S*)-chroman-4-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (200 mg, 0.41 mmol), (1s,5s)-3,7-dioxa-9-azabicyclo[3.3.1]nonane (80 mg, 0.62 mmol), DMSO (5.00 mL) and DIEA (159 mg, 1.23 mmol). The resulting solution was stirred for 4 hours at 75 °C. After cooling to room temperature, the resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified with silica gel chromatography (petroleum ether: ethyl acetate = 2: 1) to give the crude product. The crude product (90 mg) was further purified by Prep-HPLC [Mobile Phase A: Water (10mmoL/L NH_4HCO_3), Mobile Phase B: ACN; Gradient: 50% B to 60% B in 7 min] to give 4-((1R,5R)-3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl)-*N*-((*S*)-chroman-4-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (19.3 mg, 8.1% yield) as an off-white solid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [*ppm*] = 9.47 (d, 1H), 8.44 (d, 1H), 8.20-8.10 (m, 1H), 7.72-7.58 (m, 2H), 7.35-7.15 (m, 3H), 6.95-6.90 (m, 1H), 6.79 (d, 1H), 5.20-5.10 (m, 1H), 4.26-4.12 (m, 6H), 4.01-3.92 (m, 6H), 2.20-2.00 (m, 2H).

LC-MS (Analytical Method B1, 0.01-2.00 min 0-95% B, 2.00-2.70 min 100% B): R_t = 1.75 min; MS (ESIpos): m/z = 580 $(M+H)^+$.

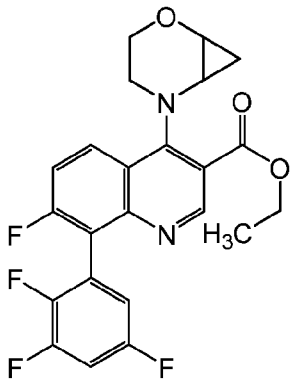
Example 12

4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-((S)-chroman-4-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



Step 1:

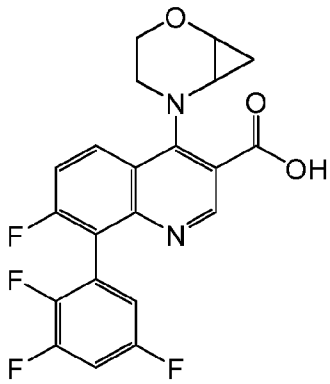
Synthesis of ethyl 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate



Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed ethyl 4-bromo-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (100 mg, 0.234 mmoL), 2-oxa-5-azabicyclo[4.1.0]heptane hydrogen chloride (38 mg, 0.281 mmoL), potassium carbonate (130 mg, 0.936 mmoL) and acetonitrile (10 mL). The resulting solution was stirred overnight at 70 °C. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified with silica gel chromatography (petroleum ether: ethyl acetate = 5:1) to give ethyl 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (100 mg, 96% yield) as a pale yellow solid.

Step 2:

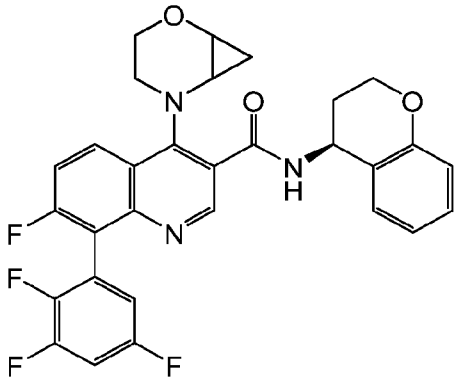
4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid



Into a 8-mL round-bottom flask, was placed ethyl 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate (80 mg, 0.179 mmol), THF (1 mL), MeOH (1 mL), H_2O (1 mL) and lithium hydroxide monohydrate (34 mg, 0.810 mmol). The resulting solution was stirred for 4 h at room temperature. Upon completion of the reaction, the THF was removed in vacuo, the pH value of the mixture was adjusted to 5 with 1 M HCl. The resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid (65 mg, 86.7% yield) as yellow oil.

Step 3:

4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-((S)-chroman-4-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



Into a 20-mL round-bottom flask was placed 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid (65 mg, 0.156 mmol), *N,N*-dimethylformamide (3 mL), (S)-chroman-4-amine (24 mg,0.161 mmol), HATU (60 mg, 0.157 mmol) and N,N-diisopropylethylamine (67 mg, 0.519 mmol). The resulting solution was stirred for 2 hours at room temperature. Upon completion of the reaction, the resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by Prep-HPLC [Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Gradient: 70% B to 75% B in 14 min] to give 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-((S)-

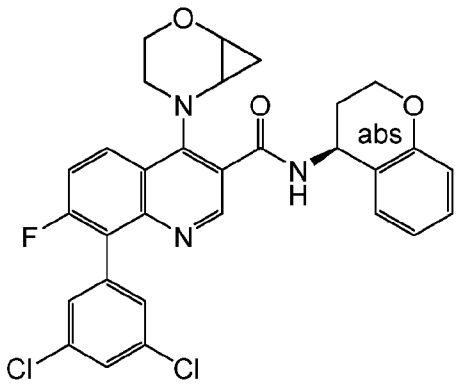
chroman-4-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (5.4 mg, 6.3% yield) as an off-white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [*ppm*] = 9.15-9.13 (m, 1H), 8.66-8.61 (m, 2H), 7.70-7.66 (m, 2H), 7.36-7.25 (m, 2H), 7.18-7.14 (m, 1H), 6.91-6.90 (m, 1H), 6.78 (d, 1H), 5.23-5.22 (m, 1H), 4.27-4.22 (m, 2H), 3.87-3.86 (m, 2H), 3.78-3.76 (m, 1H), 3.01-2.90 (m, 1H), 2.25-2.15 (m, 1H), 2.04-1.99 (m, 1H), 1.24-1.13 (m, 3H), 0.85-0.70 (m, 1H).

LC-MS (Analytical Method B1, 0.01-2.00 min 5-95% B, 2.00-2.70 min 95% B): R_{t1} = 1.87 min; MS (ESIpos): m/z = 550 $(M+H)^+$.

Example 13

4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-*N*-((*S*)-chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide



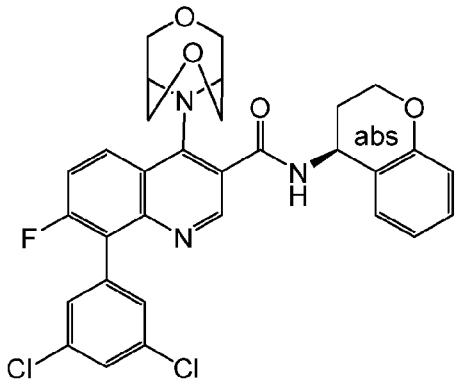
Into a 20-mL round-bottom flask was placed (*S*)-4-chloro-N-(chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide (70 mg, 0.14 mmol), 2-oxa-5-azabicyclo[4.1.0]heptane hydrogen chloride (28 mg, 0.21 mmol), DMSO (2.0 mL) and DIEA (54 mg, 0.42 mmol). The resulting solution was stirred for 4 hours at 70 °C. After cooling to room temperature, the resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified with silica gel chromatography (petroleum ether: ethyl acetate = 2:1) to give the crude product. The crude product was further purified by Prep-HPLC [Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Gradient: 80% B to 90% B in 14 min] to give 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-*N*-((*S*)-chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide (17.8 mg, 22.6% yield) as an off-white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [*ppm*] = 9.13-9.12 (m, 1H), 8.64-8.55 (m, 2H), 7.70-7.64 (m, 2H), 7.51-7.50 (m, 2H), 7.35-7.30 (m, 1H), 7.18-7.15 (m, 1H), 6.92-6.90 (m, 1H), 6.80-6.78 (m, 1H), 5.24-5.23 (m, 1H), 4.26-4.25 (m, 2H), 3.87-3.86 (m, 2H), 3.80-3.75 (m, 1H), 3.31-3.30 (m, 2H), 3.00-2.90 (m, 1H), 2.19-2.16 (m, 1H), 2.05-2.03 (m, 1H), 1.18-1.13 (m, 1H), 0.80-0.70 (m, 1H).

LC-MS (Analytical Method C1, 0.01-2.00 min 5-100% B, 2.00-2.70 min 100% B): R_t = 1.54 min; MS (ESIpos): m/z = 564 $(M+H)^+$.

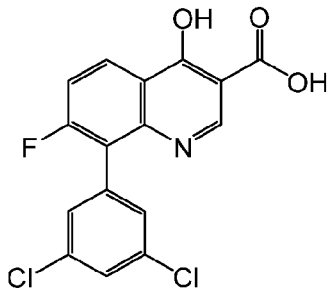
Example 14

4-((1R,5R)-3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl)-*N*-((*S*)-chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide



Step 1:

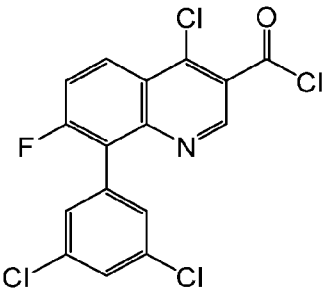
8-(3,5-dichlorophenyl)-7-fluoro-4-hydroxyquinoline-3-carboxylic acid



Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 8-bromo-7-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5.00 g, 17.54 mmol), (3,5-dichlorophenyl)boronic acid (6.67 g, 35.09 mmol), K_2CO_3 (4.84 g, 35.09 mmol), XPhos Pd G2 (1.38 g, 1.75 mmol), 1,4-dioxane (50 mL) and H_2O (10 mL). The resulting solution was stirred overnight at 80 °C. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The residue was diluted with 10% NaOH and filtered, The filtrate was washed with MTBE and the pH value of the mixture was adjusted to 5 with 1 M HCl. The resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give 8-(3,5-dichlorophenyl)-7-fluoro-4-hydroxyquinoline-3-carboxylic acid (7.2 g, 80% purity, 93.5%) as a white solid.

