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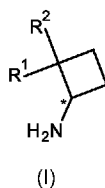
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(54) Title: PROCESS FOR THE PREPARATION OF ENANTIOMERICALLY ENRICHED ALIPHATIC AMINES

(57) Abstract: The present invention relates to a process for the preparation of enantiomerically enriched cyclobutylamines of formula (I) from α -tertiary cyclobutanones and reacting said enantiomerically enriched cyclobutylamines to enantiomerically enriched cyclobutylamides. Such compounds are useful intermediates in the synthesis of microbiocidal thiazole compounds.



PROCESS FOR THE PREPARATION OF ENANTIOMERICALLY ENRICHED ALIPHATIC AMINES

The present invention relates to a process for the preparation of enantiomerically enriched cyclobutylamines from α -tertiary cyclobutanones and reacting said enantiomerically enriched cyclobutylamines to enantiomerically enriched cyclobutylamides. Such compounds are useful intermediates in the synthesis of microbiocidal thiazole compounds, which have microbiocidal activity, in particular fungicidal activity. Such compounds are known, for example, from WO2010/012793, WO2017/207362, WO2019/105933, WO2020/109511, WO2020/109509, WO2021/244952 and processes for making such compounds are also known.

Enantiomerically enriched aliphatic amines are ubiquitous in agrochemicals and are extremely valuable as they are important building blocks for active ingredients in agrochemicals. The synthesis of enantiomerically enriched aliphatic amines is known from the prior art. Despite the widespread relevance of chiral amines, traditional synthetic methods such as resolution are still being used. To overcome their intrinsic limitations, the use of catalytic methods has been widely investigated in recent decades, with asymmetric catalysis being a key research field in modern synthetic chemistry. Although biocatalytic and organocatalytic strategies have gained importance, the catalytic approach based on transition metals is still, arguably, the method most widely used. Transition metal-catalyzed reductive amination represents a step-economic and efficient strategy by directly converting carbonyl compounds into amines in the presence of amine sources and reductants.

However, most of the existing processes the synthesis of chiral amines from prochiral ketones involve multistep procedures or the use of expensive stoichiometric amounts of reagents, and most of the atom-efficient processes are effective for aryl-alkyl ketones and not successfully applicable for the synthesis of enantiomerically enriched amines derived from alkyl-alkyl ketones, and in particular not from α -tertiary alkyl-alkyl ketones

One known approach to enantiomerically enriched amines from the corresponding prochiral ketones was reported in *J. Am. Chem. Soc.* **2018**, 140, 355-361 using ammonia and hydrogen, or in *J. Am. Chem. Soc.* **2018**, 140, 2024-2027 by using stoichiometric amounts of ammonium salt and hydrogen. However, these methods are effective for amines derived from aryl-alkyl ketones, whereas poor yield and enantiocontrol were obtained for the conversion of alkyl-alkyl ketones to the corresponding chiral amines with these catalytic systems.

Another known synthesis involves the conversion of ketones and cyclic ketones to enantiomerically enriched amines and cyclic amines via the use of chiral auxiliaries in a three-step sequence that involves: a) reaction of ketones or cyclic ketones with chiral auxiliaries to produce a chiral imine; b) diastereoselective reduction of said chiral imines under various conditions; c) and subsequent removal of the chiral auxiliary. Examples of widely used chiral auxiliaries are Ellman's tert-butyl sulfinamides as disclosed in *J. Org. Chem.* **2015**, 80, 11441-11446, or in *Eur. J. Org. Chem.* **2014**, 7034-7038. This process offers a more scalable process with better safety profile, but it consists of a plurality of component operations, and as such is technologically difficult

to control in the case of sizable batches, and a large amount of waste is generated. Therefore, such a process is not ideal for large scale production and therefore a new, more efficient synthesis method is desired to avoid the generation of undesirable by-products.

A further known process for the preparation of enantiomerically enriched cyclic amines involves palladium-catalyzed asymmetric hydrogenation of an in situ-generated imine sulfonamide from an acid-catalyzed aza-Pinacol rearrangement, providing efficient access to chiral cyclic arylsulfonamides, followed by removal of the arylsulfonamide group under Birch dissolving metal reduction conditions, as for example disclosed in CN105585516 and *J. Am. Chem. Soc.* **2014**, 136, 15837–15840. These reactions are reported to produce high levels of enantioselectivity but require the use of expensive starting materials and the use of precious or highly reactive, and stoichiometric metals, which is hazardous and technically difficult to control, and generates a large amount of wastewater. As such, an industrial synthesis employing these conditions is cumbersome and expensive making it not suitable for industrial production without great difficulties.

Lately a ruthenium catalyzed asymmetric reductive amination (ARA) of purely aliphatic ketones with good yields and moderate enantioselectivities was reported in *Eur. J. Org. Chem.* **2020**, 4796 – 4800. In this report they achieved an e.e. of up to 74% for chiral aliphatic primary amines by using a 1:1 mixture of toluene/methanol as solvent and at least stoichiometric amounts of ammonium iodide in the ruthenium catalyzed ARA. However, this system did not work for α -tertiary aliphatic ketones.

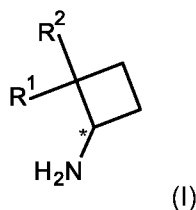
Therefore, there is a need for an atom-efficient approach for the synthesis of enantiomerically pure or enriched chiral aliphatic amines from α -tertiary alkyl-alkyl ketones. Accordingly, there is a need in the field for better processes to synthesize enantiomerically enriched cyclobutylamines from α -tertiary alkyl-alkyl ketones, and their corresponding enantiomerically enriched cyclobutylamide compounds, especially those at scale. Such processes are advantageous in that they will improve the impurity profile, lower commercial manufacturing costs, and improve efficiency and atom economy.

It is an object of the present invention to provide a novel process for the synthesis of enantiomerically enriched cyclobutylamines from α -tertiary alkyl-alkyl ketones, in particular from α -tertiary cyclobutanones, and their corresponding enantiomerically enriched cyclobutylamide compounds, which is more efficient and economical as known in the prior art.

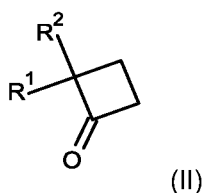
Surprisingly, we have now found that such enantiomerically enriched 2,2-disubstituted cyclobutylamines and cyclobutylamides can be prepared a reaction between a compound of 2,2-disubstituted cyclobutanones with ammonia, an ammonium salt and hydrogen (H_2) in presence of a chiral transition metal catalyst, which can be further reacted with an activated heteroarylaminothiazole carboxylic acid derivative to produce enantiomerically enriched 2,2-disubstituted cyclobutylamides. Such a process is more convergent and very atom efficient, which may be more cost effective and produce less waste products.

According to the first aspect of the present invention, there is provided a process for the preparation of a compound of formula (I):

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wherein R^1 and R^2 are independently selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl; or R^1 and R^2 form with the carbon to which they are attached a C_3 - C_6 -cycloalkyl ring; said process comprising reaction of a compound of formula (II)

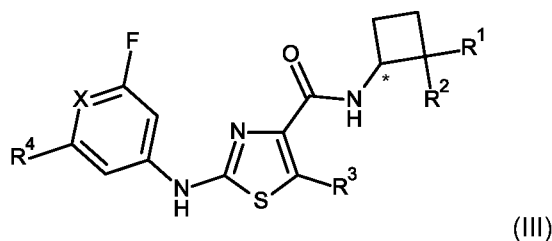


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wherein R^1 and R^2 are defined as for compounds of formula (I),

in the presence of ammonia, an ammonium salt and hydrogen in the presence of a chiral transition metal catalyst to produce a compound of formula (I), wherein said compound of formula (I) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center.

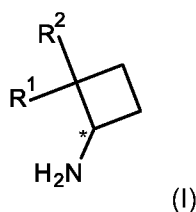
10 According to a second aspect of the invention, there is provided a process for the preparation of a compound of formula (III):



wherein

X is selected from CH, or N;

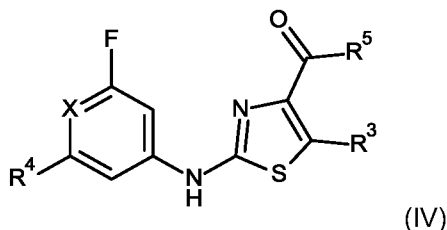
15 R^1 and R^2 are independently selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl; or R^1 and R^2 form with the carbon to which they are attached a C_3 - C_6 -cycloalkyl ring; R^3 is selected from hydrogen, or C_1 - C_3 -alkyl; and R^4 is selected from hydrogen, or halogen; said process comprising the reaction of a compound of formula (I)



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wherein R^1 and R^2 are defined as for compounds of formula (III), and wherein said compound of formula (I) is the (*S*) or (*R*) enantiomer, wherein the asterisk marks the stereogenic center;

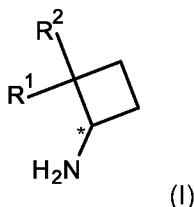
with a compound of formula (IV)



- 5 wherein R^3 , R^4 , and X are defined as for compounds of formula (III), and wherein R^5 is selected from hydroxy, halogen, or OR^6 ; wherein R^6 is selected from C_1 - C_6 -alkyl, C_3 - C_6 -alkylcarbonyl, C_3 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylsulfonyl, benzoyl, heteroarylcarbonyl, phenylsulfonyl, heteroarylsulfonyl, or heteroaryl, wherein said heteroaryl is a 5 to 6 membered aromatic heterocycle which comprises 1, 2, 3, or 4 heteroatoms individually selected from N, O or S, and wherein said phenyl, benzoyl and heteroaryl are
- 10 unsubstituted or substituted with 1, 2, or 3 substituents individually selected from halogen, C_1 - C_3 -alkyl, or C_1 - C_3 -alkoxy; and

wherein said compound of formula (III) is the (*S*) or (*R*) enantiomer, wherein the asterisk marks the stereogenic center.

According to a third aspect of the invention, there is provided a compound of formula (I)



- 15 wherein R^1 and R^2 are independently selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl, or R^1 and R^2 form with the carbon to which they are attached a C_3 - C_6 -cycloalkyl ring; and wherein the compound of formula (I) is the (*S*) or (*R*) enantiomer, wherein the asterisk marks the stereogenic center.
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In one embodiment the compound of formula (I), is the (*S*) enantiomer.

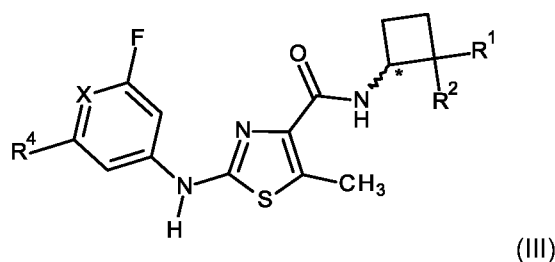
In one embodiment, the compound of formula (I), or any of the preferred embodiments, is the (*S*) enantiomer.

In another embodiment the compound of formula (I) is the (*R*) enantiomer.

- In another embodiment, the compound of formula (I), or any of the preferred embodiments, is the (*R*) enantiomer.
- 25

According to a fourth aspect of the invention, there is provided a compound of formula (III)

5



wherein

X is selected from CH, or N;

R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl, or

5 R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring;

R³ is selected from hydrogen, or C₁-C₃-alkyl;

R⁴ is selected from hydrogen, or halogen; and

wherein the compound of formula (III) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center.

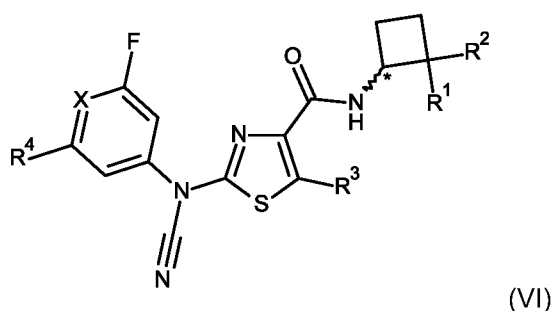
10 In one embodiment the compound of formula (III) is the (S) enantiomer.

In one embodiment, the compound of formula (III), or any of the preferred embodiments, is the (S) enantiomer.

In another embodiment the compound of formula (III) is the (R) enantiomer.

In another embodiment, the compound of formula (III), or any of the preferred embodiments, is the (R) enantiomer.

15 According to a fifth aspect of the invention, there is provided a compound of formula (VI)



wherein

X is selected from CH, or N;

R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl, or

20 R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring;

R³ is selected from hydrogen, or C₁-C₃-alkyl;

R⁴ is selected from hydrogen, or halogen; and

wherein the compound of formula (VI) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center.

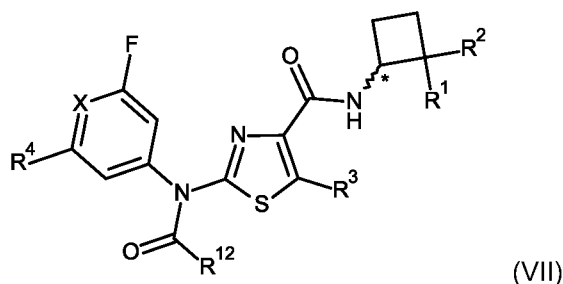
25 In one embodiment the compound of formula (VI) is the (S) enantiomer.

In one embodiment, the compound of formula (VI), or any of the preferred embodiments, is the (*S*) enantiomer.

In another embodiment the compound of formula (VI) is the (*R*) enantiomer.

In another embodiment, the compound of formula (VI), or any of the preferred embodiments, is the (*R*) enantiomer.

- 5 According to a sixth aspect of the invention, there is provided a compound of formula (VII)



wherein

X is selected from CH, or N;

R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl; or

- 10 R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring;

R³ is selected from hydrogen, or C₁-C₃-alkyl;

R⁴ is selected from hydrogen, or halogen;

R¹² is selected from hydrogen, C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxyC₁-C₂-alkyl, C₃-C₄-cycloalkyl, C₁-C₂-alkoxy-C₁-C₂-alkoxy, C₁-C₃-alkoxycarbonyl-C₁-C₃-alkyl, C₁-C₂-alkoxycarbonyloxy-C₁-C₂-alkyl, C₁-C₂-alkylcarbonyloxy-C₁-C₂-alkyl, C₃-C₄-alkynyloxy, C₁-C₃-alkylsulfanyl, or

- 15 heterocyclyl, wherein said heterocyclyl moiety is a 4-, 5- or 6-membered non-aromatic monocyclic ring comprising 1 heteroatom selected from oxygen; and

wherein the compound of formula (VII) is the (*S*) or (*R*) enantiomer, wherein the asterisk marks the stereogenic center.

- 20 In one embodiment the compound of formula (VII) is the (*S*) enantiomer.

In one embodiment, the compound of formula (VII), or any of the preferred embodiments, is the (*S*) enantiomer.

In another embodiment the compound of formula (VII) is the (*R*) enantiomer.

In another embodiment, the compound of formula (VII), or any of the preferred embodiments, is the (*R*) enantiomer.

- 25 According to a seventh aspect of the invention, there is provided an agrochemical composition comprising a fungicidally effective amount of a compound of formula (III), (VI) or (VII) according to the invention. Such an agricultural composition may further comprise at least one additional active ingredient and/or an agrochemically-acceptable dilutant or carrier.

According to an eighth aspect of the invention, there is provided a method of controlling or preventing infestation of useful plants by phytopathogenic microorganisms, wherein a fungicidally effective amount of a compound of formula (III), (VI) or (VII) according to the invention, or a composition comprising said compound is applied to the plants, to parts thereof or the locus thereof.

- 5 According to a ninth aspect of the invention, there is provided the use of a compound of formula (III), (VI) or (VII) according to the invention as a fungicide. According to this particular aspect of the invention, the use may exclude methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body.

- 10 It has been found that the processes according to the invention result in high yielding syntheses of the enantiomerically enriched compounds according to formula (I). Furthermore, the processes according to the invention may provide accelerated reaction rates. Additionally, the processes according to the invention are suitable for the large-scale preparation of compounds according to formulae (I).

- Further it has been surprisingly found that the compounds of formula (III), (VI) and (VII) have, for practical purposes, a very advantageous level of biological activity for protecting plants against diseases that are caused by fungi.
- 15

- Compounds of formula (I), (III) or (IV) which have at least one basic centre can form, for example, acid addition salts, for example with strong inorganic acids such as mineral acids, for example perchloric acid, sulfuric acid, nitric acid, nitrous acid, a phosphorus acid or a hydrohalic acid, with strong organic carboxylic acids, such as C₁-C₄-alkanecarboxylic acids which are unsubstituted or substituted, for example by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid or phthalic acid, such as hydroxycarboxylic acids, for example ascorbic acid, lactic acid, malic acid, tartaric acid or citric acid, or such as benzoic acid, or with organic sulfonic acids, such as C₁-C₄ alkane- or aryl sulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluene sulfonic acid. Compounds of formula (I) which have at least one acidic group
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- can form, for example, salts with bases, for example mineral salts such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower-alkylamine, for example ethyl-, diethyl-, triethyl- or dimethyl propylamine, or a mono-, di- or trihydroxy-lower-alkylamine, for example mono-, di- or triethanolamine.
- 25

- 30 In each case, the compounds of formula (I), (III) or (IV) according to the invention are in free form, in oxidized form as a N-oxide or in salt form, e.g., an agronomically usable salt form. N-oxides are oxidized forms of tertiary amines or oxidized forms of nitrogen containing heteroaromatic compounds. They are described for instance in the book "Heterocyclic N-oxides" by A. Albini and S. Pietra, CRC Press, Boca Raton 1991.

- The compounds of formula (I), (III), or (IV) according to the invention also include hydrates which may be formed during the salt formation.
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As used herein, the term "hydroxyl" or "hydroxy" means an -OH group.

As used herein, the term "halogen" or "halo" refers to fluorine (fluoro), chlorine (chloro), bromine (bromo) or iodine (iodo), preferably fluorine, chlorine, or bromine. This also applies, correspondingly, to halogen in combination with other meanings, such as haloalkyl, haloalkenyl, haloalkynyl, haloalkoxy, and halocycloalkyl.

As used herein, the term "C₁-C_n-alkyl" refers to a saturated straight-chain or branched hydrocarbon radical attached via any of the carbon atoms having 1 to n carbon atoms, for example, any one of the radicals methyl, ethyl, n-propyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2, 2-dimethylpropyl, 1-ethylpropyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, or 1-ethyl-2-methylpropyl.

As used herein, the term "C₃-C_n-cycloalkyl" refers to three (3) to n membered cycloalkyl radical such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, the term "C₁-C_n-alkoxy" refers to a straight-chain or branched saturated alkyl radical having one (1) to n carbon atoms (as mentioned above) which is attached via an oxygen atom, i.e., for example, any one of the radicals methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 1-methylpropoxy, 2-methylpropoxy, and 1,1-dimethylethoxy. The term "C₂-C_n-alkenyloxy" as used herein refers to a straight-chain or branched alkenyl chain having two (2) to n carbon atoms (as mentioned above) which is attached via an oxygen atom.

As used herein, the term "C₁-C_n-alkylsulfonyl-C₁-C_n-alkyl" refers to an a C₁-C_n-alkyl radical substituted with a C₁-C_nalkylsulfonyl group.

As used herein, the term "C₁-C_n-alkylcarbonyl" refers to a C₁-C_n-alkyl group linked through the carbon atom of a carbonyl (C=O) group.

As used herein, the term "C₁-C_n-alkoxycarbonyl" refers to a C₁-C_n-alkoxy moiety linked through a carbon atom of a carbonyl (or C=O) group.

As used herein, the term "benzoyl" refers to a phenyl group linked through the carbon atom of a carbonyl (C=O) group.

As used herein, the term "heteroarylcarbonyl" refers to a heteroaryl group linked through the carbon atom of a carbonyl (C=O) group.

As used herein, the term "phenylsulfonyl" refers to a phenyl group substituted with a C₁-C_nalkylsulfonyl group.

As used herein, the term "heteroarylsulfonyl" refers to a heteroaryl group substituted with a C₁-C_nalkylsulfonyl group.

As used herein, the term "heteroaryl" refers to a 5- or 6-membered aromatic monocyclic ring radical which comprises 1, 2, 3 or 4 heteroatoms individually selected from N, O and S. Examples of heteroaryl include, but are not limited to, furanyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, pyrimidyl or pyridyl. The term "heteroaryl-C₁-C_n-alkyl" or "heteroaryl-

C₃-C_n-cycloalkyl" refers to an C₁-C_n-alkyl or C₃-C_n-cycloalkyl radical respectively substituted by a heteroaryl group. The heteroaryl-C₁-C_n-alkyl or heteroaryl-C₃-C_n-cycloalkyl radical may be substituted on heteroaryl, alkyl and/or cycloalkyl group as appropriate.

The term "enantiomerically enriched" means that one of the enantiomers of the compound is present in excess in comparison to the other enantiomer. This excess will hereafter be referred to as enantiomeric excess, e.e. or ee. The ee may be determined by chiral GC, HPLC or SFC analysis. The ee is equal to the difference between amounts of enantiomers divided by the sum of the amounts of the enantiomers, which quotient can be expressed as a percentage after multiplication by 100. The ee can also be referred to as the absolute difference between the mole fraction of each enantiomer in the mixture. For example, when there is an isomer with an enantiomeric excess (e.e.) of 40% this means that the mole fraction (or percent) of such excess isomer is 70%. Accordingly, in one embodiment, the term "enantiomerically enriched" also refers to an enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%. The term "enantiomeric excess" can be used interchangeably with "ee" or "e.e." or "enantiomeric ratio".

As used herein, the term "activating agent" refers to a compound which reversibly or irreversibly transfers a molecule into a nearly identical chemical or physical state, with the defining characteristic being that this resultant state exhibits an increased propensity to undergo a specified chemical reaction. An activating agent may include, but not limited to benzoyl chloride, 2-methylpropanoyl chloride, or 2,2-dimethylpropanoyl chloride.

As used herein, the term "peptide coupling agent" refers to a reagent used in peptide coupling chemistry to generate an active ester from a carboxylic acid. A peptide coupling agent may include, but not limited to carbodiimides such as dicyclohexyl-carbodiimide (DCC) and diisopropylcarbodiimide (DIC), aminium/uronium or phosphonium salt of a non-nucleophilic anion (tetrafluoroborate or hexafluorophosphate), e.g., aminium/uronium reagents include **HATU** (hexafluorophosphate azabenzotriazole tetramethyl uronium), (HOAt), e.g., phosphonium reagents include PyBOP ((benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate) and PyAOP ((7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate)), or propanephosphonic acid anhydride.

As used herein the term "mixed anhydride" refers to a carboxylic acid anhydride that has the following general structural formula $R^x C(=O)OC(=O)R^y$, $R^x C(=O)OC(=O)OR^y$, or $R^x C(=O)OS(=O)_2 R^y$, wherein R^x and R^y are the same or different and are selected from alkyl or aryl. They are further classified into symmetrical and unsymmetrical anhydrides based on their geometry.

As used herein the term "leaving group", refers to an atom or group of atoms that detaches from the main or residual part of a substrate during a reaction or elementary step of a reaction. Leaving groups are generally anions or neutral species, departing from neutral or cationic substrates, respectively, though in rare cases, cations leaving from a dicationic substrate are also known. Common anionic leaving groups are halides such as chlorine, bromine, and iodine and sulfonate esters such as mesylate (MsO^-) or tosylate (TsO^-), while water (H_2O), alcohols ($R-OH$), and amines (R_3N) are common neutral leaving groups.

As used herein, the term "α-tertiary cyclobutanones" refers to a cyclobutanone compound possessing a quaternary carbon center in α -position to the ketone-group.

As used herein, the "asterisk" marks the stereogenic center of the compounds, if not otherwise indicated.

As used herein, the term "room temperature" or "RT" or "rt" refer to a temperature of about 15° C to about 35° C. For example, rt can refer to a temperature of about 20° C to about 30° C.

As used herein, the term "one-pot synthesis" refers to a synthesis, where reagents are added to the same reaction vessel or reactor without isolation of the intermediate stages and /or without work-up. This is a strategy to improve the efficiency of a chemical reaction in which a reactant is subjected to successive chemical reactions in just one reactor. The term "one-pot synthesis" can be used interchangeably with "sequential one-pot synthesis" or "one-pot process".

As used herein, the term "controlling" refers to reducing the number of pests, eliminating pests and/or preventing further pest damage such that damage to a plant or to a plant derived product is reduced.

As used herein, the term "pest" refers to insects, and molluscs that are found in agriculture, horticulture, forestry, the storage of products of vegetable origin (such as fruit, grain, and timber); and those pests associated with the damage of man-made structures. The term pest encompasses all stages in the life cycle of the pest.

As used herein, the term "effective amount" refers to the amount of the compound, or a salt thereof, which, upon single or multiple applications provides the desired effect.

An effective amount is readily determined by the skilled person in the art, using known techniques and by observing results obtained under analogous circumstances. In determining the effective amount, a number of factors are considered including, but not limited to the type of plant or derived product to be applied; the pest to be controlled and its lifecycle; the particular compound applied; the type of application; and other relevant circumstances.

The process of the present invention can be carried out in separate process steps, wherein the intermediate compounds can be isolated at each stage. Alternatively, the process can be carried out as a one-pot synthesis wherein the intermediate compounds produced are not isolated. Thus, it is possible for the process of the present invention to be conducted in a batch wise or continuous fashion.

The following list provides definitions, including preferred definitions, for substituents R¹, R², R³, R⁴, R⁵, R⁶, and X with reference to the compounds of formula (I), (II), (III) and (IV) of the present invention. For any one of these substituents, any of the definitions given below may be combined with any definition of any other substituent given below or elsewhere in this document.

In one embodiment of the invention X is selected from CH, or N. In one embodiment X is CH. In another embodiment X is N. Preferably X is N.

In one embodiment of the invention R^1 is selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl. Preferably R^1 is C_1 - C_3 -alkyl, or cyclopropyl or cyclobutyl. More preferably R^1 is C_1 - C_3 -alkyl. Even more preferably, R^1 is methyl, or ethyl. Still more preferably, R^1 is methyl.

5 In one embodiment of the invention R^2 is selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl. Preferably R^2 is hydrogen, C_1 - C_3 -alkyl, or cyclopropyl or cyclobutyl. More preferably R^2 is C_1 - C_3 -alkyl. Even more preferably R^2 is methyl, or ethyl. Still more preferably R^2 is methyl.

10 In one embodiment of the invention, R^1 and R^2 are independently selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl. Preferably R^1 and R^2 are independently selected from C_1 - C_3 -alkyl, or cyclopropyl or cyclobutyl. More preferably R^1 and R^2 are independently selected from or C_1 - C_3 -alkyl. Even more preferably R^1 and R^2 are methyl.

In one embodiment of the invention R^1 and R^2 form with the carbon to which they are attached a C_3 - C_6 -cycloalkyl ring. Preferably R^1 and R^2 form with the carbon to which they are attached a C_4 - C_6 -cycloalkyl ring. More preferably R^1 and R^2 form with the carbon to which they are attached a cyclobutylring, or cyclopentylring.

15 In another embodiment of the invention, R^1 and R^2 are independently selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl; or R^1 and R^2 form with the carbon to which they are attached a C_3 - C_6 -cycloalkyl ring. Preferably, R^1 and R^2 are independently selected from C_1 - C_3 -alkyl, or cyclopropyl or cyclobutyl; or R^1 and R^2 form with the carbon to which they are attached a cyclobutylring, or cyclopentylring. More preferably R^1 and R^2 are independently selected from or C_1 - C_3 -alkyl, or R^1 and R^2 form with the carbon to which they are attached a cyclobutylring, or cyclopentylring. Even more preferably R^1 and R^2 are methyl; or R^1 and R^2 form with the
20 carbon to which they are attached a cyclobutylring, or cyclopentylring.

In one embodiment of the invention, R^3 is selected from hydrogen, or C_1 - C_3 -alkyl. Preferably R^3 is C_1 - C_3 -alkyl. More preferably, R^3 is methyl, or ethyl. Even more preferably, R^3 is methyl.

In one embodiment of the invention, R^4 is selected from hydrogen, or halogen. Preferably R^4 is halogen. More preferably R^4 is chloro, or fluoro. Even more preferably R^4 fluoro.

25 In one embodiment of the invention, R^5 is selected from hydroxy, halogen, or OR^6 . Preferably R^5 is OH, chloro, fluoro, or OR^6 . More preferably R^5 is chloro, OSO_2CH_3 , $OC(=O)-C(CH_3)_3$, or iso-butoxycarbonyloxy. Most preferably, R^5 is chloro.

30 In one embodiment of the invention R^6 is selected from C_1 - C_6 -alkyl, C_3 - C_6 -alkylcarbonyl, C_3 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylsulfonyl, benzoyl, heteroarylcarbonyl, phenylsulfonyl, heteroarylsulfonyl, or heteroaryl, wherein said heteroaryl is a 5 to 6 membered aromatic heterocycle which comprises 1, 2, 3, or 4 heteroatoms individually selected from N, O or S, and wherein said phenyl, benzoyl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents individually selected from C_1 - C_3 -alkyl, halogen, or C_1 - C_3 -alkoxy. Preferably R^6 is selected from C_1 - C_3 -alkyl, C_3 - C_6 -alkylcarbonyl, or C_3 - C_6 -alkoxycarbonyl. More preferably R^6 is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl).

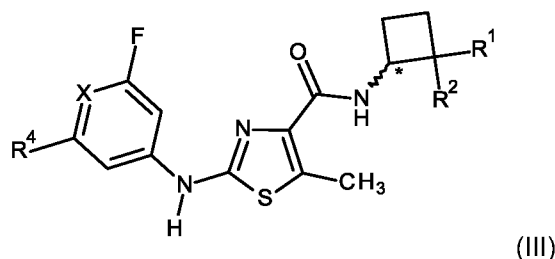
In one embodiment of the invention, R^{12} is hydrogen, C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxy-C₁-C₂-alkyl, C₃-C₄-cycloalkyl, C₁-C₂-alkoxy-C₁-C₂-alkoxy, C₁-C₃-alkoxycarbonyl-C₁-C₃-alkyl, C₁-C₂-alkoxycarbonyloxy-C₁-C₂-alkyl, C₁-C₂-alkylcarbonyloxy-C₁-C₂-alkyl, C₃-C₄-alkynyloxy, C₁-C₃-alkylsulfanyl, or heterocyclyl, wherein said heterocyclyl moiety is a 4-, 5- or 6-membered non-aromatic monocyclic ring comprising 1 heteroatom selected from oxygen. Preferably R^{12} is C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-alkoxy-C₁-C₂-alkyl, or heterocyclyl, wherein said heterocyclyl moiety is a 4-, 5- or 6-membered non-aromatic monocyclic ring comprising 1 heteroatom selected from oxygen. More preferably R^{12} is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl.