Step 2:

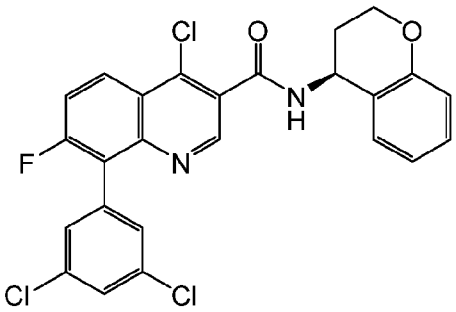
4-chloro-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carbonyl chloride



Into a 250-mL 8-(3,5-dichlorophenyl)-7-fluoro-4-hydroxyquinoline-3-carboxylic acid (7.2 g, 80% purity, 16.6 mmol), DCM (100 mL), oxalyl dichloride (20 mL) and DMF (0.02 mL). The resulting solution was stirred for 1 h at room temperature. Upon completion of the reaction, the resulting solution was concentrated in vacuo to give 4-chloro-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carbonyl chloride (crude) used for next step directly.

Step 3:

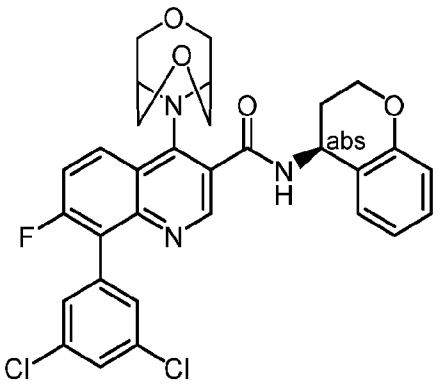
(*S*)-4-chloro-*N*-(chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide



Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-chloro-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carbonyl chloride (crude), DCM (100 mL), (*S*)-chroman-4-amine (2.47 g, 16.6 mmol) and TEA (3.35 g, 22.2 mmol). The resulting solution was stirred 2 h at rt. Upon completion of the reaction, the reaction mixture was diluted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified with silica gel chromatography (petroleum ether : ethyl acetate = 3:1) to give (*S*)-4-chloro-*N*-(chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide (6.1 g , 74% yield) as an off-white solid.

Step 4:

4-((1R,5R)-3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl)-*N*-((*S*)-chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide



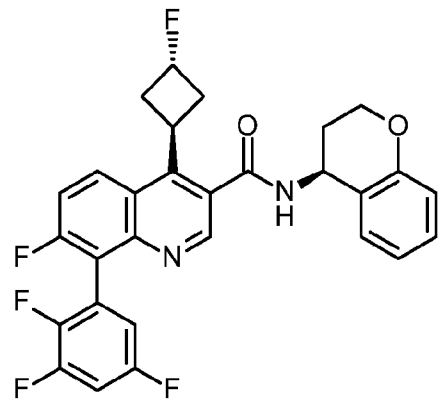
Into a 20-mL round-bottom flask was placed (*S*)-4-chloro-N-(chroman-4-yl)-8-(3,5-dichlorophenyl)7-fluoroquinoline-3-carboxamide (200 mg, 0.400 mmol), (1*s*,5*s*)-3,7-dioxa-9-azabicyclo[3.3.1]nonane (77 mg, 0.60 mmol), DMSO (5.00 mL) and DIEA (155 mg, 1.20 mmol). The resulting solution was stirred for 4 hours at 75°C. After cooling to room temperature, the resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified with silica gel chromatography (petroleum ether : ethyl acetate = 2:1) to give crude product. The crude product was further purified by Prep-HPLC [Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Gradient: 50% B to 90% B in 8 min] to give 4-((1*R*,5*R*)-3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl)-*N*-((*S*)-chroman-4-yl)-8-(3,5-dichlorophenyl)-7-fluoroquinoline-3-carboxamide (17.1 mg, 7.2% yield) as an off-white solid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [*ppm*] = 9.36 (d, 1H), 8.45 (s, 1H), 8.14-8.07 (m, 1H), 7.73-7.71 (m, 1H), 7.67-7.49 (m, 3H), 7.35-7.32 (m, 1H), 7.26-7.16 (m, 1H), 6.96-6.91 (m, 1H), 6.81-6.80 (m, 1H), 5.19-5.15 (m, 1H), 4.28-4.23 (m, 2H), 4.16-4.11 (m, 4H), 4.01-3.94 (m, 6H), 2.18-2.01 (m, 2H).

LC-MS (Analytical Method B1, 0.01-2.00 min 0-95% B, 2.00-2.70 min 95% B): R_t = 1.92 min; MS (ESIpos): m/z = 594 $(M+H)^+$.

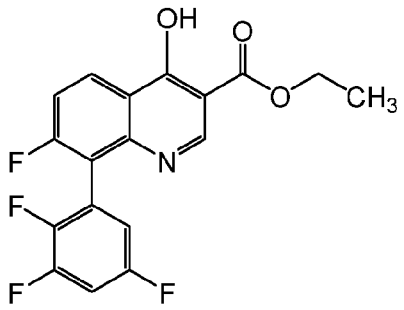
Example 15

N-((*S*)-chroman-4-yl)-7-fluoro-4-((1*R*,3*S*)-3-fluorocyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



Step 1:

Ethyl 7-fluoro-4-hydroxy-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate

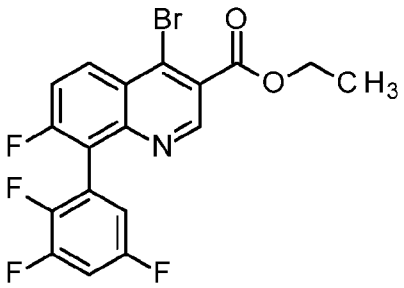


To a solution of ethyl 8-bromanyl-7-fluoranyl-4-oxidanyl-quinoline-3-carboxylate (10.00 g, 31.84 mmol) in toluene (100 mL) and water (25 mL), was added [2,3,5-tris(fluoranyl)phenyl]boronic acid (6.72 g, 38.20 mmol), XPhos Pd G3 (2.70 g, 3.18 mmol), and CsF (6.31 g, 95.51 mmol). The reaction mixture was stirred for 16 hour 100 °C under nitrogen atmosphere. After cooling to room temperature, the resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was slurred with petroleum ether. The precipitated solids were collected by filtration and washed with petroleum ether to afford ethyl 7-fluoranyl-4-oxidanyl-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxylate (4.00 g, 10.95 mmol, 34.40% yield) as a black solid.

LC-MS (Analytical Method A3,1.20-1.90 min 95% B): R_t = 1.012 min; MS (ESIpos): m/z = 366 $(M+H)^+$.

Step 2:

Ethyl 4-bromo-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate



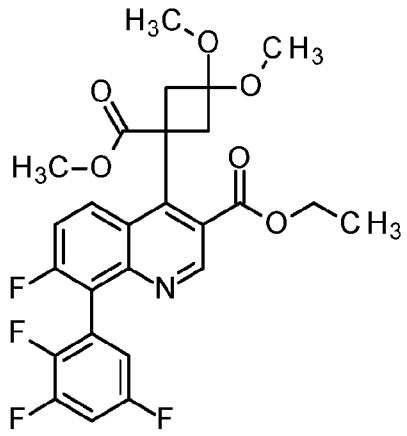
To a solution of ethyl 7-fluoranyl-4-oxidanyl-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxylate (3.93 g, 10.76 mmol) in DCM (40 mL) and DMF (8 mL) was added $POBr_3$ (4.63 g, 16.14 mmol) in portions at 0 °C. The resulting mixture was stirred for 2 hours at rt. The resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether = 0-50%) to afford ethyl 4-

bromanyl-7-fluoranyl-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxylate (3.37 g, 7.87 mmol, 73.15% yield).

LC-MS (Analytical Method A3,1.20-1.90 min 95% B): R_t = 1.262 min; MS (ESIpos): m/z = 428 $(M+H)^+$.

Step 3:

Ethyl 4-(3,3-dimethoxy-1-(methoxycarbonyl)cyclobutyl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylate

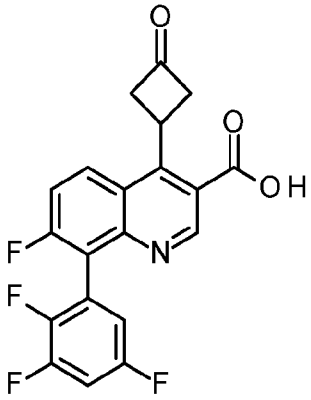


To a solution of methyl 3,3-di(methoxy)cyclobutanecarboxylate (2.00 g, 11.46 mmol) in THF (20 mL) were added LiHMDS (15.3 mL, 15.27 mmol, 1M in THF) dropwise at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -78 °C. To the above mixture was added ethyl 4-bromanyl-7-fluoranyl-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxylate (3.27 g, 7.64 mmol) in THF (20 mL) dropwise at -78 °C. The resulting mixture was stirred for additional 1 hour at -78 °C. The reaction was quenched with sat. aqueous NH_4Cl solution at 0 °C. The resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether = 0-30%) to afford ethyl 4-[3,3-di(methoxy)-1-methoxycarbonyl-cyclobutyl]-7-fluoranyl-8-[2,3,5 tris(fluoranyl)phenyl]quinoline-3-carboxylate (2.9 g, 5.56 mmol, 72.82% yield).

LC-MS (Analytical Method A3, 1.20-1.90 min 95% B): R_t = 1.295 min; MS (ESIpos): m/z = 522 $(M+H)^+$.