The present invention, accordingly, makes available compounds of formula (I), (II), (III), (IV), (V), (VI), and (VII) having X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{12} as defined above in all combinations / each permutation.

Further the present invention, accordingly, makes available processes involving compounds of formula (I), (II), (III), (IV), (V), (VI), and (VII) having X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{12} as defined above in all combinations / each permutation.

Embodiments according to the invention are provided as set out below.

In one embodiment of the invention, a compound of formula (III),



wherein the asterisk marks the stereogenic center; wherein X is CH or N; R^1 and R^2 are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R^1 and R^2 form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R^3 is C₁-C₃-alkyl; R^4 is hydrogen or halogen; and wherein the absolute configuration at the stereogenic center is the (R) configuration.

In another embodiment of the invention, a compound of formula (III), wherein X is CH or N; R^1 and R^2 are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R^1 and R^2 form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R^3 is C₁-C₃-alkyl; R^4 is hydrogen or halogen; and wherein the absolute configuration at the stereogenic center is the (S) configuration, wherein the asterisk marks the stereogenic center.

In a preferred embodiment of the invention, a compound of formula (III), wherein X is N; R^1 and R^2 are methyl, or R^1 and R^2 form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R^3 is methyl; R^4 is fluoro; and wherein the absolute configuration at the stereogenic center is the (R) configuration.

In another preferred embodiment of the invention, a compound of formula (III), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and wherein the absolute configuration at the stereogenic center is the (S) configuration.

5 In another preferred embodiment of the invention, a compound of formula (III), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and wherein the absolute configuration at the stereogenic center is the (R) configuration.

In still another preferred embodiment of the invention, a compound of formula (III), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and wherein the absolute configuration at the stereogenic center is the (S) configuration.

10 In another embodiment of the invention, the compounds of formula (III), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In still another embodiment of the invention, the compounds of formula (III), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

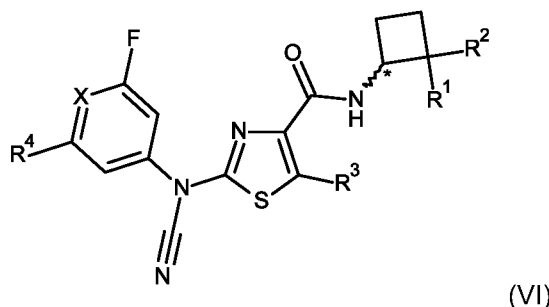
25 In another embodiment of the invention, the compounds of formula (III), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

30 In still another embodiment of the invention, the compounds of formula (III), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

35 In another preferred embodiment of the invention, the compounds of formula (III), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another preferred embodiment of the invention, the compounds of formula (III), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In one embodiment of the invention, a compound of formula (VI),



wherein the asterisk marks the stereogenic center; wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; and wherein the absolute configuration at the stereogenic center is the (R) configuration.

In another embodiment of the invention, a compound of formula (VI), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; and wherein the absolute configuration at the stereogenic center is the (S) configuration, wherein the asterisk marks the stereogenic center.

In a preferred embodiment of the invention, a compound of formula (VI), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and wherein the absolute configuration at the stereogenic center is the (R) configuration.

In another preferred embodiment of the invention, a compound of formula (VI), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and wherein the absolute configuration at the stereogenic center is the (S) configuration.

In another preferred embodiment of the invention, a compound of formula (VI), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and wherein the absolute configuration at the stereogenic center is the (R) configuration.

In still another preferred embodiment of the invention, a compound of formula (VI), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and wherein the absolute configuration at the stereogenic center is the (S) configuration.

In another embodiment of the invention, the compounds of formula (VI), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In still another embodiment of the invention, the compounds of formula (VI), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

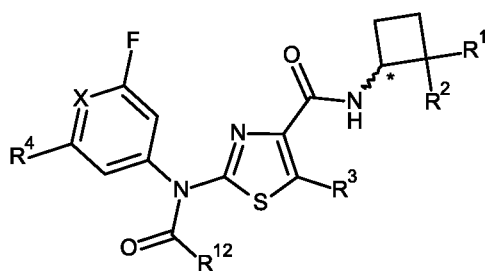
In another embodiment of the invention, the compounds of formula (VI), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In still another embodiment of the invention, the compounds of formula (VI), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another preferred embodiment of the invention, the compounds of formula (VI), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another preferred embodiment of the invention, the compounds of formula (VI), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In one embodiment of the invention, a compound of formula (VII),



(VII)

wherein the asterisk marks the stereogenic center; wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; and wherein the absolute configuration at the stereogenic center is the (*R*) configuration.

In another embodiment of the invention, a compound of formula (VII), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; and wherein the absolute configuration at the stereogenic center is the (*S*) configuration, wherein the asterisk marks the stereogenic center.

In a preferred embodiment of the invention, a compound of formula (VII), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those represented by the (*R*) absolute configuration at the stereogenic center.

In another preferred embodiment of the invention, a compound of formula (VII), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those represented by the (*S*) absolute configuration at the stereogenic center.

In another preferred embodiment of the invention, a compound of formula (VII), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those represented by the (*R*) absolute configuration at the stereogenic center.

In still another preferred embodiment of the invention, a compound of formula (VII), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl,

oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those represented by the (S) absolute configuration at the stereogenic center.

In another embodiment of the invention, the compounds of formula (VI), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another embodiment of the invention, the compounds of formula (VI), wherein X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another embodiment of the invention, the compounds of formula (VII), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another preferred embodiment of the invention, the compounds of formula (VII), wherein X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another preferred embodiment of the invention, the compounds of formula (VII), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another preferred embodiment of the invention, the compounds of formula (VII), wherein X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; are those either in (S)
 5 enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

Preferably, the compounds of formula (III), according to the present invention are selected from compounds as listed in any of tables A.3.

10 More preferably, the compound of formula (III), according to the present invention is selected from compound A-1, A-2, A-7, A-8, A-13, A-14, A-19, or A-20 as listed in table A.

Even more preferably, the compound of formula (III), according to the present invention is selected from compound A-1, A-7, A-13, or A-19 as listed in table A.

15 Preferably, the compounds of formula (VI) according to the present invention are selected from compounds as listed in any of tables A.4.

More preferably, the compound of formula (VI), according to the present invention is selected from compound A-3, A-4, A-9, A-10, A-15, A-16, A-21, or A-22 as listed in table A.

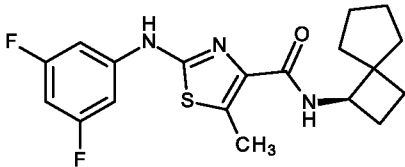
Even more preferably, the compound of formula (VI), according to the present invention is selected from compound A-3, A-9, A-15, or A-21 as listed in table A.

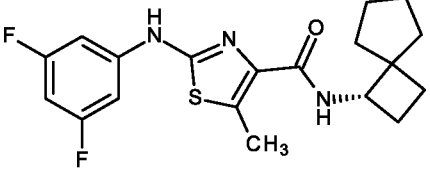
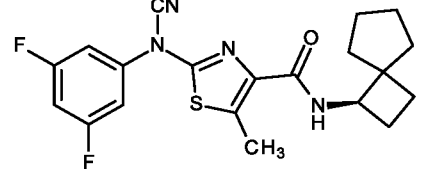
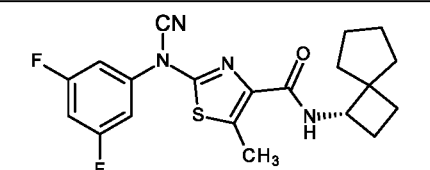
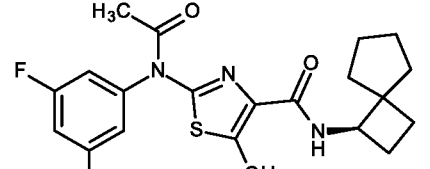
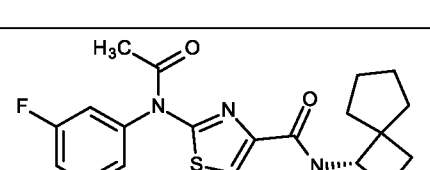
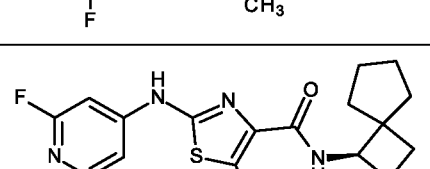
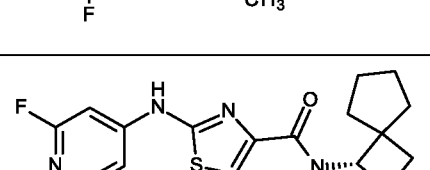
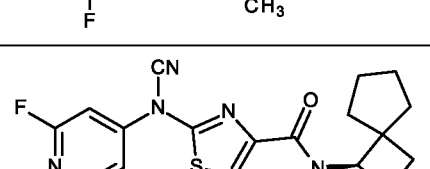
20 Preferably, the compounds of formula (VII) according to the present invention are selected from compounds as listed in any of tables A.5.

More preferably, the compound of formula (VII) according to the present invention, is selected from compound A-5, A-6, A-11, A-12, A-17, A-18, A-23, or A-24 as listed in table A.

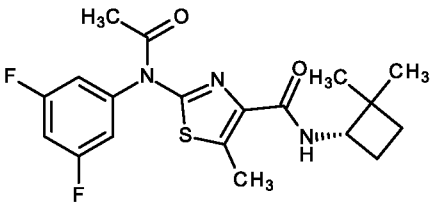
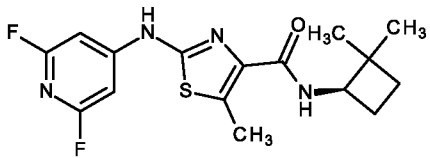
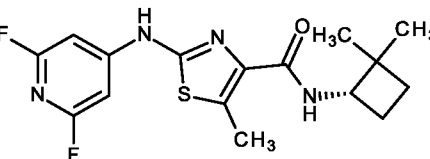
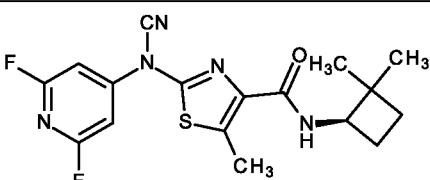
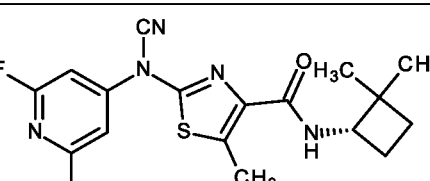
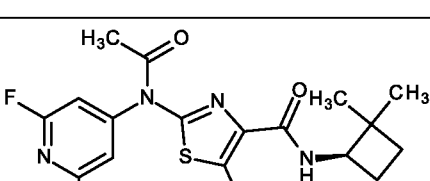
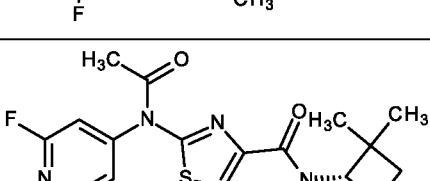
25 Even more preferably, the compound of formula (VII) according to the present invention, is selected from compound A-5, A-11, A-17, or A-23 as listed in table A.

Table A: Compounds of formula (III), (VI) and (VII) according to the present invention

Entry	IUPAC-name	Structure	Enantiomer
A-1	2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R-Enantiomer

A-2	2-(3,5-difluoroanilino)-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		S-Enantiomer
A-3	2-(N-cyano-3,5-difluoro-anilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R-Enantiomer
A-4	2-(N-cyano-3,5-difluoro-anilino)-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		S-Enantiomer
A-5	2-(N-acetyl-3,5-difluoro-anilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R-Enantiomer
A-6	2-(N-acetyl-3,5-difluoro-anilino)-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		S-Enantiomer
A-7	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R-Enantiomer
A-8	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		S-Enantiomer
A-9	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R-Enantiomer

A-10	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		S-Enantiomer
A-11	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R-Enantiomer
A-12	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		S-Enantiomer
A-13	2-(3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer
A-14	2-(3,5-difluoroanilino)-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		S-Enantiomer
A-15	2-(N-cyano-3,5-difluoro-anilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer
A-16	2-(N-cyano-3,5-difluoro-anilino)-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		S-Enantiomer
A-17	2-(N-acetyl-3,5-difluoro-anilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer

A-18	2-(N-acetyl-3,5-difluoro-anilino)-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		S-Enantiomer
A-19	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(1R)-2,2-dimethylcyclobutyl]thiazole-4-carboxamide		R-Enantiomer
A-20	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(1S)-2,2-dimethylcyclobutyl]thiazole-4-carboxamide		S-Enantiomer
A-21	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer
A-22	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		S-Enantiomer
A-23	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer
A-24	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		S-Enantiomer

The (S) or (R) enantiomer of the compounds of formula (III), (VI), (VII) according to the present invention, and mixtures of said enantiomers can be prepared by the stereoselective methods as disclosed below.

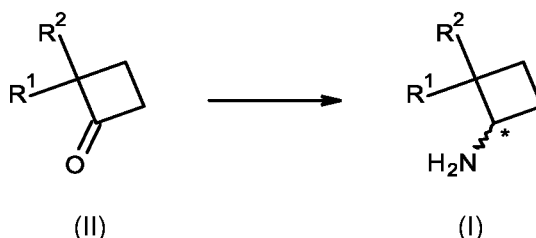
Or the individual enantiomers of the compounds of formula (III), (VI), (VII) according to the present invention may be obtained either after separation of a racemic mixture using known resolution methods or obtained by means of a stereoselective synthesis. For example, first and second eluting enantiomers may be obtained by

chromatographic separation using a chiral stationary phase (such as amylose- or cellulose-based CHIRALPAK® columns).

Process for the preparation of compounds of formula (I)

- 5 In one embodiment of the invention the process for the preparation of compound of formula (I), wherein said process comprises reaction of a compound of formula (II) in the presence of ammonia, an ammonium salt and hydrogen, in the presence of a chiral transition metal catalyst, to produce a compound of formula (I), and wherein said compound of formula (I) is the (S) or (R) enantiomer according to Scheme 1, wherein R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl; or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; and wherein the compound of formula (I) is the (S) or (R) enantiomer.

Scheme 1: Process for the preparation of compounds of formula (I)



- 15 Preferably in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, R¹ and R² are independently selected from or C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring. Even more preferably R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring.

- 20 In one embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, R¹ and R² are independently selected from or C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring, and the compound of formula (I) is the (S) enantiomer.

- 25 In another embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, R¹ and R² are independently selected from C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring, and the compound of formula (I) is the (R) enantiomer.

- In a preferred embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring, and the compound of formula (I) is the (S) enantiomer.

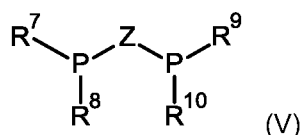
- 30 In another preferred embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, R¹ and R² are methyl, or R¹ and R² form with the

carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring, and the compound of formula (I) is the (*R*) enantiomer.

In the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, the chiral transition metal catalyst comprises a transition metal selected from Ru, Rh, Ir, and Pd, and a chiral ligand.

Chiral ligands are known in the art and may be used in the present invention, examples are given in „Catalytic asymmetric synthesis“, Iwao Ojima, third Edition, Wiley-VCH 2010 and the literature cited therein; typical classes which are known to a person skilled in the art include but are not limited to TADDOL ($\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol), DUPHOS (phospholane ligand), BOX (bis(oxazoline) ligand), BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), BINOL (1,1'-Bi-2-naphthol), DIOP (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane), WALPHOS, TANIAPHOS, MANDYPHOS, CHENPHOS, JOSIPHOS, BIPHEMP, MeO-BIPHEP, SEGPPOS, CHIRAPHOS, PPHOS, TUNEPHOS and SYNPHOS.

Preferably, the chiral ligand is a bidentate phosphorus containing ligand of the general formula (V)



wherein Z is a linking group and R^7 , R^8 , R^9 and R^{10} are independently selected from aryl, heteroaryl, C_1 - C_6 -alkyl or C_3 - C_6 -cycloalkyl, each of which is unsubstituted or substituted. Typical substituents for R^7 , R^8 , R^9 and R^{10} are selected from C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkyl and halogen. Preferably, the linking group Z is selected from (R or S)-1,1'-binaphthyl, (R or S)-4,4'-bi-1,3-benzodioxole, (R or S)-2,2',6,6'-tetramethoxy-3,3'-bipyridine, (R or S)-6,6'-dimethoxy-1,1'-biphenyl, (R or S)-4,4',6,6'-tetramethoxy-1,1'-biphenyl, 2,2'-bis-[(R or S)-cx-(dimethylamino)benzyl]ferrocene, ferrocenyl methyl, ferrocene, benzene and ethyl. More preferably, the bidentate ligand of formula (V) is selected from BINAP, WALPHOS, JOSIPHOS, TANIAPHOS, MANDYPHOS, CHENPHOS, MeO-BIPHEP, PPHOS, DUPHOS, TUNEPHOS, SYNPHOS and SEGPPOS classes of ligands.

Suitable chiral ligands in the current invention include but are not limited to (R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, (R)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl, (S)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl, (R)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl, (S)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl, (R)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, (S)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, (R)-5,5'-bis(di [3,5-xylyl] phosphino)-4,4'-bi-1,3-benzodioxole, (S)-5,5'-bis(di [3,5-xylyl] phosphino)-4,4'-bi-1,3-benzodioxole, (R)-1,13-bis(diphenylphosphino)-7,8-dihydro-6H-dibenzo[f,h][1,5]dioxin, (S)-1,13-bis(diphenylphosphino)-7,8-dihydro-6H-dibenzo[f,h][1,5]dioxin, (R)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, (S)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, (R)-2,2',6,6'-tetramethoxy-4,4'-bis(di(3,5-xylyl)phosphino)-3,3'-bipyridine, (S)-2,2',6,6'-tetramethoxy-4,4'-bis(di(3,5-xylyl)phosphino)-3,3'-bipyridine, (R)-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-

biphenyl, (R)-bis(diphenylphosphino)-4,4', 6,6'-tetra methoxy-1,1'-biphenyl, (S)-bis(diphenylphosphino)-4,4',6,6'-tetra methoxy-1,1'-biphenyl, (R)-6,6'-bis(diphenylphosphino)-2,2',3,3'-tetra hydro-5,5'-bi-1,4-benzodioxin, (S)-6,6'-bis(diphenylphosphino)-2,2',3,3'-tetra hydro-5,5'-bi-1,4-benzodioxin, (R)-5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole, (S)-5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole, (R)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole, (S)-(+)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole, (S,S) Fc-1,1'-Bis[bis(3,5-dimethylphenyl)phosphino]-2,2'-bis[(S,S)C-(N,N-dimethylamino)phenylmethyl] ferrocene, (R,R) Fc-1,1'-Bis[bis(3,5-dimethylphenyl)phosphino]-2,2'-bis[(R,R)C-(N,N-dimethylamino)phenylmethyl] ferrocene, (R)-2,2'-bis[bis(3,5-diisopropyl-4-dimethylaminophenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis[bis(3,5-diisopropyl-4-dimethylaminophenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis[bis(3,4,5-trimethoxyphenyl)phosphino]-4,4',5,5',6,6'-hexamethoxy-1,1'-biphenyl, (R)-2,2'-bis[bis(3,4,5-trimethoxyphenyl)phosphino]-4,4',5,5',6,6'-hexamethoxy-1,1'-biphenyl, (R)-1-diphenylphosphino-2-[(R)-(N,N-dimethylamino)[2-(diphenylphosphino)phenyl]methyl]ferrocene, (S)-1-diphenylphosphino-2-[(S)-(N,N-dimethylamino)[2-(diphenylphosphino)phenyl]methyl]ferrocene, (R)-(+)-2,2'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl, (S)-(-)-2,2'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl, (R)-1-[(R)-1-[bis(3,5-bis(trifluoromethyl)phenyl)phosphino]ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene, (S)-1-[(S)-1-[bis(3,5-bis(trifluoromethyl)phenyl)phosphino]ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene, (R)-2,2'-bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (R)-2,2'-bis[di-3,5-xylylphosphino]-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis[di-3,5-xylylphosphino]-6,6'-dimethoxy-1,1'-biphenyl, (R)-1-[(R)-1-(Diphenylphosphino)ethyl]-2-[2-(diphenylphosphino)-phenyl]ferrocene, (S)-1-[(S)-1-(Diphenylphosphino)ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene, (R)-2,2'-bis(di-*p*-dimethylaminophenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis(di-*p*-dimethylaminophenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (R)-2,2'-bis[bis(3,5-di-*tert*-butylphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis[bis(3,5-di-*tert*-butylphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (R)-1-[(R)-1-[di(3,5-xylyl)phosphino]ethyl]-2-[2-[di(3,5-xylyl)phosphino]phenyl]ferrocene, (S)-1-[(R)-1-[di(3,5-xylyl)phosphino]ethyl]-2-[2-[di(3,5-xylyl)phosphino]phenyl]ferrocene, (R)-2,2'-bis(di-*m*-dimethylaminophenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis(di-*m*-dimethylaminophenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (R)-2,2'-bis[bis(3,5-diisopropyl-4-dimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis[bis(3,5-diisopropyl-4-dimethoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (-)-1,2-bis[(2*S*,5*S*)-2,5-diisopropylphospholano]benzene, (+)-1,2-bis[(2*R*,5*R*)-2,5-diisopropyl-phospholano]benzene, (R)-2,2'-bis(di-*p*-tolylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis(di-*p*-tolylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (R)-2,2'-bis(di-6-methoxy-2-naphthalenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis(di-6-methoxy-2-naphthalenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (R)-2,2'-bis[bis(3,5-diisopropylphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (S)-2,2'-bis[bis(3,5-diisopropylphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, 1-Dicyclohexylphosphino-1'-[(S)_P]-[(S)_{FC}-2-[(R)_C-1-dimethylamino]ethyl]ferrocenyl]phenylphosphino]ferrocene, 1-Dicyclohexylphosphino-1'-[(R)_P]-[(R)_{FC}-2-[(S)_C-1-dimethylamino]ethyl]ferrocenyl]phenylphosphino]ferrocene.

Preferred chiral ligands are selected from (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, (*R*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphtyl, (*R*)-2,2'-bis(di(3,5-xylyl)phosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(di(3,5-xylyl)phosphino)-1,1'-binaphtyl, (*R*)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, (*S*)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, (*R*)-5,5'-bis(di[3,5-xylyl]phosphino)-4,4'-bi-1,3-benzodioxole, (*S*)-5,5'-bis(di[3,5-xylyl]phosphino)-4,4'-bi-1,3-benzodioxole, (*R*)-5,5'-bis(di[3,5-di-*t*-butyl-4-methoxyphenyl]phosphino)-4,4'-bi-1,3-benzodioxole, (*S*)-5,5'-bis(di[3,5-di-*t*-butyl-4-methoxyphenyl]phosphino)-4,4'-bi-1,3-benzodioxole, (*R*)-1,13-bis(diphenylphosphino)-7,8-dihydro-6H-dibenzo[f,h][1,5]dioxin, (*S*)-1,13-bis(diphenylphosphino)-7,8-dihydro-6H-dibenzo[f,h][1,5]dioxin, (*R*)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, (*S*)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, (*R*)-2,2',6,6'-tetramethoxy-4,4'-bis(di[3,5-xylyl]phosphino)-3,3'-bipyridine, (*S*)-2,2',6,6'-tetramethoxy-4,4'-bis(di[3,5-xylyl]phosphino)-3,3'-bipyridine, (*R*)-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (*S*)-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (*R*)-bis(diphenylphosphino)-4,4',6,6'-tetramethoxy-1,1'-biphenyl, (*S*)-bis(diphenylphosphino)-4,4',6,6'-tetramethoxy-1,1'-biphenyl, (*R*)-6,6'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin, (*S*)-6,6'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin, (*R*)-(+)-2,2'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl, (*S*)-(-)-2,2'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl, (*R*)-5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole, (*S*)-5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole, (*R*)-1-[(*R*)-1-[di(3,5-xylyl)phosphino]ethyl]-2-[2-[di(3,5-xylyl)phosphino]phenyl]ferrocene, (*S*)-1-[(*S*)-1-[di(3,5-xylyl)phosphino]ethyl]-2-[2-[di(3,5-xylyl)phosphino]phenyl]ferrocene, (*R*)-1-[(*R*)-1-[bis(3,5-bis(trifluoromethyl)phenyl)phosphino]ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene, or (*S*)-1-[(*S*)-1-[bis(3,5-bis(trifluoromethyl)phenyl)phosphino]ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene.

More preferably, the chiral ligand is selected from (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, (*R*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphtyl, (*R*)-2,2'-bis(di(3,5-xylyl)phosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(di(3,5-xylyl)phosphino)-1,1'-binaphtyl, (*R*)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, (*R*)-5,5'-bis(di[3,5-xylyl]phosphino)-4,4'-bi-1,3-benzodioxole, (*R*)-5,5'-bis(di[3,5-di-*tert*-butyl-4-methoxyphenyl]phosphino)-4,4'-bi-1,3-benzodioxole, (*S*)-1,13-bis(diphenylphosphino)-7,8-dihydro-6H-dibenzo[f,h][1,5]dioxin, (*R*)-2,2',6,6'-tetramethoxy-4,4'-bis(di(3,5-xylyl)phosphino)-3,3'-bipyridine, (*R*)-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl, (*R*)-2,2'-bis(diphenylphosphino)-4,4',6,6'-tetramethoxy-1,1'-biphenyl, (*R*)-6,6'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin, (*R*)-(+)-2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl, (*R*)-(+)-2,2'-bis(di-3,5-xylylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl, (*R*)-5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole, (*S*)-1-[(*S*)-1-[di(3,5-xylyl)phosphino]ethyl]-2-[2-[di(3,5-xylyl)phosphino]phenyl]ferrocene, or (*S*)-1-[(*S*)-1-[bis(3,5-bis(trifluoromethyl)phenyl)phosphino]ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene.

Even more preferably, the chiral ligand is selected from (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, (*R*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphtyl, (*S*)-2,2'-bis(di-*p*-

tolylphosphino)-1,1'-binaphtyl, (*R*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl, or (*S*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl.

Even more preferably, the chiral ligand is selected from (*R*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl, or (*S*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl.

5 In one embodiment of the invention the chiral ligand is (*R*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl.

In another embodiment of the invention the chiral ligand is (*S*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl.

In one embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, the chiral transition metal catalyst comprises a transition metal selected from Ru, Rh, Ir, and Pd, and a chiral ligand selected from (*R*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl, or (*S*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl.

In one embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, the chiral transition metal catalyst comprises a transition metal selected from Ru, Rh, Ir, and Pd, and a chiral ligand selected from (*R*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl.

15 In another embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, the chiral transition metal catalyst comprises a transition metal selected from Ru, Rh, Ir, and Pd, and a chiral ligand selected from (*S*)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl.

The transition metal catalyst may consist of a preformed complex. Such preformed complexes may generally be formed by reacting the chiral ligand with a suitable transition metal precursor compound.

The complexes thus obtained may then be used as the catalyst in the process for the preparation of compound of formula(I) according to scheme 1. Transition metal precursor compounds comprise at least the transition metals selected from Ru, Rh, Ir, and Pd, and typically comprise ligands that are easily displaced by the chiral ligand or it may comprise a ligand that is easily removed by hydrogenation. Preferred transition metal catalysts are Ru complexes.

Suitable transition metal precursor compounds include but are not limited to RuCl₃, RuCl₃·nH₂O, [RuCl₂(η⁶-benzene)]₂, [RuCl₂(η⁶-cymene)]₂, [RuCl₂(η⁶-mesitylene)]₂, [RuCl₂(η⁶-hexamethylbenzene)]₂, [RuBr₂(η⁶-benzene)]₂, [RuI₂(η⁶-benzene)]₂, trans-RuCl₂(DMSO)₄, RuCl₂(PPh₃)₃, RuCl₂(COD) (in which COD is 1,5-cyclooctadiene), Ru(COD)(methylallyl)₂, Ru(COD)(trifluoroacetate)₂, [Ir(COD)Cl]₂, Rh(COD)Cl, Rh(COD)₂BF₄, Rh(COD)₂(OTf)₂, Ru(COD)(OAc)₂. Preferred transition metal precursor compounds are selected from [RuCl₂(η⁶-benzene)]₂, [RuCl₂(η⁶-cymene)]₂, RuCl₂(COD), Ru(COD)(methylallyl)₂ and Ru(COD)(trifluoroacetate)₂.

Examples of preformed Ru catalyst complexes include but are not limited to [RuCl(p-cymene)((*S*)-DM-SEGPPOS)]Cl, [RuCl(p-cymene)((*R*)-DM-SEGPPOS)]Cl, [NH₂Me₂][(RuCl((*R*)-xylbinap))₂(u-Cl)₃], [NH₂Me₂][(RuCl((*S*)-xylbinap))₂(u-Cl)₃], Ru(OAc)₂((*R*)-binap), Ru(OAc)₂((*S*)-binap), Ru(OAc)₂((*R*)-xylbinap),

Ru(OAc)₂[(S)-xylbinap], RuCl₂[(R)-xylbinap][(R)-daipen], RuCl₂[(S)-xylbinap][(S)-daipen], RuCl₂[(R)-xylbinap][(R,R)-dpen], RuCl₂[(S)-xylbinap][(S,S)-dpen]. Preferred Ru catalyst complexes are selected from [RuCl(p-cymene)((R)-xylbinap)]Cl, [NH₂Me₂][(RuCl((R)-xylbinap))₂(u-Cl)₃], Ru(OAc)₂[(S)-xylbinap], Ru(OAc)₂[(R)-xylbinap], [NH₂Me₂][(RuCl((S)-xylbinap))₂(u-Cl)₃], [NH₂Me₂][(RuCl((R)-H8-binap))₂(u-Cl)₃], [RuCl(p-cymene)((R)-H8-binap)]Cl, Ru(OAc)₂[(R)-H8-binap], [NH₂Me₂][(RuCl((R)-H8-xylbinap))₂(u-Cl)₃], [RuCl(p-cymene)((R)-H8-xylbinap)]Cl, Ru(OAc)₂[(R)-H8-xylbinap], [NH₂Me₂][(RuCl((S)-1-[(S)-1-[bis[3,5-bis(trifluoromethyl)phenyl]phosphino)ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene))₂(u-Cl)₃], [RuCl(p-cymene)((S)-1-[(S)-1-[bis[3,5-bis(trifluoromethyl)phenyl]phosphino)ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene)]Cl and (S)-1-[(S)-1-[bis[3,5-bis(trifluoromethyl)phenyl]phosphino)ethyl]-2-[2-(diphenylphosphino)phenyl]ferrocene]. More preferred Ru catalyst complexes are selected from [NH₂Me₂][(RuCl((S)-xylbinap))₂(u-Cl)₃], [NH₂Me₂][(RuCl((R)-xylbinap))₂(u-Cl)₃], Ru(OAc)₂[(S)-xylbinap], and Ru(OAc)₂[(R)-xylbinap].