Step 4:

7-fluoro-4-(3-oxocyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid

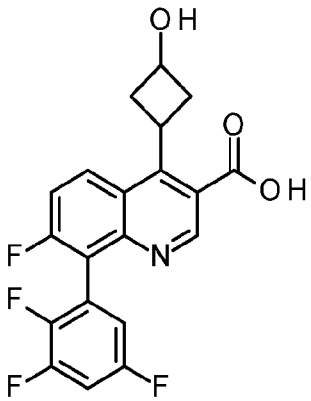


To a solution of ethyl 4-[3,3-di(methoxy)-1-methoxycarbonyl-cyclobutyl]-7-fluoranyl-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxylate (2.85 g, 5.47 mmol) in DME (30 mL), was added NaOH (874 mg, 21.86 mmol) in water (2.4 mL). The reaction mixture was stirred for 16 hours at 60 °C. Then to the above mixture was added aqueous HCl solution (9 N, 3.6 mL) at 60 °C. The resulting mixture was stirred for additional 2 hours at 60 °C. After cooling to room temperature, the resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 7-fluoranyl-4-(3-oxidanylidenecyclobutyl)-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxylic acid (2.60 g, 6.68 mmol).

LC-MS (Analytical Method B3, 1.40-1.90 min 95% B): R_t = 0.929 min; MS (ESIpos): m/z = 390 $(M+H)^+$.

Step 5:

7-fluoro-4-((1r,3r)-3-hydroxycyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxylic acid



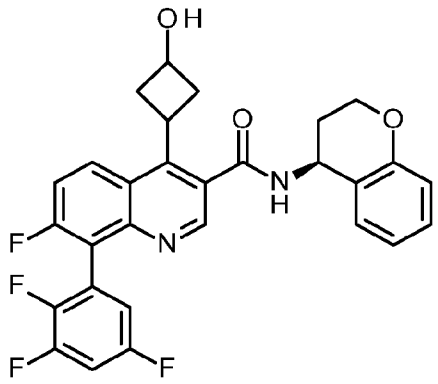
To a solution of 7-fluoranyl-4-(3-oxidanylidenecyclobutyl)-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxylic acid (2.50 g, 6.42 mmol) in MeOH (20 mL) was added sodium borohydride (364 mg, 9.63 mmol) in portions at 0 °C. The resulting mixture was stirred for 2 hours at rt. The resulting mixture was treated with water and acidified to pH = 5 with HCl (2 N). The resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and

concentrated under reduced pressure to afford 7-fluoranyl-8-(3-fluoranyl-2,5-difluoro-phenyl)-4-(3-hydroxycyclobutyl)quinoline-3-carboxylic acid (1.20 g, 3.07 mmol, 47.75% yield).

LC-MS (Analytical Method C3, 0.01-1.20 min 2-100% B, 1.20-1.75 min 100% B): R_t = 1.035 min; MS (ESIpos): m/z = 392 $(M+H)^+$.

Step 6:

N-((*S*)-chroman-4-yl)-7-fluoro-4-((1*R*,3*S*)-3-hydroxycyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide

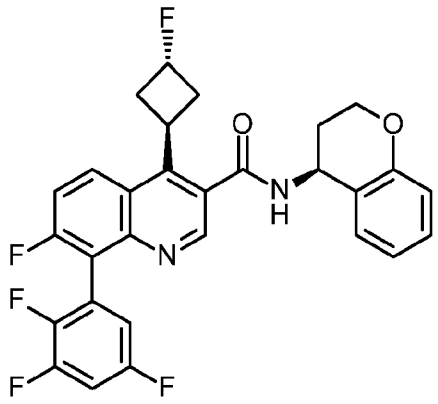


To a solution of 7-fluoranyl-8-(3-fluoranyl-2,5-difluoro-phenyl)-4-(3-hydroxycyclobutyl)quinoline-3-carboxylic acid (640 mg, 1.64 mmol) in DMF (6 mL), was added (4*S*)-chroman-4-amine (488 mg, 3.27 mmol), HATU (932.81 mg, 2.45 mmol) and DIEA (634 mg, 4.91 mmol), The reaction mixture was stirred for 1 hour at rt. The resulting mixture was treated with water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether = 0-50%) to afford *N*-[(4*S*)-chroman-4-yl]-7-fluoro-4-(3-hydroxycyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (280 mg, 535.90 μmol, 32.77% yield) as a white solid.

LC-MS (Analytical Method A3, 1.20-1.90 min 95% B): R_t = 1.135 min; MS (ESIpos): m/z = 523 $(M+H)^+$.

Step 7:

N-((*S*)-chroman-4-yl)-7-fluoro-4-((1*R*,3*S*)-3-fluorocyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide



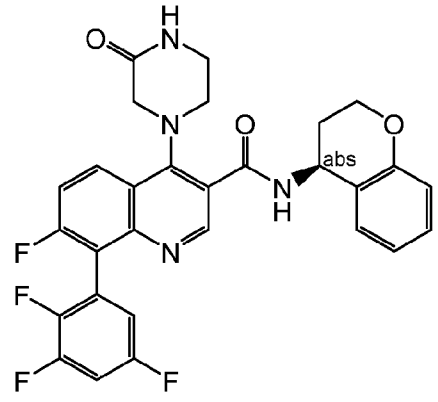
To a stirred solution of *N*-[(4*S*)-chroman-4-yl]-7-fluoro-4-(3-hydroxycyclobutyl)-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (272 mg, 520.58 μmol) in DCM (3 mL) was added BAST (346 mg, 1.56 mmol) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 hour at 0 °C under nitrogen atmosphere. the resulting mixture was treated with water and extracted with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Prep-TLC (ethyl acetate: petroleum ether = 1:2) and further purified by Prep-HPLC (Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Gradient: 47% B to 72% B in 9 min) to afford *N*-[(4*S*)-chroman-4-yl]-7-fluoranyl-4-(3-fluorocyclobutyl)-8-[2,3,5-tris(fluoranyl)phenyl]quinoline-3-carboxamide (32.3 mg, 60.66 μmol, 11.65% yield, 98.5% purity) as a white solid.

^{1}H-NMR (400 MHz, DMSO-D6): δ [*ppm*] = 9.17 (d, 1H), 8.77 (d, 1H), 8.28-8.25 (m, 1H), 7.76-7.68 (m, 2H), 7.34-7.29 (m, 2H), 7.18-7.15 (m, 1H), 6.92-6.91 (m, 1H), 6.79 (d, 1H), 5.28-5.14 (m, 2H), 4.76-4.72 (m, 1H), 4.28-4.20 (m, 2H), 2.92-2.62 (m, 4H), 2.25-2.15 (m, 1H), 2.05-2.00 (m, 1H).

LC-MS (Analytical Method B3, 0.01-1.90 min 30-70% B, 1.90-2.00 min 70-95% B, 2.00-2.70 min 95% B): R_{t1} = 1.846 min; MS (ESIpos): m/z = 525 $(M+H)^+$.

Example 16

N-((*S*)-chroman-4-yl)-7-fluoro-4-(3-oxopiperazin-1-yl)-8-(2,3,5-trifluorophenyl) quinoline-3-carboxamide



Step 1:

To a solution of 4-chloro-*N*-((*S*)-chroman-4-yl)-7-fluoro-8-(2,3,5-trifluorophenyl)quinoline-3-carboxamide (100 mg, 0.205 mmol) in ACN (3 mL) was added potassium carbonate (85 mg, 0.616 mmol) and piperazin-2-one (31 mg, 0.308 mmol). The reaction mixture was stirred for 36 h at 70 °C. The reaction was then quenched by the addition of 5 mL of water. The resulting solution was extracted with ethyl acetate, and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated in vacuo. The reside was purified with silica gel column chromatography (dichloromethane/methanol 10:1) and further purified by prep-HPLC (Column: XBridge Prep OBD C18 Column, 30 × 150 mm 5 um; Mobile Phase A: Water (10 MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40 % to 55% in 8 min; 254 nm; RT1:6.6.) to afford 35.0 mg (30.71%) of the product as a white solid.

LC-MS (Analytical Method A3, 0-3.00 min 5-95% B): Rt = 1.598 min; MS (ESIpos): m/z = 551 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.28-9.26 (m, 1H), 8.72 (d, 1H), 8.37-8.33 (m, 1H), 8.12 (s, 1H), 7.74-7.66 (m, 2H), 7.39-7.37 (m, 1H), 7.31-7.25 (m, 1H), 7.19-7.15 (m, 1H), 6.80-6.78 (m, 1H), 5.23-5.22 (m, 1H), 4.27-4.22 (m, 2H), 3.84 (s, 2H), 3.53-3.44 (m, 4H), 2.27-2.20 (m, 1H), 2.15-2.02 (m, 1H).

EXPERIMENTAL SECTION – BIOLOGICAL ASSAYS

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values or median values calculated utilizing data sets obtained from testing of one or more synthetic batch.

The in vitro activity of the compounds of the present invention were demonstrated in the following assays:

***In vitro* assay 1: *D. immitis* Slo-1 - Action at a recombinant *D. immitis* cell line**

Generation of a stable *D. immitis* Slo-1 CHO cell line

A CHO cell line was obtained from ATCC, code ATCC CRL-9096. For transfection with plasmid DNA to express *D. immitis* Slo-1 (based on Protein sequence JQ730003 , codon optimized for hamster) CHO cells were passaged to 40% confluence before adding the transfection solution to the cell culture. The transfection solution included 300 µL OptiMEM (Life Technologies, Nr.: 31985), 2 µL (= 6 µg) of

plasmid DNA containing the *D. immitis* Slo-1 gene and 9µL FugeneHD (Promega, Nr.: E2311), and was added to the cells prior to incubation for 48 hours at 37°C, 5% CO_2. The transfection medium was exchanged for the selection medium which contains additional G418 (2 mg/ml, Invitrogen, Nr.: 10131) and the cells were seeded into 384 well plates (300 cells/well). After a few weeks, the remaining surviving cells were tested with a voltage sensitive dye (Membrane Potential Assay Kit, Molecular Devices Nr.: R8034) for K+ channel expression. Positive cell clones were purified by the limited dilution technique. For this the clone with the highest and most robust signal in the voltage sensitive dye assay was further subcloned (incubated) in 384 well plates (0.7 cells/well) in order to obtain clonal purity. This generated a final stable CHO cell line expressing the *D. immitis* Slo-1.

Cell culture conditions

Cells were cultured at 37 °C and 5% CO_2 in MEMalpha with Gutamax I (Invitrogen, Nr.: 32571), supplemented with 10% (v/v) heat inactivated fetal bovine serum (Invitrogen, Nr.: 10500), G418 (1 mg/ml, Invitrogen, Nr.: 10131). Cells were detached using Accutase (Sigma, Nr.: A6964).

Membrane potential measurements

Laboratory compound testing was performed on 384-well microtiter plates (MTPs, Greiner, Nr.: 781092). 8000 cells/well were plated onto 384-well MTPs and cultured for 20 to 24 hours at 37 °C and 5% CO_2. After removal of the cell culture medium, the cells were washed once with tyrode (150 mM NaCl, 0.3 mM KCl, 2 mM $CaCl_2$, 1mM $MgCl_2$, 0.8 mM NaH_2PO_4, 5mM Glucose, 28 mM Hepes, pH 7.4) and then loaded with the voltage sensitive dye of the Membrane Potential Assay Kit diluted in tyrode for 1 h at room temperature.

After starting the measurement of fluorescence using a FLIPR Tetra (Molecular Devices, Exc. 510-545 nm, Emm. 565-625 nm), test compounds were added followed by the addition of KCl tyrode (final assay concentration: 70 mM KCl, 2 mM $CaCl_2$, 1mM $MgCl_2$, 0.8 mM NaH_2PO_4, 5mM Glucose, 28 mM Hepes, pH 7.4, including the voltage sensitive dye). The measurement was completed after 7 minutes.

Statistics

The data were evaluated by using the ActivityBase XLfit software (IDBS) for curve fitting and calculation of the half-maximal effective concentration (EC_{50}) and are reported as negative decadic logarithm (pE_{50}).

Alternatively, EC_{50} values were calculated using a four parameter plotting by the Scilligence ELN /Regmol Software Tool, Bioassay.

For the following examples, EC_{50} of >1 nM to 10 nM has been found for: 1, 7, 8, 9, 10, 12, 13, 15.

For the following examples, EC_{50} >10 nM to 100 nM has been found for: 3.

For the following examples, pE_{50} >100 nM – 1 µM has been found for: 6.

***In vitro* assay 2: *Nippostrongylus brasiliensis* (NIPOBR)**

Adult *Nippostrongylus brasiliensis* were washed with saline buffer containing 100 U/ml penicillin, 0.1 mg/ml streptomycin and 2.5 µg/ml amphotericin B. Test compounds were dissolved in DMSO and worms were incubated in medium in a final concentration of 10 µg/ml (10 ppm) respectively 1µg/ml (1 ppm). An aliquot of the medium was used to determine the acetylcholine esterase activity in comparison to a negative control. The principle of measuring acetylcholine esterase as readout for anthelmintic activity was described in Rapson et al (1986) and Rapson et al (1987).

For the following examples, EC_{50} was ≤0.1 ppm: 7, 8, 9, 10, 15, 16.

***In vitro* assay 3: *Dirofilaria immitis* microfilariae (DIROIM L1)**

≥ 250 *Dirofilaria immitis* microfilariae, which were freshly purified from blood, were added to wells of a microtitre plate containing a nutrient medium and the test compound in DMSO. Compounds were tested in concentration-response assay in duplicate. Larvae exposed to DMSO and no test compounds were used as negative controls. Larvae were evaluated after 72 h of incubation with the compound. Efficacy was determined as the reduction of motility in comparison to the negative control. Based on the evaluation of a wide concentration range, concentration-response curves as well as EC_{50}-values were calculated.

For the following examples, the EC_{50} was < 0.1 ppm: 1, 3, 6, 7, 8, 9, 10, 13, 15.

***In vitro* assay 4: *Dirofilaria immitis* (DIROIM L4)**

10 *Dirofilaria immitis* third-stage larvae, which were freshly isolated from their vector (intermediate host), were added to wells of a microtitre plate containing a nutrient medium and the test compound in DMSO. Compounds were tested in concentration-response assay in duplicate. Larvae exposed to DMSO and no test compounds were used as negative controls. Larvae were evaluated after 72 h of incubation with the compound. Within these 72 h of incubation the majority of larvae in negative control moult to fourth-stage larvae. Efficacy was determined as the reduction of motility in comparison to the negative control. Based on the evaluation of a wide concentration range, concentration-response curves as well as EC_{50}-values were calculated.

For the following examples, the EC50 was < 0.1 ppm: 1, 7, 8, 9, 10, 15.

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***In vitro* assay 5: *Haemonchus contortus* (HAEMCO)**

Solvent: dimethyl sulfoxide

To produce a suitable preparation of active compound, 10 mg of active compound are dissolved in 0.5 ml solvent, and the concentrate is diluted with "Ringer's solution" to the desired concentration.

Approximately 40 larvae of the red stomach worm (*Haemonchus contortus)* are transferred into a test tube containing compound solution.

After 5 days the percentage of larval mortality is recorded. 100 % efficacy means all larvae are killed, 0% efficacy means no larvae are killed.

Formulation Example

Exemplary formulations consisted of the active substance in 10% Transcutol, 10% Cremophor EL and 80% isotonic saline solution. First the active substance was dissolved in Transcutol. After solution in Transcutol, Cremophor and isotonic saline solution were added. These formulations were used as service formulations in the following *in vivo* assay.

An example for a formulation according to the present invention is the following formulation Example F1. Therein, the active substance was dissolved in Transcutol to form a stock solution A. Then 0.100 mL of this stock solution A were taken and 0.100 mL Cremophor EL and 0.800 mL isotonic saline solution were added. The resulting liquid formulation (formulation example F1) had a volume of 1 mL.

Stock solution A:

4.0 mg compound of example 2,

0.100 mL Transcutol.

Formulation example F1:

0.100 mL stock solution A,

0.100 mL Cremophor EL, and

0.800 mL isotonic saline solution.

In vivo assays

In vivo assay 1: Filarial nematodes of A. viteae (Acanthocheilonema viteae)

Jirds (*Meriones unguiculatus*), experimentally infected with infective *A. viteae* larvae via subcutaneous injection were subsequently treated once with the formulated test compound by oral gavage or intraperitoneally. At necropsy 12 weeks after infection, efficacy was expressed as a % reduction in worm numbers in comparison with the placebo treated group, using the Abbot's formula.

In vivo assay 2: Filarial nematodes of L. sigmodontis (Litomosoides sigmodontis)

Mice, experimentally infected with infective *L. sigmodontis* larvae via subcutaneous injection were subsequently treated once with the formulated test compound by oral gavage or intraperitoneally. At necropsy 5 weeks after infection, efficacy was calculated by counting developed larvae vs. untreated animals using Abbot's formula.

In vivo assay 3: Gastro intestinal nematodes of H. contortus (Haemonchus contortus) and T. colubriformis (Trichostrongylus colubriformis)

Jirds (*Meriones unguiculatus*), immunosuppressed by administration of rodent feed containing hydrocortisone 21-acetate, were experimentally infected with third instar larvae each of *T. colubriformis* and *H. contortus* by oral gavage and were treated once orally or intraperitoneally with the formulated test

compound on Day 6 after infection. Three days after treatment, jirds were euthanized and dissected to recover *H. contortus* from stomach and *T. colubriformis* from the small intestine. Efficacy is expressed as a % reduction in worm numbers in comparison with a placebo treated group, using the Abbot's formula.

The following examples were tested in the in vivo tests 1, 2, and/or 3 and had an activity of

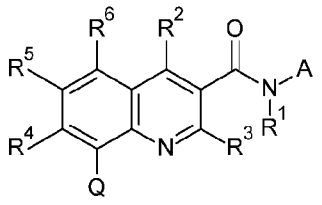
100 % at ≤ 25.0 mg/kg per oral against *A. viteae*: 1;

80 % or higher at ≤ 3.0 mg/kg per oral or intraperitoneal against *L. sigmodontis*: 4, 15;

100 % at ≤ 1.0 mg/kg intraperitoneal against *H. contortus* and/or *T. colubriformis*: 1, 5, 8, 9, 10, 15, and 16.