In one embodiment of the invention, Ru catalyst complexes are selected from [NH₂Me₂][(RuCl((S)-xylbinap))₂(u-Cl)₃], [NH₂Me₂][(RuCl((R)-xylbinap))₂(u-Cl)₃], Ru(OAc)₂[(S)-xylbinap], or Ru(OAc)₂[(R)-xylbinap].

In another embodiment of the invention, the Ru catalyst complexes are selected from [NH₂Me₂][(RuCl((S)-xylbinap))₂(u-Cl)₃], or Ru(OAc)₂[(S)-xylbinap].

In another embodiment of the invention, the Ru catalyst complexes are selected from [NH₂Me₂][(RuCl((R)-xylbinap))₂(u-Cl)₃], or Ru(OAc)₂[(R)-xylbinap].

In one embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, the chiral catalyst system is a Ru catalyst complex selected from [NH₂Me₂][(RuCl((S)-xylbinap))₂(u-Cl)₃], [NH₂Me₂][(RuCl((R)-xylbinap))₂(u-Cl)₃], Ru(OAc)₂[(S)-xylbinap], or Ru(OAc)₂[(R)-xylbinap].

In one embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, the chiral catalyst system is a Ru catalyst complex selected from [NH₂Me₂][(RuCl((S)-xylbinap))₂(u-Cl)₃], or Ru(OAc)₂[(S)-xylbinap].

In another embodiment of the invention, in the process for the preparation of compound of formula (I), from compounds of formula (II) according to Scheme 1, the chiral catalyst system is a Ru catalyst complex selected from [NH₂Me₂][(RuCl((S)-xylbinap))₂(u-Cl)₃], or Ru(OAc)₂[(R)-xylbinap].

As mentioned above, the process for the preparation of a compound of formula (I) according to Scheme 1, also requires the presence of an ammonium salt. Ammonium salts may be generated *in situ* by adding ammonia or substituted ammonia and the appropriate acid. Ammonium salts may also be prepared from ammonia or substituted ammonia and the appropriate acid and then added to the reaction mixture.

The acids, used to generate the ammonium salts, suitable for the preparation of a compound of formula (I) according to the present invention include, but not limited to, protic acids such as inorganic acids, for example hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid or sodium hydrogen sulfate, or organic acids, for example formic acid, acetic acid, trifluoroacetic acid, methane sulfonic acid,

trifluoromethane sulfonic acid, toluene sulfonic acid, methoxyacetic acid, phenoxacetic acid, lactic acid, or mandelic acid.

Preferably, the process for the preparation of a compound of formula (I) according to Scheme 1, is carried out in the presence of acetic acid, methane sulfonic acid, hydrogen chloride, hydrogen bromide, or sulfuric acid.

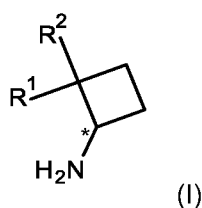
5 More preferably the process for the preparation of a compound of formula (I) is carried out in the presence of hydrogen chloride (HCl), or hydrogen bromide (HBr).

The amines used to generate the ammonium salts suitable for the preparation of a compound of formula (I) according to the present invention include, but not limited to, ammonia, primary amines, for example methyl amine, isopropyl amine, tert-butyl amine, aniline, benzyl amine, α -phenethylamine, β -phenethylamine and
 10 amines of formula (I), secondary amines, for example dimethylamine, pyrrolidine, piperidine, morpholine, tertiary amines, for example, trimethyl amine, triethyl amine, DABCO, Quinuclidine, N,N-dimethyl aniline, Diisopropylethyl amine, or N-methylmorpholine.

Other ammonium salts suitable for the preparation of a compound of formula (I) according to the present invention include, but not limited to, tetrasubstituted ammonium salts, for example tetramethyl ammonium,
 15 tetraethyl ammonium, tetrabutyl ammonium, benzyltrimethyl ammonium, or cetyltrimethyl ammonium halides, wherein halide is chloride, bromide, or iodide.

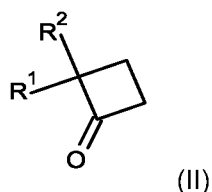
Preferably, the process for the preparation of a compound of formula (I) according to Scheme 1, is carried out in the presence of ammonium chloride, ammonium bromide, triethyl ammonium chloride or tetra-butyl ammonium chloride. More preferably the process for the preparation of a compound of formula (I) is carried
 20 out in the presence of ammonium chloride or ammonium bromide.

In one embodiment of the present invention, there is provided a process for the preparation of a compound of formula (I):



wherein R^1 and R^2 are independently selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl; or R^1 and R^2 form with the
 25 carbon to which they are attached a C_3 - C_6 -cycloalkyl ring;

said process comprising conversion of a compound of formula (II)



wherein R^1 and R^2 are defined as for compounds of formula (I),

in the presence of ammonia, an ammonium salt and hydrogen, in the presence of a chiral transition metal catalyst to produce a compound of formula (I), wherein said compound of formula (I) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center;

wherein said ammonium salt is selected from ammonium chloride or ammonium bromide; and

- 5 wherein said chiral transition metal catalyst is selected from $[\text{NH}_2\text{Me}_2][(\text{RuCl}((S)\text{-xylbinap}))_2(\text{u-Cl})_3]$, $[\text{NH}_2\text{Me}_2][(\text{RuCl}((R)\text{-xylbinap}))_2(\text{u-Cl})_3]$, $\text{Ru}(\text{OAc})_2[(S)\text{-xylbinap}]$, or $\text{Ru}(\text{OAc})_2[(R)\text{-xylbinap}]$.

In another embodiment of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein R^1 and R^2 are independently selected from $\text{C}_1\text{-C}_4\text{-alkyl}$, or $\text{C}_3\text{-C}_6\text{-cycloalkyl}$; or R^1 and R^2 form with the carbon to which they are attached a $\text{C}_3\text{-C}_6\text{-cycloalkyl}$ ring; said process comprising reaction
10 of a compound of formula (II), wherein R^1 and R^2 are defined as for compounds of formula (I), in the presence of ammonia, an ammonium salt and hydrogen, in the presence of a chiral transition metal catalyst to produce a compound of formula (I), wherein said compound of formula (I) is the (S) or (R) enantiomer, wherein said ammonium salt is selected from ammonium chloride or ammonium bromide; and wherein said chiral transition metal catalyst is selected from $[\text{NH}_2\text{Me}_2][(\text{RuCl}((S)\text{-xylbinap}))_2(\text{u-Cl})_3]$, or $\text{Ru}(\text{OAc})_2[(S)\text{-xylbinap}]$.

15 In another embodiment of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein R^1 and R^2 are independently selected from $\text{C}_1\text{-C}_4\text{-alkyl}$, or $\text{C}_3\text{-C}_6\text{-cycloalkyl}$; or R^1 and R^2 form with the carbon to which they are attached a $\text{C}_3\text{-C}_6\text{-cycloalkyl}$ ring; said process comprising reaction of a compound of formula (II), wherein R^1 and R^2 are defined as for compounds of formula (I), in the presence of ammonia, an ammonium salt and hydrogen, in the presence of a chiral transition metal catalyst to produce
20 a compound of formula (I), wherein said compound of formula (I) is the (S) or (R) enantiomer, wherein said ammonium salt is selected from ammonium chloride or ammonium bromide; and wherein said chiral transition metal catalyst is selected from $[\text{NH}_2\text{Me}_2][(\text{RuCl}((R)\text{-xylbinap}))_2(\text{u-Cl})_3]$, or $\text{Ru}(\text{OAc})_2[(R)\text{-xylbinap}]$.

In another embodiment of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein R^1 and R^2 are methyl; or R^1 and R^2 form with the carbon to which they are attached a
25 cyclobutylring, or cyclopentylring; said process comprising reaction of a compound of formula (II), wherein R^1 and R^2 are defined as for compounds of formula (I), in the presence of ammonia, an ammonium salt and hydrogen, in the presence of a chiral transition metal catalyst to produce a compound of formula (I), wherein said compound of formula (I) is the (S) or (R) enantiomer, wherein said ammonium salt is selected from ammonium chloride or ammonium bromide; and wherein said chiral transition metal catalyst is selected from
30 $[\text{NH}_2\text{Me}_2][(\text{RuCl}((S)\text{-xylbinap}))_2(\text{u-Cl})_3]$, or $\text{Ru}(\text{OAc})_2[(S)\text{-xylbinap}]$.

In another embodiment of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein R^1 and R^2 are methyl; or R^1 and R^2 form with the carbon to which they are attached a cyclobutylring, or cyclopentylring; said process comprising reaction of a compound of formula (II), wherein R^1 and R^2 are defined as for compounds of formula (I), in the presence of ammonia, an ammonium salt and
35 hydrogen, in the presence of a chiral transition metal catalyst to produce a compound of formula (I), wherein said compound of formula (I) is the (S) or (R) enantiomer, wherein said ammonium salt is selected from

ammonium chloride or ammonium bromide; and wherein said chiral transition metal catalyst is selected from $[\text{NH}_2\text{Me}_2][(\text{RuCl}((R)\text{-xylbinap}))_2(\text{u-Cl})_3]$, or $\text{Ru}(\text{OAc})_2[(R)\text{-xylbinap}]$.

A person skilled in the art understands that process for the preparation of compound of formula (I) according to Scheme 1 is carried out in a suitable solvent. A suitable solvent may be selected from the following classes of solvents: alcohols, ethers, esters, chlorinated or non-chlorinated hydrocarbons and aromatics. Suitable solvents include but are not limited to methanol, ethanol, 2,2,2-trifluoroethanol-1-ol, 2-propanol, tert-amyl alcohol, dichloromethane, and toluene. Preferred solvents are alcohols, in particular methanol.

The process for the preparation of compound of formula (I) according to Scheme 1 is carried out in the presence of hydrogen gas (H_2). The hydrogen gas pressure within the reaction vessel may be between 1 and 500 bar, in particular between 1 and 250 bar, more particularly between 1 and 50 bar, even more particularly between 5 and 30 bar.

Typically, the temperature of the process for the preparation of compound of formula (I) according to Scheme 1 is between 0°C and 150°C , preferably between 30°C and 140°C , more preferably between 50°C and 130°C , even more preferably between 80°C and 120°C , still even more preferably between 80°C and 100°C .

The process for the preparation of compound of formula (I) according to Scheme 1 may be carried out in the presence of other additives. Examples of additives may include but are not limited to drying agents like molecular sieves, magnesium sulfate, titanium ethoxide, or titanium isopropoxide.

Preferred process parameters for preparation of compound of formula (I) according to Scheme 1 are as follows:

The transition metal catalyst is added to the reaction mixture in an amount of 0.0001 and 0.1 mole equivalents relative to the compound of formula (II). Preferably between 0.0002 and 0.02 mole equivalents, more preferably between 0.0005 and 0.01 mole equivalents, relative to the compound of formula (II) is added.

Transition metal catalysts may be pre-formed or may be formed *in situ* by adding the chiral ligands and the transition metal precursors into the reaction mixture. A skilled person is well aware of the formation of transition metal catalysts *in situ*, e.g., as disclosed in EP1153908A2.

In one embodiment, in the process for the preparation of a compound of formula (I) according to the present invention, the amount of ammonia can be from 1.0 to 3.0 equivalents, from 1.0 to 2.0 eq., from 1.0 to 1.5 eq., from 0.5 to 1.2 eq., from 0.5 to 1.1 eq., from 1.0 to 1.05 eq. Preferably from 1.0 to 2.1 eq, more preferably from 1.0 to 1.5 eq.

In one embodiment, in the process for the preparation of a compound of formula (I) according to the present invention, the amount of the ammonium salt can be from 0.1 to 2.0 equivalents, from 0.2 to 1.5 eq., from 0.5 to 1.3 eq., from 0.7 to 1.2 eq., from 1.0 to 1.1 eq. Preferably from 0.5 to 1.0 eq.

In the present invention, the expression “molar equivalents” in the process for the preparation of a compound of formula (I) is based on the number of moles (mol) of the compound of formula (II), unless if indicated otherwise.

The skilled person understands that the pH of the reaction mixture may influence the outcome of the reaction.

- 5 Typically, the pH of the reaction mixture is between 4 and 12, preferably between 5 and 11 and even more preferably between 6 and 10.

The concentration of the compound of formula (II) is preferably 1 to 30 % by weight of the reaction mixture.

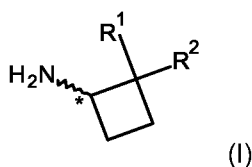
Optionally, 0.01 to 2 mole equivalents relative to the compound of formula (II) of one or more additives are added to the reaction mixture.

- 10 Preferably, the process for the preparation of compound of formula (I) according to Scheme 1 provides the enantiomers of compounds of formula (I) in an e.e. of 50% or higher, preferably of 75% or higher, more preferably 80% or higher. In one embodiment of the invention, the process for the preparation of compound of formula (I) according to Scheme 1 provides the enantiomers of compounds of formula (I) in an e.e. (S) of 50% or higher, preferably of 75% or higher, more preferably 80% or higher. In another embodiment of the invention,
- 15 the process for the preparation of compound of formula (I) according to Scheme 1 provides the enantiomers of compounds of formula (I) in an e.e. (R) of 50% or higher, preferably of 75% or higher, more preferably 80% or higher.