CLAIMS

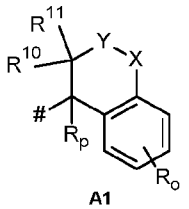
1. A compound of general formula (I):



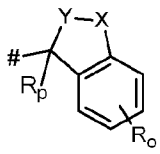
(I)

in which :

A is A1 or A2,



A1



A2

o is 0, 1, 2, 3 or 4,

R is selected from the group consisting of hydrogen, halogen, cyano, nitro, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl, –S(O)-C_1-C_4-halogenoalkyl and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, S, and N-R^9, wherein at least one of X and Y is CR^7R^8, or

X, Y form together a ring member selected from the group consisting of -C(O)-O-, -C(O)-NR^9-, -S(O)-NR^9-, -SO_2-NR^9- and -SO_2-O-,

R^1 is selected from the group consisting of hydrogen, cyano, -CHO, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, C_3-C_6-halogenocycloalkyl having 1 to 5 halogen atoms, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, cyano-C_1-C_4-alkyl, -NH-C_1-C_4-alkyl, -N(C_1-C_4-alkyl)$_2$, NH_2-C_1-C_4-alkyl-, C_1-C_4-alkyl-NH-C_1-C_4-alkyl-, (C_1-C_4-alkyl)$_2$N-C_1-C_4-alkyl-, C_1-C_4-alkyl-C(O)-, C_1-C_4-halogenoalkyl-C(O)- having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C(O)-, benzyloxy-C(O)-, C_1-C_4-alkoxy-C_1-C_4-alkyl-C(O)-, -SO_2-C_1-C_4-alkyl, and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

phenyl-C_1-C_4-alkyl, optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of halogen, -OH, -NO_2, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, –S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

heterocyclyl-C_1-C_4-alkyl, wherein the heterocyclyl substituent is selected from the group consisting of 4- to 10-membered heterocycloalkyl, 5-membered heteroaryl and 6-membered heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of halogen, -OH, -NO_2, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, -S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 1,1-dioxido-1,2-thiazetidin-3-yl, 1,1-dioxido-1,2-thiazetidin-4-yl, 1-oxido-1,2-thiazetidin-3-yl, 1-oxido-1,2-thiazetidin-4-yl, 2-oxido-1,2-oxathietan-3-yl, 2-oxido-1,2-oxathietan-4-yl, 2,2-dioxido-1,2-oxathietan-3-yl, 2,2-dioxido-1,2-oxathietan-4-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 4-thioxoazetidin-2-yl, 2-thioxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-mercaptocyclobutyl, 3-mercaptocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-chlorocyclobutyl, 3-chlorocyclobutyl, 2,2-dichlorocyclobutyl, 3,3-dichlorocyclobutyl, 2-bromocyclobutyl, 3-bromocyclobutyl, 2,2-dibromocyclobutyl, 3,3-dibromocyclobutyl, 2-iodocyclobutyl, 3-iodocyclobutyl, 2,2-diiodocyclobutyl, 3,3-diiodocyclobutyl, 3-methoxyiminocyclobutyl, 2-fluoro-3-(methoxyimino)cyclobutyl, 2,2-difluoro-3-(methoxyimino)cyclobutyl, 2-chloro-3-(methoxyimino)cyclobutyl, 2,2-dichloro-3-(methoxyimino)cyclobutyl, 2-bromo-3-(methoxyimino)cyclobutyl, 2,2-dibromo-3-(methoxyimino)cyclobutyl, 2-iodo-3-(methoxyimino)cyclobutyl, 2,2-diiodo-3-(methoxyimino)cyclobutyl, 3-(hydroxyimino)cyclobutyl, 2-fluoro-3-(hydroxyimino)cyclobutyl, 2,2-difluoro-3-(hydroxyimino)cyclobutyl, 2-chloro-3-(hydroxyimino)cyclobutyl, 2,2-dichloro-3-(hydroxyimino)cyclobutyl, 2-bromo-3-(hydroxyimino)cyclobutyl, 2,2-dibromo-3-(hydroxyimino)cyclobutyl, 2-iodo-3-(hydroxyimino)cyclobutyl, 2,2-diiodo-3-(hydroxyimino)cyclobutyl,

5- to 10-membered heterocycloalkyl, 5-membered heteroaryl and 6-membered heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from the group

consisting of halogen, -OH, -oxo, -NO_2, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, -S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R^3 is hydrogen or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl,

R^7 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^8 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

or R^7 and R^8 together form an oxo group (=O),

or R^7 and R^8 form, together with the carbon atom to which they are attached, a 3- to 6-membered ring selected from the group consisting of C_3-C_6-cycloalkyl and 3- to 6-membered heterocycloalkyl,

R^9 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and C_1-C_4-alkoxy,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^{11} is selected from the group consisting of hydrogen, C_1-C_4-alkyl and C_1-C_4-alkoxy,

or R^{10} and R^{11} form, together with the carbon atom to which they are attached, a 3- to 6-membered ring selected from the group consisting of C_3-C_6-cycloalkyl and 3- to 6-membered heterocycloalkyl,

Q represents phenyl having 1 to 5 halogen atoms,

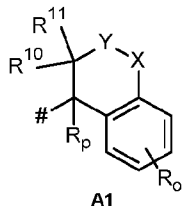
wherein when Y is O, S or N-R^9, none of R^7, R^8, R^{10} and R^{11} is -OH or C_1-C_4-alkoxy, and

wherein when X is O, S or N-R^9, none of R^7 and R^8 is -OH or C_1-C_4-alkoxy,

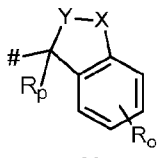
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. The compound according to claim 1, wherein:

A is A1 or A2,



A1



A2

o is 0, 1, 2, 3 or 4,

R is selected from the group consisting of hydrogen, halogen, cyano, nitro, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl, –S(O)-C_1-C_4-halogenoalkyl and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, S, and N-R^9, wherein at least one of X and Y is CR^7R^8, or

X, Y form together a ring member selected from the group consisting of -C(O)-O-, -C(O)-NR^9-, -S(O)-NR^9-, -SO_2-NR^9- and -SO_2-O-,

R^1 is selected from the group consisting of hydrogen, cyano, -CHO, -OH, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_3-C_6-cycloalkyl, C_3-C_6-halogenocycloalkyl having 1 to 5 halogen atoms, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, cyano-C_1-C_4-alkyl, -NH-C_1-C_4-alkyl, -N(C_1-C_4-alkyl)$_2$, NH_2-C_1-C_4-alkyl-, C_1-C_4-alkyl-NH-C_1-C_4-alkyl-, (C_1-C_4-alkyl)$_2$N-C_1-C_4-alkyl-, C_1-C_4-alkyl-C(O)-, C_1-C_4-halogenoalkyl-C(O)- having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C(O)-, benzyloxy-C(O)-, C_1-C_4-alkoxy-C_1-C_4-alkyl-C(O)-, -SO_2-C_1-C_4-alkyl, and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

phenyl-C_1-C_4-alkyl, optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of halogen, -OH, -NO_2, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-

halogenoalkyl having 1 to 5 halogen atoms, –S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms;

heterocyclyl-C_1-C_4-alkyl, wherein the heterocyclyl substituent is selected from the group consisting of 4- to 10-membered heterocycloalkyl, 5-membered heteroaryl and 6-membered heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from the group consisting of halogen, -OH, -NO_2, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, –S-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, –S(O)-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and –SO_2-C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 1,1-dioxido-1,2-thiazetidin-3-yl, 1,1-dioxido-1,2-thiazetidin-4-yl, 1-oxido-1,2-thiazetidin-3-yl, 1-oxido-1,2-thiazetidin-4-yl, 2-oxido-1,2-oxathietan-3-yl, 2-oxido-1,2-oxathietan-4-yl, 2,2-dioxido-1,2-oxathietan-3-yl, 2,2-dioxido-1,2-oxathietan-4-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 4-thioxoazetidin-2-yl, 2-thioxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-mercaptocyclobutyl, 3-mercaptocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-chlorocyclobutyl, 3-chlorocyclobutyl, 2,2-dichlorocyclobutyl, 3,3-dichlorocyclobutyl, 2-bromocyclobutyl, 3-bromocyclobutyl, 2,2-dibromocyclobutyl, 3,3-dibromocyclobutyl, 2-iodocyclobutyl, 3-iodocyclobutyl, 2,2-diiodocyclobutyl, 3,3-diiodocyclobutyl, 3-methoxyiminocyclobutyl, 2-fluoro-3-(methoxyimino)cyclobutyl, 2,2-difluoro-3-(methoxyimino)cyclobutyl, 2-chloro-3-(methoxyimino)cyclobutyl, 2,2-dichloro-3-(methoxyimino)cyclobutyl, 2-bromo-3-(methoxyimino)cyclobutyl, 2,2-dibromo-3-(methoxyimino)cyclobutyl, 2-iodo-3-(methoxyimino)cyclobutyl, 2,2-diiodo-3-(methoxyimino)cyclobutyl, 3-(hydroxyimino)cyclobutyl, 2-fluoro-3-(hydroxyimino)cyclobutyl, 2,2-difluoro-3-(hydroxyimino)cyclobutyl, 2-chloro-3-(hydroxyimino)cyclobutyl, 2,2-dichloro-3-(hydroxyimino)cyclobutyl, 2-bromo-3-(hydroxyimino)cyclobutyl, 2,2-dibromo-3-(hydroxyimino)cyclobutyl, 2-iodo-3-(hydroxyimino)cyclobutyl, 2,2-diiodo-3-(hydroxyimino)cyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2,5-dihydrofuran-3-yl, 2,3-dihydrofuran-3-yl, 4,5-dihydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 2,5-dihydrofuran-2-yl, 2,3-dihydrofuran-2-yl, furan-3-yl, furan-2-yl, tetrahydrothiophen-3-yl, tetrahydrothiophen-2-yl, 2,5-dihydrothiophen-3-yl, 2,3-dihydrothiophen-3-yl, 4,5-dihydrothiophen-3-yl, 4,5-dihydrothiophen-2-yl, 2,5-dihydrothiophen-2-yl, 2,3-dihydrothiophen-2-yl, thiophen-3-yl, thiophen-2-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 4,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-2-yl, 3,4-dihydro-

2H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, 4,5-dihydro-1H-pyrrol-3-yl, 3,4-dihydro-2H-pyrrol-4-yl, 3,4-dihydro-2H-pyrrol-3-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-3-yl, 2H-pyrrol-5-yl, 3H-pyrrol-2-yl, 2H-pyrrol-4-yl, 1H-pyrrol-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 4-alkyl-3-oxopiperazin-1-yl, 4-alkyl-2-oxopiperazin-1-yl, wherein the alkyl is C_1-C_6-alkyl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen, or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$,

R^7 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^8 is selected from the group consisting of hydrogen, -OH, fluorine, C_1-C_4-alkyl and C_1-C_4-alkoxy,

or R^7 and R^8 together form an oxo group (=O),

R^9 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms and C_1-C_4-alkoxy,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^{11} is selected from the group consisting of hydrogen, C_1-C_4-alkyl and C_1-C_4-alkoxy,

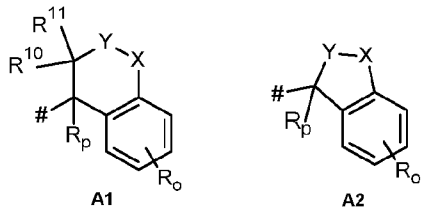
Q represents phenyl having 1 to 5 halogen atoms,

wherein when Y is O, S or N-R^9, none of R^7, R^8, R^{10} and R^{11} is -OH or C_1-C_4-alkoxy, and wherein when X is O, S or N-R^9, none of R^7 and R^8 is -OH or C_1-C_4-alkoxy,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

3. The compound according to claim 1 or 2, wherein:

A is A1 or A2,



o is 0, 1 or 2,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl and C_1-C_4-alkoxy, cyano, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X, Y are independently selected from the group consisting of CR^7R^8, O, S, and N-R^9, wherein at least one of X and Y is CR^7R^8,

R^1 is selected from the group consisting of hydrogen, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, cyano-C_1-C_4-alkyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^9 is hydrogen or C_1-C_4-alkyl,

R^{10} is selected from the group consisting of hydrogen, -OH, C_1-C_4-alkyl and C_1-C_4-alkoxy,

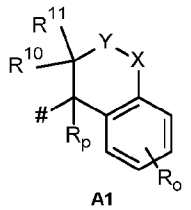
R^{11} is hydrogen,

Q represents phenyl having 1 to 5 substituents independently selected from fluorine, chlorine, or bromine

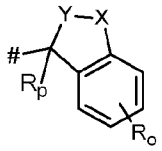
wherein when Y is O, S or N-R^9, R^{10} is not -OH or C_1-C_4-alkoxy, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

4. The compound according to claim 1, 2 or 3, wherein:

A is A1 or A2,



A1



A2

o is 0, 1 or 2,

R is selected from the group consisting of hydrogen, halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, and cyano,

R_p is selected from the group consisting of hydrogen, C_1-C_4-alkyl,

X is selected from the group consisting of CR^7R^8, O, S, and N-R^9,

Y is CR^7R^8 or O,

R^1 is hydrogen or C_1-C_4-alkyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or C_1-C_4-alkyl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, halogen, -OH, $-NH_2$, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms,

R^6 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy,

R^7 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

R^8 is selected from the group consisting of hydrogen and C_1-C_4-alkyl,

or R^7 and R^8 together form an oxo group (=O),

R^9 is hydrogen or C_1-C_4-alkyl,

R^{10} is selected from the group consisting of hydrogen, -OH and C_1-C_4-alkyl,

R^{11} is hydrogen,

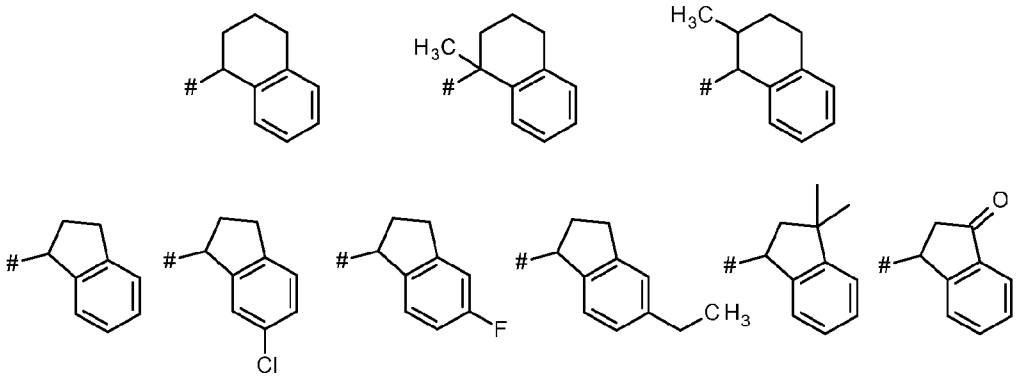
Q represents phenyl having 2 or 3 substituents independently selected from fluorine, chlorine, or bromine

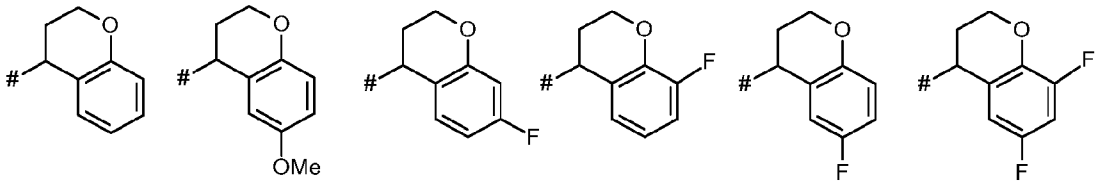
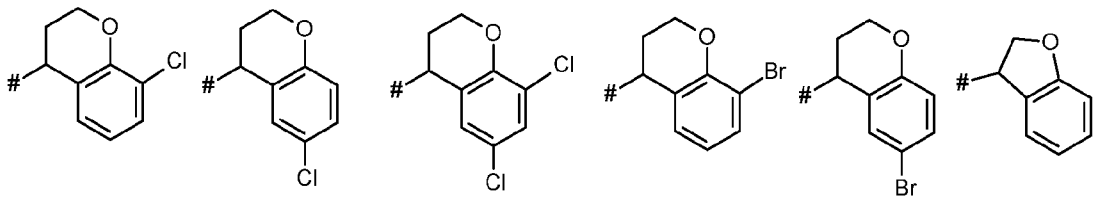
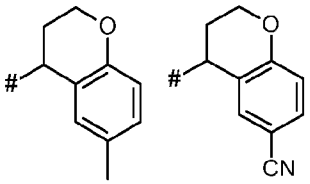
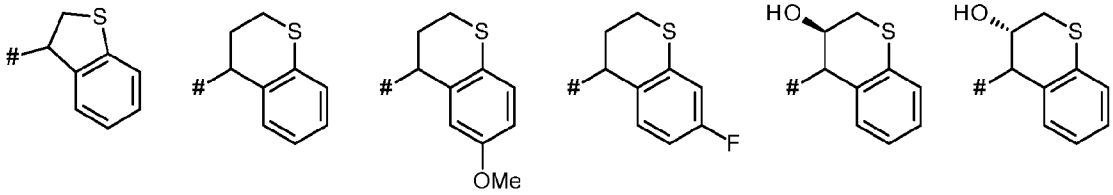
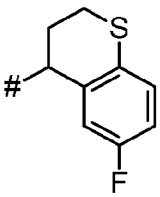
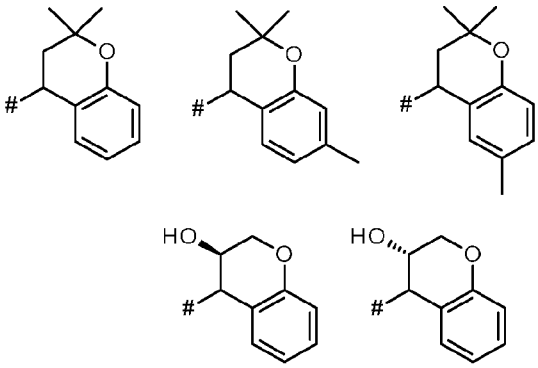
wherein when Y is O, R^{10} is not –OH,

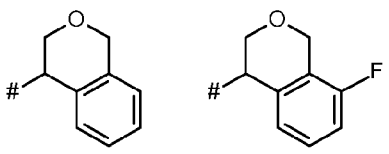
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5. The compound according to claim 1, 2, 3 or 4, wherein:

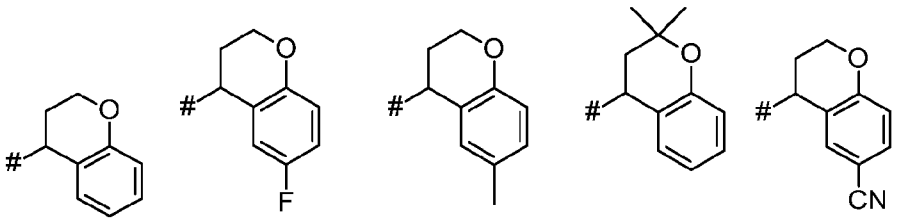
A is selected from the group consisting of

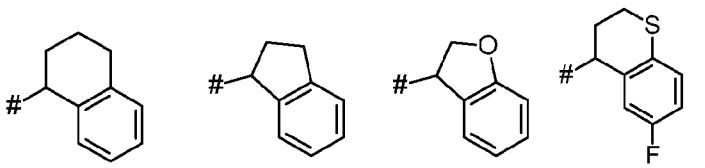




preferably





R[1] is hydrogen or methyl,

R[2] is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R[3] is hydrogen or methyl,

R[4] is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl, methoxy, trifluoromethyl, isopropoxy, and trifluoromethoxy, preferably hydrogen, fluorine, chlorine, methoxy and isopropoxy,

R[5] is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy and NH_2,

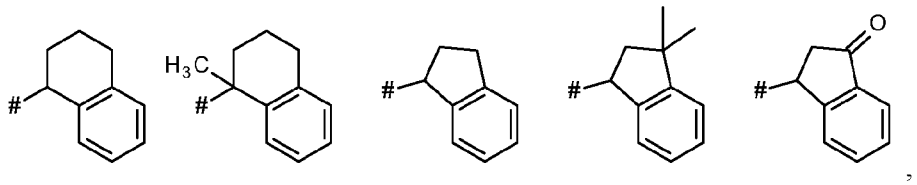
R[6] is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl and methoxy,

Q is selected from the group consisting of 2,3-dichlorophenyl, 3,5-dichlorophenyl, and 2,3,5-trifluorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