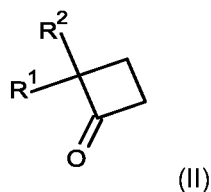
Process for the preparation of compound of formula (III), (VI) and (VII) from compounds of formula (I)

- 20 The process of the present invention may be used in the preparation of any of the compounds of formula (III) (VI) and (VII) according to step (2-i) to step (2-iii), and with reference to disclosure and examples of WO2017/207362, WO2019/105933, WO2020/109511, WO2020/109509 and WO2021/244952:

(2-i) the preparation of a compound of formula (I)



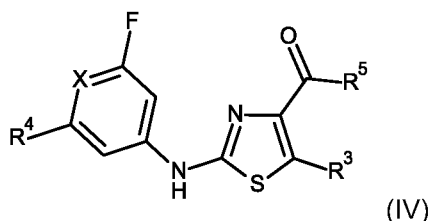
- 25 comprising the conversion of a compound of formula (II)



in the presence of ammonia, an ammonium salt and hydrogen, in the presence of a chiral transition metal catalyst to produce a compound of formula (I), wherein said compound of formula (I) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center; wherein R¹ and R² are independently selected

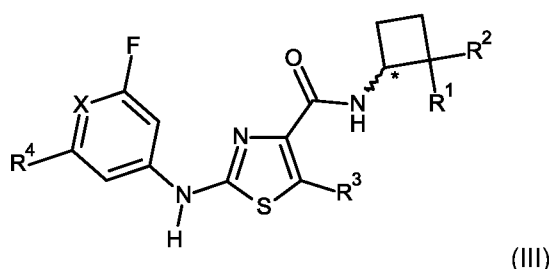
from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl; or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring;

(2-ii) reacting the compound of formula (I) with a compound of formula (IV),



- 5 wherein X is CH or N; R⁴ is hydrogen or fluoro; and R⁵ is selected from hydroxy, halogen, or OR⁶; wherein R⁶ is selected from C₁-C₆-alkyl, C₃-C₆-alkylcarbonyl, C₃-C₆-alkoxycarbonyl, C₁-C₆-alkylsulfonyl, benzoyl, heteroarylcarbonyl, phenylsulfonyl, heteroarylsulfonyl, or heteroaryl, wherein said heteroaryl is a 5 to 6 membered aromatic heterocycle which comprises 1, 2, 3, or 4 heteroatoms individually selected from N, O or S, and wherein said phenyl, benzoyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 substituents
- 10 individually selected from halogen, C₁-C₃-alkyl, or C₁-C₃-alkoxy;

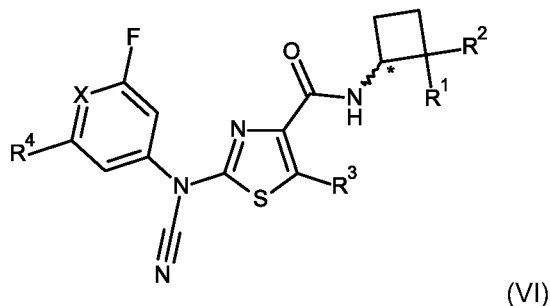
to form a compound of formula (III)



wherein R¹ and R² are defined as for step (2-i), wherein said compound of formula (III) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center; and

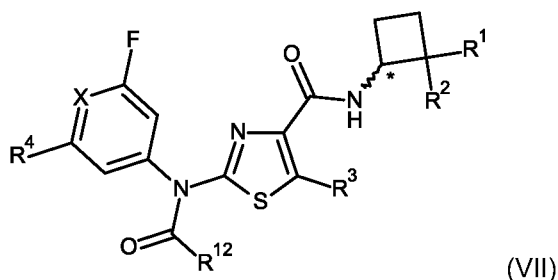
- 15 (2-iii) reacting said compound of formula (III) with

(2-iii-a) a compound of formula R¹¹-CN (VIII), wherein R¹¹ is a leaving group, preferably halogen, optionally in the presence of a base, to form a compound of formula (VI),



wherein X, R¹, R², R³, and R⁴ are defined as for step (2-ii); and wherein said compound of formula (VI) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center; or

(2-iii-b) a compound of formula $R^{12}-C(=O)X^a$ (IX), wherein R^{12} is hydrogen, C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxy-C₁-C₂-alkyl, C₃-C₄-cycloalkyl, C₁-C₂-alkoxy-C₁-C₂-alkoxy, C₁-C₃-alkoxycarbonyl-C₁-C₃-alkyl, C₁-C₂-alkoxycarbonyloxy-C₁-C₂-alkyl, C₁-C₂-alkylcarbonyloxy-C₁-C₂-alkyl, C₃-C₄-alkynyloxy, C₁-C₃-alkylsulfanyl, or heterocyclyl, wherein said heterocyclyl moiety is a 4-, 5- or 6-membered non-aromatic monocyclic ring comprising 1 heteroatom selected from oxygen; and wherein X^a is a leaving group, optionally in the presence of a base, to form a compound of formula (VII),



wherein X, R¹, R², R³, and R⁴ are defined as for step (2-ii), wherein R¹² is defined as for compound of formula (IX); and wherein said compound of formula (VII) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center.

It is understood that the preferred embodiments for X, R¹, R², R³ and R⁴ in accordance with the present invention may apply equally to steps (2-i) to (2-iii).

In one embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (R) or (S) enantiomer.

In another embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is CH or N; R¹ and R² are independently selected from hydrogen, C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (S) enantiomer.

In another embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is CH or N; R¹ and R² are independently selected from hydrogen,

C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or halogen; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (R) enantiomer.

In a preferred embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is N; R¹ and R² are methyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl or cyclopentylring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (R) or (S) enantiomer.

In another preferred embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl or cyclopentylring; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (S) enantiomer.

In another preferred embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl or cyclopentylring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (R) enantiomer.

In another preferred embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl or cyclopentylring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (R) or (S) enantiomer.

In a still another preferred embodiment of the invention, in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl or cyclopentylring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (S) enantiomer.

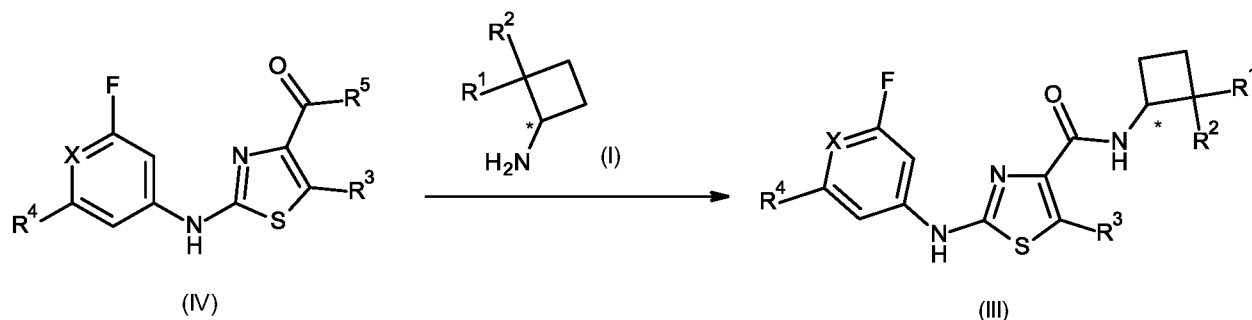
In a still another preferred embodiment of the invention in the preparation of any of the compounds of formula (III), (VI) and (VII) according to step (2-i) to step (2-iii), X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl or cyclopentylring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; R¹¹ is bromo; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; X^a is halogen; and the compounds of formula (I), (III), (VI), and (VII) are the (R) enantiomer.

Process for the preparation of compound of formula (III) from compounds of formula (I)

In one embodiment of the invention a process for the preparation of compound of formula (III), wherein X is selected from CH, or N; R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is selected from hydrogen, or C₁-C₃-alkyl; and R⁴ is selected from hydrogen, or halogen; said process comprising reaction of a compound of formula (IV) wherein R³, R⁴, and X are defined as for compounds of formula (III), and wherein R⁵ is selected from hydroxy, halogen, or OR⁶; wherein R⁶ is selected from C₁-C₆-alkyl, C₃-C₆-alkylcarbonyl, C₃-C₆-alkoxycarbonyl, C₁-C₆-alkylsulfonyl, benzoyl, heteroarylcarbonyl, phenylsulfonyl, heteroarylsulfonyl, or heteroaryl, wherein said heteroaryl is a 5 to 6 membered aromatic heterocycle which comprises 1, 2, 3, or 4 heteroatoms individually selected from N, O or S, and wherein said phenyl, benzoyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 substituents individually selected from C₁-C₃ alkyl, halogen, or C₁-C₃ alkoxy, with a compound of formula (I), wherein R¹ and R² are defined as for compounds of formula (III) optionally in the presence of an activation agent, and optionally in the presence of a base, to produce a compound of formula (III) according to Scheme 2; and wherein the compound of formula (III) is the (S) or (R) enantiomer.

Compounds of formula (IV) can be prepared as disclosed in WO2017/207362, WO2019/105933, WO2020/109511, WO2020/109509, or WO2021/244952.

Scheme 2: Process for the preparation of compounds of formula (III)



It will be appreciated that any of the preferred features for process for the preparation of compound of formula (I) according to Scheme 1 may be combined with one or more other preferred features of process for the preparation of compound of formula (III) according to Scheme 2.

Preferably in the process for the preparation of compound of formula (III) according to Scheme 2, X is CH or N; R¹ and R² are independently selected from or C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; and R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl. Even more preferably R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R⁵ is selected from hydroxy, halogen, or OR⁶; and R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl).

In one embodiment of the invention, X is CH; R¹ and R² are independently selected from or C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; and the compound of formula (I) is the (S) enantiomer.

In another embodiment of the invention, X is CH; R¹ and R² are independently selected from C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; and the compound of formula (I) is the (R) enantiomer.

In one embodiment of the invention, X is N; R¹ and R² are independently selected from C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; and the compound of formula (I) is the (S) enantiomer.

In another embodiment of the invention, X is N; R¹ and R² are independently selected from C₁-C₃-alkyl, or R¹ and R² form with the carbon to which they are attached a C₄-C₆-cycloalkyl ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl; and the compound of formula (I) is the (R) enantiomer.

In a preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are

attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is the (S) enantiomer.

5 In another preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is the (R) enantiomer.

10 In still another preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is a mixture of the (S) and (R) enantiomer, wherein the ratio of the (S) and (R) enantiomer is between 85 to 15, 90 to 10, 95 to 5, 98 to 2, 99 to 1, 15 to 85, 10 to 90, 5 to 95, 2 to 98, or 1 to 99.

15 In still another preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is a mixture of the (S) and (R) enantiomer, wherein the ratio of the (S) and (R) enantiomer is between 9:1 and 1: 9.

20 In a preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is the (S) enantiomer.

25 In another preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is the (R) enantiomer.

30 In still another preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is a mixture of the (S) and (R) enantiomer, wherein the ratio of the (S) and (R) enantiomer is between 85 to 15, 90 to 10, 95 to 5, 98 to 2, 99 to 1, 15 to 85, 10 to 90, 5 to 95, 2 to 98, or 1 to 99.

35

In still another preferred embodiment of the invention, in the process for the preparation of compound of formula (III) according to Scheme 2, X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl-, or cyclopentyl-ring; R³ is methyl; R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; R⁶ is iso-butoxycarbonyl, or tert-butylcarbonyl (or pivalyl); and the compound of formula (I) is a mixture of the (S) and (R) enantiomer, wherein the ratio of the (S) and (R) enantiomer is between 9:1 and 1: 9.

In one embodiment of the invention, the compounds of formula (II) are those represented by the (R) absolute configuration at the stereogenic center.

In another embodiment of the invention, the compounds of formula (III) are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another embodiment of the invention, the compounds of formula (III) are those represented by the (S) absolute configuration at the stereogenic center.

In still another embodiment of the invention, the compounds of formula (III) are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

Preferred process parameters for the process for the preparation of compound of formula (III) from compound of formula (I) (Scheme 2)

Compounds of formula (III) can be prepared by reacting a compound of formula (I) with a compound of formula (IV) wherein the substituents are defined as herein disclosed.

When R⁵ is hydroxy, such reactions are usually carried out in the presence of a coupling reagent, such as N,N'-dicyclohexylcarbodiimide ("DCC"), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride ("EDC") or bis(2-oxo3-oxazolidinyl)phosphonic chloride ("BOP-Cl"), or an activation agent, such as methane sulfonyl chloride (MsCl) or iso-butyl chloroformate, in the presence of a base, and optionally in the presence of a nucleophilic catalyst, such as hydroxybenzotriazole ("HOBT"). Suitable bases include carbonates, hydroxides, nitrogen-based organic bases such as amines, pyridines, and derivatives thereof, e.g., Na₂CO₃, K₂CO₃, NaHCO₃, NaOH, triethylamine, pyridine, N-methyl morpholine and diisopropylethylamine.

When R⁵ is chloro, such reactions are usually carried out in the presence of a base, and optionally in the presence of a nucleophilic catalyst such as 4-dimethylamino pyridine ("DMAP") or 1-methyl imidazole. Suitable bases include carbonates, hydroxides, nitrogen-based organic bases such as amines, pyridines, and derivatives thereof, e.g., Na₂CO₃, K₂CO₃, NaHCO₃, NaOH, KOH, triethylamine, pyridine, N-methyl morpholine and diisopropylethylamine.

The dilutants (e.g., solvents, suspending agents) suitable for the preparation of a compound of formula (III) according to the present invention include, but not limited to, aromatic hydrocarbons, for example toluene or xylenes as single isomers or as a mixture of isomers, aliphatic and aromatic halohydrocarbons, for example, chloroform, dichloromethane, dichloroethane, monochlorobenzene, dichlorobenzene, trichlorobenzene, or trifluorotoluene, nitriles, for example acetonitrile, propionitrile, butyronitrile, isobutyronitrile or benzonitrile, ethers, for example diethyl ether, dibutyl ether, tert-butyl methyl ether, cyclopentyl methyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethoxymethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, anisole or dioxane, cyclic and acyclic esters, for example ethyl acetate, isopropylacetate, or γ -valerolactone, ketones, for example acetone, 2-butanone, methylisobutylketone, cyclic and acyclic carbonates, for example dimethyl carbonate, diethyl carbonate, or propylene carbonate, N-substituted lactams, for example N-methyl-2-pyrrolidone (NMP or 1-methyl-2-pyrrolidone), amides, for example N,N-dimethylformamide (DMF) or dimethylacetamide (DMA), cyclic ureas, for example N,N'-dimethylethyleneurea (DMI), or mixtures of such dilutants. Water may also be used as a component of a biphasic mixture.

In one embodiment, the process for the preparation of a compound of formula (III) according to the present invention is carried out in the presence of a dipolar aprotic solvent. Preferably, the process for the preparation of a compound of formula (III) is carried out in the presence of a dipolar aprotic dilutant, such as dichloromethane, ethyl acetate, isopropylacetate, γ -valerolactone, butyronitrile, 2-methyl-tetrahydrofuran, or propylene carbonate. More preferably dichloromethane, ethyl acetate, isopropyl acetate, or 2-methyl-tetrahydrofuran.

In one embodiment, the process for the preparation of a compound of formula (III) according to the present invention is carried out in a biphasic system comprising an organic solvent, e.g., ethyl acetate, isopropyl acetate, toluene, xylenes as single isomers or as a mixture of isomers or dichloromethane, and an aqueous solvent, preferably a solution of sodium hydrogen carbonate or sodium carbonate or sodium hydroxide, or an organic amine such as triethylamine or diisopropylethyl amine.

In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is chloro, according to the present invention, the amount of base can be from 1.0 to 4.0 equivalents, from 1.0 to 3.0 eq., from 1.0 to 2.5 eq., from 1.0 to 2.2 eq., from 2.0 to 3.0 eq., from 2.0 to 2.5 eq., from 2.0 to 2.1 eq. Preferably from 2.0 to 3.0 eq, more preferably from 1.0 to 2.1 eq.

In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is chloro, according to the present invention, the amount of compound of formula (I), based on the amount of compound of formula (IV), can be from 1.0 to 2.0 equivalents, from 1.0 to 1.5 eq., from 1.0 to 1.3 eq., from 1.0 to 1.2 eq., from 1.0 to 1.1 eq., from 1.0 to 1.05 eq., from 1.0 to 1.01 eq., from 1.0 to 1.0 eq. Preferably from 1.0 to 1.2 eq, more preferably from 1.0 to 1.01 eq.

In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is chloro, according to the present invention, optionally 0.001 to 0.25 equivalents of a nucleophilic catalyst, based on the

amount of compound of formula (IV), such as 4-dimethylamino pyridine ("DMAP") or 1-methyl imidazole can be used. Preferably from 0.005 to 0.05 eq, more preferably from 0.005 to 0.02 eq.

5 In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is hydroxy, according to the present invention, the amount of coupling reagent, based on the amount of compound of formula (IV), can be from 1.0 to 4.0 equivalents, from 1.0 to 3.0 eq., from 1.0 to 2.5 eq., from 1.0 to 2.2 eq., from 2.0 to 3.0 eq., from 2.0 to 2.5 eq., from 2.0 to 2.1 eq. Preferably from 1.0 to 2.0 eq, more preferably from 1.0 to 1.2 eq.

10 In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is hydroxy, according to the present invention, optionally 0.1 to 2.0 equivalents of a nucleophilic catalyst, based on the amount of compound of formula (IV), such as hydroxybenzotriazole ("HOBT") can be used. Preferably from 0.5 to 1.2 eq, more preferably from 1.0 to 1.1 eq.

15 In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is hydroxy, according to the present invention, the amount of base, based on the amount of compound of formula (IV), can be from 1.0 to 4.0 equivalents, from 1.0 to 3.0 eq., from 1.0 to 2.5 eq., from 1.0 to 2.2 eq., from 2.0 to 3.0 eq., from 2.0 to 2.5 eq., from 2.0 to 2.1 eq. Preferably from 2.0 to 3.0 eq, more preferably from 1.0 to 2.1 eq.

20 In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is hydroxy, according to the present invention, the amount of compound of formula (I), based on the amount of compound of formula (IV), can be from 1.0 to 2.0 equivalents, from 1.0 to 1.5 eq., from 1.0 to 1.3 eq., from 1.0 to 1.2 eq., from 1.0 to 1.1 eq., from 1.0 to 1.05 eq., from 1.0 to 1.01 eq., from 1.0 to 1.0 eq. Preferably from 1.0 to 1.2 eq, more preferably from 1.0 to 1.01 eq.

In one embodiment, in the process for the preparation of a compound of formula (III), wherein R⁵ is hydroxy, according to the present invention, optionally 0.001 to 0.25 equivalents of a nucleophilic catalyst, based on the amount of compound of formula (IV), such as 4-dimethylamino pyridine ("DMAP") or 1-methyl imidazole can be used. Preferably from 0.005 to 0.05 eq, more preferably from 0.005 to 0.02 eq.

25 In the present invention, the expression "molar equivalents" in the process for the preparation of a compound of formula (III) is based on the number of moles (mol) of the compound of formula (IV), if not indicated otherwise.

The reaction can be carried out at a temperature from -20°C to 100°C, preferably from -10°C to 50°C, and more preferably from 0° to 30°C.

30 The concentration of the compound of formula (II) is preferably 1-30 % by weight of the reaction mixture, calculated on the total weight of the reaction mixture.

Compounds of formula (IV), wherein R⁵ is chloro, may be formed from compounds of formula (IV), wherein R⁵ is hydroxy, by adding activating agents, such as thionyl chloride, phosgene, oxalyl chloride or cyanuric chloride into the reaction mixture. A skilled person is well aware of the preparation and use of acid chlorides, as reported

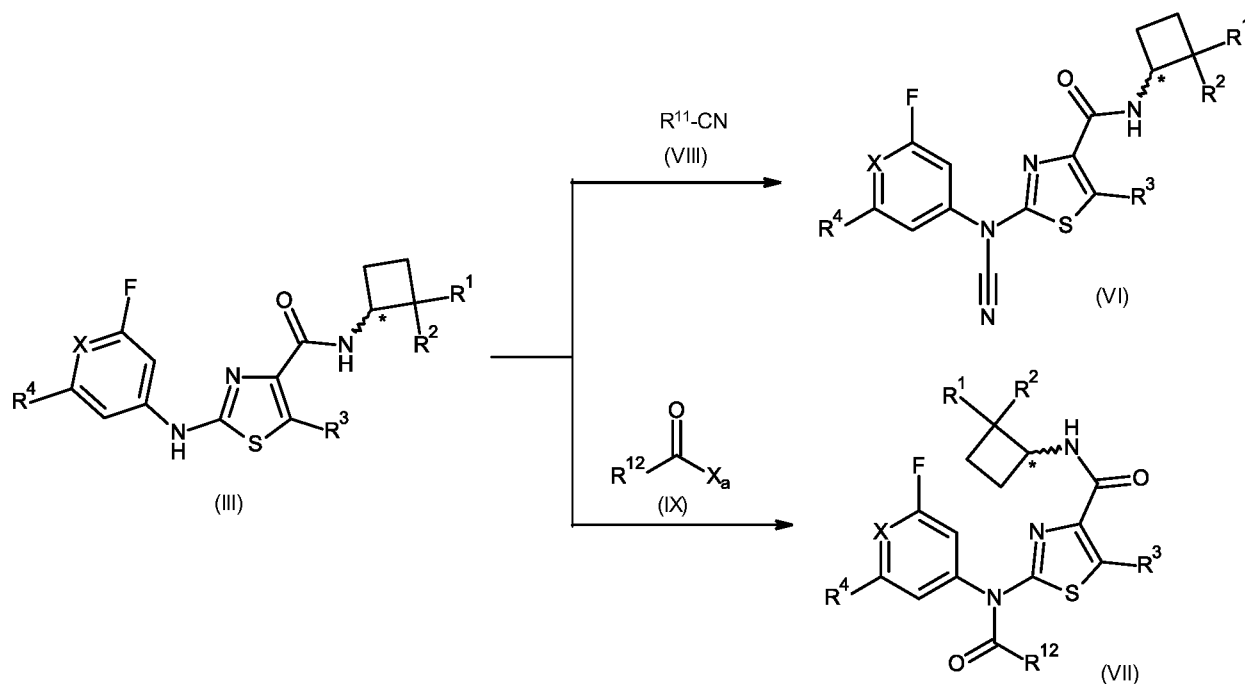
in "March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 8th ed by M. B. Smith. Wiley Interscience: New York. 2020. ISBN 1119371805".

Conversion of compounds of formula (III) to compounds of formula (VI) and (VII)

According to Scheme 3, the compounds of formula (III), wherein X, R¹, R², R³ and R⁴ are defined according to the present invention, can be converted

- a) to compounds of formula (VI), wherein X, R¹, R², R³ and R⁴ are defined as for compounds of formula (III) of the present invention, by reaction with a compound of formula (VIII), wherein R¹¹ is a leaving group preferably halogen, such as bromo, either by thermal heating, or with the aid of a base (as shown in Scheme 3 below); or
- b) to compounds of formula (VII), wherein R¹, R², R³ and R⁴ are defined as for compounds of formula (III) of the present invention, and R¹² is hydrogen, C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxy-C₁-C₂-alkyl, C₃-C₄-cycloalkyl, C₁-C₂-alkoxy-C₁-C₂-alkoxy, C₁-C₃-alkoxycarbonyl-C₁-C₃-alkyl, C₁-C₂-alkoxycarbonyloxy-C₁-C₂-alkyl, C₁-C₂-alkylcarbonyloxy-C₁-C₂-alkyl, C₃-C₄-alkynyloxy, C₁-C₃-alkylsulfanyl, or heterocyclyl, wherein said heterocyclyl moiety is a 4-, 5- or 6-membered non-aromatic monocyclic ring comprising 1 heteroatom selected from oxygen; by reaction with a compound of formula (IX), wherein R¹² is defined as for compounds of formula (VII), and wherein X_a is a leaving group preferably halogen, such as chloro, either by thermal heating, or with the aid of a base. This is shown in Scheme 3 below.

Scheme 3: Preparation of compounds of formula (VI) and (VII) from compounds of formula (III) according to the present invention



It is understood that the preferred embodiments for X, R¹, R², R³, R⁴, and R¹² in accordance with the present invention may apply equally to the reaction steps of Scheme 3.

Preferably, in the process for the preparation of compound of formula (VI), from compounds of formula (III) according to Scheme 2, in the compound of formula (III) and (VI), X is CH or N; R¹ and R² are independently selected from C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R⁴ is fluoro; R³ is methyl; and wherein the compounds of formula (III) and (V) are the (S) or (R) enantiomer.

Preferably, in the process for the preparation of compound of formula (VII), from compounds of formula (III) according to Scheme 2, in the compound of formula (III), X is CH or N; R¹ and R² are independently selected from C₁-C₂-alkyl, or C₃-C₆-cycloalkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R⁴ is fluoro; R³ is methyl; and in the compounds of formula (VII), X, R¹, R², R³, and R⁴ are defined as for compounds of formula (III), and R¹² is C₁-C₃-alkyl, C₁-C₃-alkoxy, C₁-C₃-alkoxy-C₁-C₂-alkyl, or heterocyclyl, wherein said heterocyclyl moiety is a 4-, 5- or 6-membered non-aromatic monocyclic ring comprising 1 heteroatom selected from oxygen, and wherein the compounds of formula (III) and (V) are the (S) or (R) enantiomer.

More preferably, in the process for the preparation of compound of formula (VI), from compounds of formula (III) according to Scheme 2, in the compound of formula (III) and (VI), X is CH or N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; R³ is methyl; and wherein the compounds of formula (III) and (V) are the (S) or (R) enantiomer.

More preferably, in the process for the preparation of compound of formula (VII), from compounds of formula (III) according to Scheme 2, in the compound of formula (III), X is CH or N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; and R³ is methyl, and in the compounds of formula (VII), X, R¹, R², R³, and R⁴ are defined as for compounds of formula (III), and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl, and wherein the compounds of formula (III) and (V) are the (S) or (R) enantiomer.

In one embodiment of the invention, in the process for the preparation of compound of formula (VI), from compounds of formula (III) according to Scheme 2, in the compound of formula (III) and (VI), X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; R³ is methyl, and wherein the compounds of formula (III) and (V) are the (S) enantiomer.

In one embodiment of the invention, in the process for the preparation of compound of formula (VI), from compounds of formula (III) according to Scheme 2, in the compound of formula (III) and (VI), X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; R³ is methyl, and wherein the compounds of formula (III) and (V) are the (R) enantiomer.

In another embodiment of the invention, in the process for the preparation of compound of formula (VI), from compounds of formula (III) according to Scheme 2, in the compound of formula (III) and (VI), X is N; R¹ and R²

are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; R³ is methyl; and wherein the compounds of formula (III) and (V) are the (S) enantiomer.

In another embodiment of the invention, in the process for the preparation of compound of formula (VI), from compounds of formula (III) according to Scheme 2, in the compound of formula (III) and (VI), X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; R³ is methyl; and wherein the compounds of formula (III) and (V) are the (R) enantiomer.

In one embodiment of the invention, in the process for the preparation of compound of formula (VII), from compounds of formula (III) according to Scheme 2, in the compound of formula (III), X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; and R³ is methyl, and in the compounds of formula (VII), X, R¹, R², R³, and R⁴ are defined as for compounds of formula (III), and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl, and wherein the compounds of formula (III) and (V) are the (S) enantiomer.

In one embodiment of the invention, in the process for the preparation of compound of formula (VII), from compounds of formula (III) according to Scheme 2, in the compound of formula (III), X is CH; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; and R³ is methyl, and in the compounds of formula (VII), X, R¹, R², R³, and R⁴ are defined as for compounds of formula (III), and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl, and wherein the compounds of formula (III) and (V) are the (R) enantiomer.

In another embodiment of the invention, in the process for the preparation of compound of formula (VII), from compounds of formula (III) according to Scheme 2, in the compound of formula (III), X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; and R³ is methyl, and in the compounds of formula (VII), X, R¹, R², R³, and R⁴ are defined as for compounds of formula (III), and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl, and wherein the compounds of formula (III) and (V) are the (S) enantiomer.

In another embodiment of the invention, in the process for the preparation of compound of formula (VII), from compounds of formula (III) according to Scheme 2, in the compound of formula (III), X is N; R¹ and R² are methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentyl-ring; R⁴ is fluoro; and R³ is methyl, and in the compounds of formula (VII), X, R¹, R², R³, and R⁴ are defined as for compounds of formula (III), and R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl, and wherein the compounds of formula (III) and (V) are the (R) enantiomer.

In another embodiment of the invention, the compounds of formula (VI) are those represented by the (R) absolute configuration at the stereogenic center.

In another embodiment of the invention, the compounds of formula (VI) are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

- 5 In another embodiment of the invention, the compounds of formula (VI) are those represented by the (S) absolute configuration at the stereogenic center.

In another embodiment of the invention, the compounds of formula (VI) are those either in (S) enantiomerically pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most
10 preferably at least 99%.

In another embodiment of the invention, the compounds of formula (VII) are those represented by the (R) absolute configuration at the stereogenic center.

- In another embodiment of the invention, the compounds of formula (VII) are those either in (R) enantiomerically pure form or with an R-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or
15 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

In another embodiment of the invention, the compounds of formula (VII) are those represented by the (S) absolute configuration at the stereogenic center.

- In another embodiment of the invention, the compounds of formula (VII) are those either in (S) enantiomerically
20 pure form or with an S-enantiomeric excess (e.e.) of at least 40%, for example, at least 50%, 60%, 70% or 80%, preferably at least 90%, more preferably at least 95%, yet more preferably at least 98% and most preferably at least 99%.

Process Parameters for the conversion of compounds of formula (III) to compounds of formula (VI) and (VII)

- 25 Compounds of formula (VI) can be prepared by reacting a compound of formula (III) with a compound of formula (VIII) wherein the substituents are defined as herein disclosed. Such reactions are usually carried out in the presence of a base.

- The bases suitable for the preparation of a compound of formula (VI) according to the present invention include, but not limited to, organic bases such as tertiary amine, such as trimethylamine, triethylamine (TEA),
30 tributylamine, N,N-diisopropyl-ethylamine (DIPEA), pyridine, N-methylpiperidine, N,N-dimethylaminopyridine, diazabicyclooctane (DABCO), diazabicyclononene (DBN) or diazabicycloundecene (DBU), strong organic bases such as organolithium reagents, for example methyl lithium, butyl lithium or phenyl lithium, Grignard reagents such as methyl magnesium halide or ethyl magnesium halide, inorganic bases such as alkaline earth metal or alkali metal hydroxides, carbonates, amides, or phosphates, wherein the counter ion is a lithium,
35 sodium, potassium, cesium, calcium, magnesium or ammonium; for example, sodium amide, lithium

diisopropylamide, sodium methanolate, sodium ethanolate, sodium tert-butanolate, sodium tert-amylate, sodium hydroxide, potassium hydroxide, or sodium carbonate.

Preferably, the process for the preparation of a compound of formula (VI) according to the present invention is carried out in the presence of alkali metal hydroxides, for example sodium hydroxide or potassium hydroxide, alkali metal alkoxides, for example sodium tert-butanolate or sodium tert-amylate, Grignard reagents, for example methyl magnesium halide or ethyl magnesium halide, alkyl lithium reagents, for example butyl lithium, methyl lithium or phenyl lithium. More preferable, the process for the preparation of a compound of formula (VI) according to the present invention is carried out in the presence of sodium tert-butanolate or sodium hydroxide.

The dilutants (e.g., solvents, suspending agents) suitable for the preparation of a compound of formula (VI) according to the present invention include, but not limited to, aromatic hydrocarbons, nitriles, for example acetonitrile, propionitrile, butyronitrile, isobutyronitrile, or benzonitrile, ethers, for example diethyl ether, dibutyl ether, tert-butyl methyl ether, cyclopentyl methyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethoxymethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, anisole or dioxane, cyclic and acyclic esters, for example ethyl acetate, isopropylacetate, or γ -valerolactone, ketones, for example acetone, 2-butanone, methylisobutylketone, cyclic and acyclic carbonates, for example dimethyl carbonate, diethyl carbonate, or propylene carbonate, N-substituted lactams, for example N-methyl-2-pyrrolidone (NMP or 1-methyl-2-pyrrolidone), amides, for example N,N-dimethylformamide (DMF) or dimethylacetamide (DMA), cyclic ureas, for example N,N'-dimethylethyleneurea (DMI), or mixtures of such dilutants. Water may also be used as a component of a biphasic mixture.

In one embodiment, the process for the preparation of a compound of formula (VI) according to the present invention is carried out in the presence of a dipolar aprotic solvent. Preferably, the process for the preparation of a compound of formula (III) is carried out in the presence of a dipolar aprotic dilutant, such as isopropylacetate, γ -valerolactone, butyronitrile, 2-methyl-tetrahydrofuran or propylene carbonate. More preferably ethyl acetate, isopropyl acetate, or 2-methyl-tetrahydrofuran.