6. The compound according to claim 1, 2, 3, 4 or 5, wherein:

A is selected from the group consisting of



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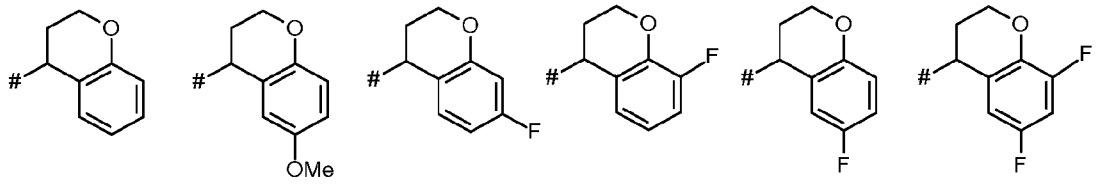

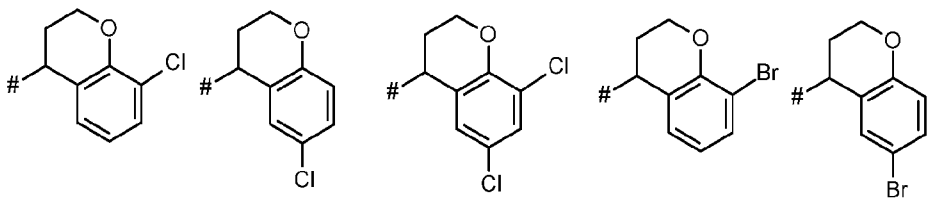

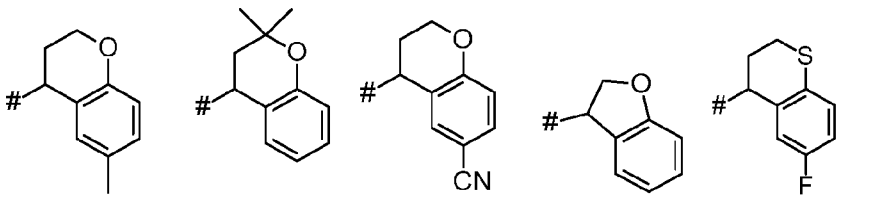

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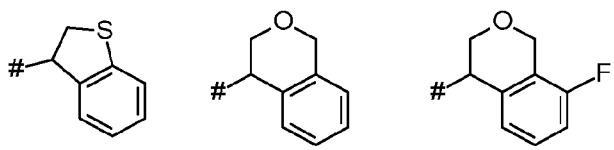
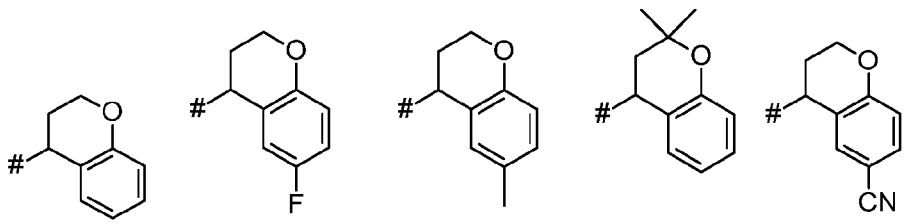
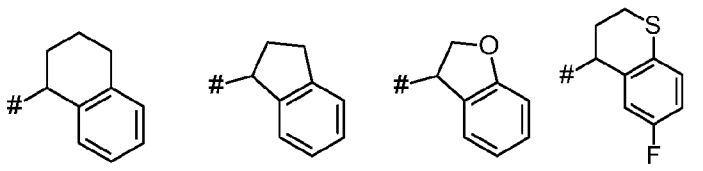


,

preferably





,

R^1 is hydrogen or methyl,

R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 3-thietanyl, 2-thietanyl, 1-oxidothietan-3-yl, 1-oxidothietan-2-yl, 1-imino-1-oxido-1-thietan-3-yl, 1-imino-1-oxido-1-thietan-2-yl, 1,1-dioxidothietan-3-yl, 1,1-dioxidothietan-2-yl, 4-oxoazetidin-2-yl, 2-oxoazetidin-3-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^3 is hydrogen or methyl,

R^4 is selected from the group consisting of hydrogen, chlorine, fluorine, methyl, methoxy, isopropoxy and trifluoromethyl, preferably hydrogen, chlorine, fluorine, methoxy and isopropoxy,

R^5 is selected from the group consisting of hydrogen, chlorine, fluorine, -OH, cyano, methyl, trifluoromethoxy and NH_2,

R^6 is selected from the group consisting of hydrogen, fluorine, chlorine, -OH, cyano, methyl and methoxy,

Q is selected from the group of 2,3-dichlorophenyl, 3,5-dichlorophenyl, and 2,3,5-trifluorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

7. The compound according to claim 1, 2, 3, 4, 5, or 6, wherein:

R^2 is selected from the group consisting of 3-oxocyclobutyl, 3-thietanyl, 1-oxidothietan-3-yl, 1-imino-1-oxido-1-thietan-3-yl, 1,1-dioxidothietan-3-yl, 2-oxoazetidin-3-yl, 3-hydroxycyclobutyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 3-oxopiperazin-1-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

Q is 2,3,5-trifluorophenyl or 3,5-dichlorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

8. The compound according to claim 1, 2, 3, 4, 5, 6, or 7, wherein:

R^2 is selected from the group consisting of 3-oxocyclobutyl, 3-thietanyl, 1-oxidothietan-3-yl, 1-imino-1-oxido-1-thietan-3-yl, 1,1-dioxidothietan-3-yl, 2-oxoazetidin-3-yl, 3-hydroxycyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-3-yl, 1-methylpyrrolidine-2-yl, 1-methylpyrrolidine-3-yl, 5-oxopyrrolidine-3-yl, 2-oxopyrrolidine-3-yl, 5-oxopyrrolidine-2-yl, tetrahydropyran-4-yl, 2-oxa-5-azabicyclo[4.1.0]heptan-5-yl, 3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl,

R^4 is selected from the group consisting of hydrogen, halogen, -OH, cyano, C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-halogenoalkyl having 1 to 5 halogen atoms, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenoalkoxy having 1 to 5 halogen atoms, C_1-C_4-alkyl-C(O)-, -S-C_1-C_4-alkyl, -S(O)-C_1-C_4-alkyl, -SO_2-C_1-C_4-alkyl, preferably hydrogen, halogen and C_1-C_4-alkoxy, more preferably fluorine, chlorine, methoxy and isopropoxy,

Q is 2,3,5-trifluorophenyl or 3,5-dichlorophenyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

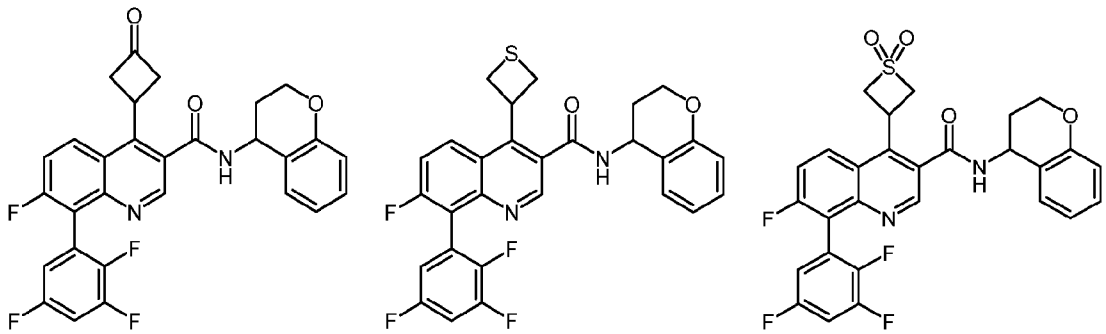
9. The compound according to claim 1, 2, 3, 4, 5, 6, 7, or 8, wherein:

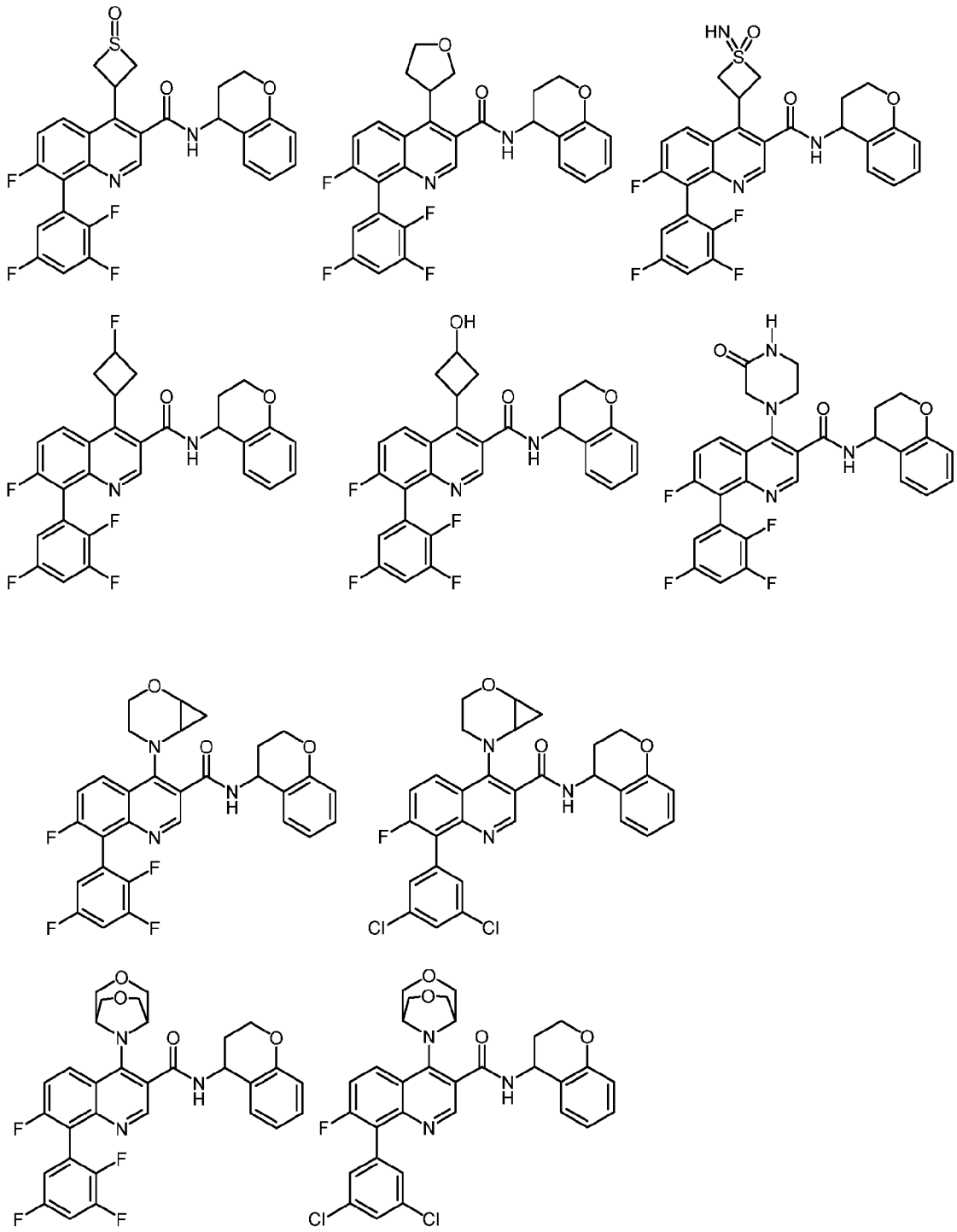
R^2 is 3-hydroxycyclobutyl, 3-fluorocyclobutyl, tetrahydrofuran-3-yl or 3-oxocyclobutyl,

Q is 2,3,5-trifluorophenyl or 3,5-dichlorophenyl

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

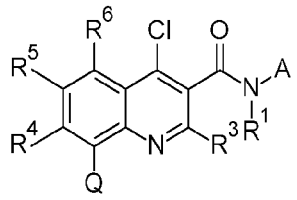
10. The compound according to claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, wherein the compound is selected from





or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

11. A method of preparing a compound of general formula (I) according to any one of claims 1 to 10, said method comprising the step of allowing an intermediate compound of general formula **1N** :



1N,

in which A, R^1, R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) according to any one of claims 1 to 10,

to react with a compound of general formula **1F** :

$R^{2\#}H$

1F,

in which $R^{2\#}$ is selected from the group consisting of methyl 2,2-dimethoxycyclobutane-1-carboxylate, methyl 3,3-dimethoxycyclobutane-1-carboxylate, methyl 2,2-bis(methylthio)cyclobutane-1-carboxylate, methyl 3,3-bis(methylthio)cyclobutane-1-carboxylate, ethyl thietane-3-carboxylate, ethyl thietane-2-carboxylate, ethyl oxetane-3-carboxylate, ethyl oxetane-2-carboxylate,

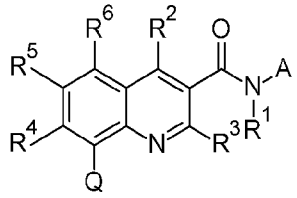
methyl 2-fluorocyclobutane-1-carboxylate, methyl 3-fluorocyclobutane-1-carboxylate, methyl 2,2-difluorocyclobutane-1-carboxylate, methyl 3,3-difluorocyclobutane-1-carboxylate,

methyl tetrahydrofuran-2-carboxylate, methyl tetrahydrofuran-3-carboxylate, methyl furan-3-carboxylate, methyl furan-2-carboxylate,

methyl tetrahydrothiophen-3-carboxylate, methyl tetrahydrothiophen-2-carboxylate, methyl thiophen-3-carboxylate, methyl thiophen-2-carboxylate, methyl 1-methylpyrrolidine-2-carboxylate, methyl 1-methylpyrrolidine-3-carboxylate, methyl 5-oxopyrrolidine-3-carboxylate, methyl 2-oxopyrrolidine-3-carboxylate, methyl 5-oxopyrrolidine-2-carboxylate, methyl tetrahydropyran-4-carboxylate,

followed by a saponification reaction in the presence of aqueous alkali metal hydroxide and optionally an oxidation step

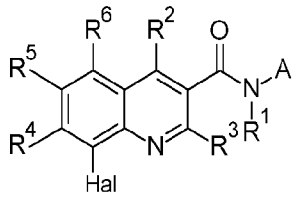
thereby giving a compound of general formula (I) :



(I),

in which A, R^1, R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) according to any one of claims 1 to 10 and R^2 is selected from the group consisting of 2-oxocyclobutyl, 3-oxocyclobutyl, 2-thiooxocyclobutyl, 3-thiooxocyclobutyl, 3-thietanyl, 2-thietanyl, oxetan-3-yl, oxetan-2-yl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, furan-3-yl, furan-2-yl, tetrahydrothiophen-3-yl, tetrahydrothiophen-2-yl, thiophen-3-yl, thiophen-2-yl, 1-methylpyrrolidin-2-yl, 1-methylpyrrolidin-3-yl, 5-oxopyrrolidin-3-yl, 2-oxopyrrolidin-3-yl, 5-oxopyrrolidin-2-yl, and tetrahydropyran-4-yl.

or the step of allowing an intermediate compound of general formula **1T** :



1T,

in which A, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for the compound of general formula (I) according to any one of claims 1 to 10, and in which Hal is halogen, particularly chlorine, bromine or iodine,

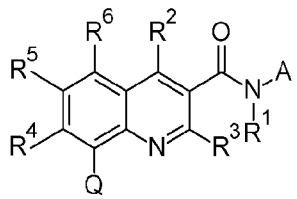
to react with a compound of general formula **1H** :

$$Q\text{-}B(OR)_2$$

1H,

in which Q is 2,3,5-trifluorophenyl, and each R may be individually H or Me or both R are pinacolate,

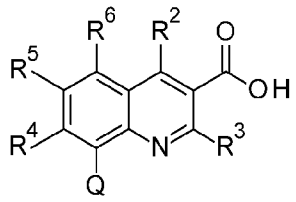
thereby giving a compound of general formula (I) :



(I),

in which A, R^1, R^2, R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) according to any one of claims 1 to 10,

or the step of allowing an intermediate compound of general formula **1W** :



1W,

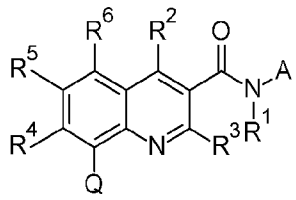
in which Q, R^2, R^3, R^4, R^5 and R^6 are as defined for the compound of general formula (I) according to any one of claims 1 to 10,

to react with a compound of general formula **1M** :

1M,

in which R^1 and A are as defined for the compound of general formula (I) according to any one of claims 1 to 10,

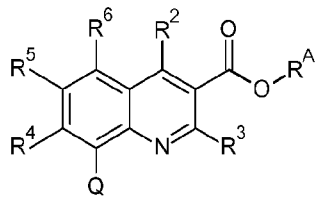
thereby giving a compound of general formula (I) :



(I),

in which A, R^1, R^2, R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) according to any one of claims 1 to 10,

12. A compound of general formula (II):



(II),

in which :

R^2 is OH, Cl, Br or as defined for the compound of general formula (I) according to any one of claims 1 to 10,

R^3, R^4, R^5, R^6, and Q are as defined for the compound of general formula (I) according to any one of claims 1 to 10, and

R^A is H or C_1-C_4-alkyl,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

13. A pharmaceutical composition comprising a compound of general formula (I) according to any one of claims 1 to 10 and one or more pharmaceutically acceptable excipients.

14. A compound of general formula (I) according to any one of claims 1 to 10 or a pharmaceutical composition according to claim 13 for use in the control, treatment and/or prevention of a disease.

15. The compound or the pharmaceutical composition according to claim 14, wherein the disease is a helminthic infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/074866

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/12 C07D405/14 C07D409/14 C07D413/14 C07D498/08
A61P33/10 A61K31/4709
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/215182 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 14 November 2019 (2019-11-14) cited in the application	1-8, 10-15
Y	abstract page 51, line 18 - page 67, line 35 * scheme 1-5 *; pages 72-76 examples 1-22 pages 103-105; compounds 2a-2c claims 1-18	9

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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 :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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
7 December 2022	15/12/2022

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	Dunet, Guillaume

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/074866

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/087036 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 17 May 2018 (2018-05-17) cited in the application abstract * schemes 1a-4 *; pages 140-147 examples 1-695 pages 341-345; tables 3a-3c claims 1-15	1-15
Y	WO 2019/115768 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 20 June 2019 (2019-06-20) abstract examples 1, 2 claims 1-15	1-15
Y	WO 2020/131629 A1 (ELANCO TIERGESUNDHEIT AG [CH]; ELANCO US INC [US]) 25 June 2020 (2020-06-25) abstract examples 1.1-7.1. claims 1-18	1-15
Y	WO 2020/247747 A1 (ELANCO TIERGESUNDHEIT AG [CH]; ELANCO US INC [US]) 10 December 2020 (2020-12-10) abstract examples 1.1.-8.2 claims 1-27	1-15
Y	WO 2020/131631 A1 (ELANCO TIERGESUNDHEIT AG [CH]; ELANCO US INC [US]) 25 June 2020 (2020-06-25) abstract examples 1.1-8.2 claims 1-21	1-15
Y	WO 2021/018839 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 4 February 2021 (2021-02-04) abstract examples I1-I15 claims 1-15	1-15
Y	WO 2019/025341 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 7 February 2019 (2019-02-07) abstract examples 1-49 claims 1-18	1-15
Y	WO 2019/002132 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 3 January 2019 (2019-01-03) abstract examples T1-1-T6-4 claims 1-15	1-15

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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		WO 2018087036 A1	17-05-2018
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