In one embodiment, the process for the preparation of a compound of formula (VI) according to the present invention is carried out in a biphasic system comprising an organic solvent, preferably isopropyl acetate, 2-methyl-tetrahydrofuran, propylene carbonate, toluene, or xylenes as single isomers or as a mixture of isomers and an aqueous solution of a base, preferably a solution of sodium hydrogen carbonate or sodium carbonate or sodium hydroxide, or an organic amine such as triethylamine or diisopropylethyl amine. Preferably the process for the preparation of a compound of formula (III) according to the present invention is carried out in a biphasic system comprising 2-methyl-tetrahydrofuran or xylenes as single isomers or as a mixture of isomers and an aqueous solution of a base, preferably a solution of sodium hydrogen carbonate or sodium hydroxide.

In one embodiment, in the process for the preparation of a compound of formula (VI) according to the present invention, the amount of base can be from 1.0 to 3.0 equivalents, 1.0 to 2.0 equivalents, from 1.0 to 1.5 eq.,

from 1.0 to 1.3 eq., from 1.0 to 1.2 eq., from 1.0 to 1.1 eq., from 1.0 to 1.05 eq. Preferably from 1.0 to 2.5 eq, more preferably from 1.0 to 2.0 eq.

In one embodiment, in the process for the preparation of a compound of formula (VI) according to the present invention, the amount of compound of formula (VIII) can be from 1.0 to 2.0 equivalents, from 1.0 to 1.5 eq.,
5 from 1.0 to 1.3 eq., from 1.0 to 1.2 eq., from 1.0 to 1.1 eq., from 1.0 to 1.05 eq., from 1.0 to 1.01 eq., from 1.0 to 1.0 eq. Preferably from 1.0 to 1.2 eq, more preferably from 1.0 to 1.01 eq.

In one embodiment, the process for the preparation of a compound of formula (VI) according to the present invention is carried out in a two-step one-pot procedure, wherein a compound of formula (III) is reacted with a base followed by the addition of compound of formula (VIII).

10 In another embodiment, the process for the preparation of a compound of formula (VI) according to the present invention is carried out in a one-step procedure, wherein a compound of formula (III) is reacted with a base, and a compound of formula (VIII) simultaneously.

In the present invention, the expression "molar equivalents" in the process for the preparation of a compound of formula (VI) is based on the number of moles (mol) of the compound of formula (III).

15 The reaction can be carried out at a temperature from -20°C to 100°C, preferably from -10°C to 50°C, and more preferably from 0° to 30°C.

The concentration of the compound of formula (III) is preferably 1-30 % by weight of the reaction mixture.

Compounds of formula (VII) can be prepared by reacting a compound of formula (III) with a compound of formula (IX) wherein the substituents are defined as herein disclosed. Such reactions are usually carried out
20 in the presence of a base.

The bases suitable for the preparation of a compound of formula (VII) according to the present invention include, but not limited to, organic bases such as tertiary amine, such as trimethylamine, triethylamine (TEA), tributylamine, N,N-diisopropyl-ethylamine (DIPEA), pyridine, N-methylpiperidine, N,N-dimethylaminopyridine, diazabicyclooctane (DABCO), diazabicyclononene (DBN), or diazabicycloundecene (DBU), strong organic
25 bases such as organolithium reagents, for example methyl lithium, butyl lithium or phenyl lithium, Grignard reagents such as methyl magnesium halide or ethyl magnesium halide, inorganic bases such as alkaline earth metal or alkali metal hydroxides, carbonates, amides, or phosphates, wherein the counter ion is a lithium, sodium, potassium, cesium, calcium, magnesium or ammonium; for example, sodium amide, lithium diisopropylamide, sodium methanolate, sodium ethanolate, sodium tert-butanolate, sodium tert-amylate,
30 sodium hydroxide, potassium hydroxide, or sodium carbonate.

Preferably, the process for the preparation of a compound of formula (VII) according to the present invention is carried out in the presence of alkali metal hydroxides, for example sodium hydroxide or potassium hydroxide, alkali metal alkoxides, for example sodium tert-butanolate, or sodium tert-amylate, Grignard reagents, for example methyl magnesium halide or ethyl magnesium halide, alkyl lithium reagents, for example butyl lithium,
35 methyl lithium or phenyl lithium. More preferable, the process for the preparation of a compound of formula

(VI) according to the present invention is carried out in the presence of sodium tert-butanolate or sodium hydroxide.

The dilutants (e.g., solvents, suspending agents) suitable for the preparation of a compound of formula (VII) according to the present invention include, but not limited to, aromatic hydrocarbons, nitriles, for example acetonitrile, propionitrile, butyronitrile, isobutyronitrile or benzonitrile, ethers, for example diethyl ether, dibutyl ether, tert-butyl methyl ether, cyclopentyl methyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethoxymethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, anisole or dioxane, cyclic and acyclic esters, for example ethyl acetate, isopropylacetate or γ -valerolactone, ketones, for example acetone, 2-butanone, methylisobutylketone, cyclic and acyclic carbonates, for example dimethyl carbonate, diethyl carbonate, or propylene carbonate, N-substituted lactams, for example N-methyl-2-pyrrolidone (NMP or 1-methyl-2-pyrrolidone), amides, for example N,N-dimethylformamide (DMF) or dimethylacetamide (DMA), cyclic ureas, for example N,N'-dimethylethyleneurea (DMI), or mixtures of such dilutants. Water may also be used as a component of a biphasic mixture.

In one embodiment, the process for the preparation of a compound of formula (VII) according to the present invention is carried out in the presence of a dipolar aprotic solvent. Preferably, the process for the preparation of a compound of formula (III) is carried out in the presence of a dipolar aprotic dilutant, such as isopropylacetate, γ -valerolactone, butyronitrile, 2-methyl-tetrahydrofuran or propylene carbonate. More preferably ethyl acetate, isopropyl acetate, or 2-methyl-tetrahydrofuran.

In one embodiment, the process for the preparation of a compound of formula (VII) according to the present invention is carried out in a biphasic system comprising an organic solvent, preferably isopropyl acetate, 2-methyl-tetrahydrofuran, propylene carbonate, toluene, or xylenes as single isomers or as a mixture of isomers and an aqueous solution of a base, preferably a solution of sodium hydrogen carbonate or sodium carbonate or sodium hydroxide, or an organic amine such as triethylamine or diisopropylethyl amine. Preferably the process for the preparation of a compound of formula (III) according to the present invention is carried out in a biphasic system comprising 2-methyl-tetrahydrofuran or xylenes as single isomers or as a mixture of isomers and an aqueous solution of a base, preferably a solution of sodium hydrogen carbonate or sodium hydroxide.

In one embodiment, in the process for the preparation of a compound of formula (VII) according to the present invention, the amount of base can be from 1.0 to 3.0 equivalents, 1.0 to 2.0 equivalents, from 1.0 to 1.5 eq., from 1.0 to 1.3 eq., from 1.0 to 1.2 eq., from 1.0 to 1.1 eq., from 1.0 to 1.05 eq. Preferably from 1.0 to 2.5 eq, more preferably from 1.0 to 2.0 eq.

In one embodiment, in the process for the preparation of a compound of formula (VII) according to the present invention, the amount of compound of formula (IX) can be from 1.0 to 2.0 equivalents, from 1.0 to 1.5 eq., from 1.0 to 1.3 eq., from 1.0 to 1.2 eq., from 1.0 to 1.1 eq., from 1.0 to 1.05 eq., from 1.0 to 1.01 eq., from 1.0 to 1.0 eq. Preferably from 1.0 to 1.2 eq, more preferably from 1.0 to 1.01 eq.

In one embodiment, the process for the preparation of a compound of formula (VII) according to the present invention is carried out in a two-step one-pot procedure, wherein a compound of formula (III) is reacted with a base followed by the addition of compound of formula (IX).

In another embodiment, the process for the preparation of a compound of formula (VII) according to the present invention is carried out in a one-step procedure, wherein a compound of formula (III) is reacted with a base, and a compound of formula (IX) simultaneously.

In the present invention, the expression "molar equivalents" in the process for the preparation of a compound of formula (VII) is based on the number of moles (mol) of the compound of formula (III).

The reaction can be carried out at a temperature from -20°C to 100°C, preferably from -10°C to 50°C, and more preferably from 0° to 30°C.

The concentration of the compound of formula (III) is preferably 1-30 % by weight of the reaction mixture.

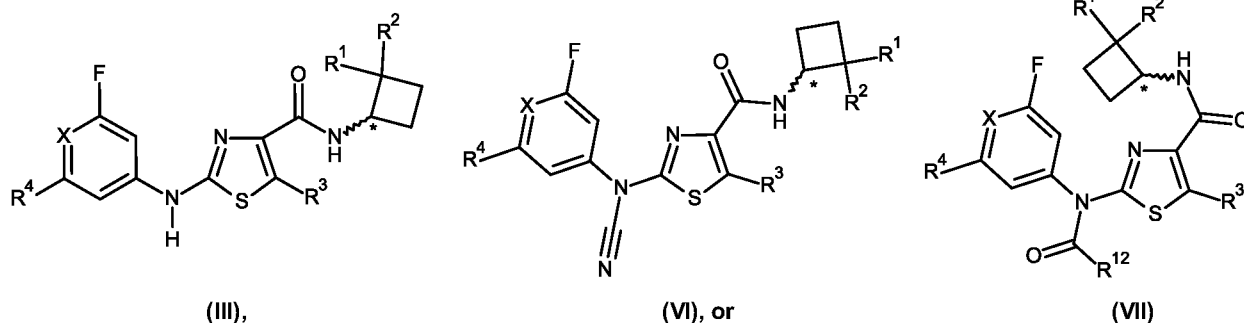
Where typical process conditions (e.g., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given to make the compounds of the present invention, minor modifications to these process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the reactant or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures as long as the reagents stay the same.

In one embodiment of the invention, the process can be performed in a packed bed reactor in a continuous flow mode or recirculation mode.

In another embodiment of the invention, the process can also be performed in a continuous stirred-tank reactor in a recirculation mode.

In one embodiment of the invention, there is provided a composition comprising a compound of formula (III), (VI), or (VII), for controlling or preventing infestation of plants by the phytopathogenic microorganism, preferably phytopathogenic fungi.

Said fungicidal composition comprising a mixture of components (A) and (B) as active ingredients, wherein component (A) is a compound selected from a compound of formula (III), (VI), or (VII),



wherein X is CH or N; R¹ and R² are independently selected from C₁-C₂-alkyl, or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R⁴ is fluoro; R³ is methyl; and R¹² is methyl, ethyl, isopropyl,

methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; or a salt or an N-oxide thereof; and wherein said compound of formula (III), (VI), or (VII), is the (S) or (R) enantiomer or a mixture thereof;

and

- 5 component (B) is a compound selected from the group consisting of azoxystrobin, trifloxystrobin, pyraclostrobin, picoxystrobin, coumoxystrobin, metyltetraprole, cyproconazole, tebuconazole, difenoconazole, hexaconazole, propiconazole, fenhexamid, prothioconazole, mefentrifluconazole, prochloraz, fenpropidin, fenpropimorph, fluxapyroxad, fluopyram, isopyrazam, sedaxane, benzovindiflupyr, pydiflumetofen, isoflucypram, bixafen, penthiopyrad, inpyrfluxam, isofetamid, pyrapropoyne, fluindapyr, fempicoxamid, 10 florylpicoxamid, acibenzolar-S-methyl, trinexepac-ethyl, fosetyl-aluminium, chlorothalonil, mancozeb, mandipropamid, oxathiapiprolin, fluazinam, fludioxonil, cyprodinil, metalaxyl-M, aminopyrifin, folpet, ipflufenquin, quinofumelin, tebufloquin, tolprocarb, tricyclazole, pyroquilon, cyflufenamid, metrafenone, N'-[2-chloro-4-(2-fluorophenoxy)-5-methyl-phenyl]-N-ethyl-N-methyl-formamidin, (this compound may be prepared from the methods described in WO 2016/202742); N'-[4-(2-bromophenoxy)-5-chloro-2-methyl-phenyl]-N-ethyl-N-methyl-formamidin, (this compound may be prepared from the methods described in WO 2016/202688); 15 N-(1-benzyl-1,3-dimethyl-butyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3,3,3-trifluoro-1-methyl-propyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3-chloro-1-methyl-but-3-enyl)-8-fluoro-quinoline-3-carboxamide, (these compounds may be prepared from the methods described in WO 2017/153380); 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 4,4-difluoro-3,3-dimethyl-1-(7-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,6-trifluoro-3,3-dimethyl-isoquinoline, (these compounds may be prepared from the methods described in WO 2017/025510); 1-(4,5-dimethylbenzimidazol-1-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline, 6-chloro-4,4-difluoro-3,3-dimethyl-1-(4-methylbenzimidazol-1-yl)isoquinoline, (these compounds may be prepared from the methods described in WO 2016/156085); N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidin, N'-[5-chloro-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidin, N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-isopropyl-N-methyl-formamidin, (these compounds may be prepared from the methods described in WO 2015/155075); N-isopropyl-N'-[5-methoxy-2-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-phenyl-ethyl)phenyl]-N-methyl-formamidin, (this compound may be prepared from the methods described in WO 2018/228896); N-methoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]cyclopropanecarboxamide, N,2-dimethoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, N-ethyl-2-methyl-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, 1-methoxy-3-methyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, 1,3-dimethoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, 3-ethyl-1-methoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, ethyl 1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]pyrazole-4-carboxylate, N,N-dimethyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-1,2,4-triazol-3-amine, (these compounds may be prepared from the methods described in WO 2017/055473, WO 2017/055469, WO 2017/093348 and WO

2017/118689); methyl (Z)-3-methoxy-2-[2-methyl-5-[3-(trifluoromethyl)pyrazol-1-yl]phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(3-propylpyrazol-1-yl)phenoxy]prop-2-enoate, methyl (Z)-2-[5-(3-isopropylpyrazol-1-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(4-propyltriazol-2-yl)phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-[4-(trifluoromethyl)triazol-2-yl]phenoxy]prop-2-enoate, (these compounds may be prepared from the methods described in WO 2020/079111); methyl (Z)-2-(5-cyclohexyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-(5-cyclopentyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(4-cyclohexylthiazol-2-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-[4-(ethoxymethyl)thiazol-2-yl]-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(4-bromothiazol-2-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-[5-(trifluoromethyl)thiazol-2-yl]phenoxy]prop-2-enoate, TAEGRO® (i.e., *Bacillus amyloliquefaciens* strain FZB24), Timorex Gold™ (plant extract comprising tea tree oil), and metarylpicoxamid.

In general, the weight ratio of component (A) to component (B) may preferably be from 100:1 to 1:100, from 50:1 to 1:50, from 20:1 to 1:40, from 15:1 to 1:30, from 12:1 to 1:25, from 10:1 to 1:20, from 5:1 and 1:15, from 3:1 to 1:10 or from 2:1 to 1:5.

In one embodiment to the present invention, there is provided a fungicidal composition comprising a mixture of component (A) and a component (B) as active ingredients, wherein component (A) is selected from a formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), and component (B) is a compound selected from the group consisting of azoxystrobin, trifloxystrobin, pyraclostrobin, picoxystrobin, coumoxystrobin, metyltetraprole, cyproconazole, tebuconazole, difenoconazole, hexaconazole, propiconazole, fenhexamid, prothioconazole, mefentrifluconazole, prochloraz, fenpropidin, fenpropimorph, fluxapyroxad, fluopyram, isopyrazam, sedaxane, benzovindiflupyr, pydiflumetofen, isoflucypram, bixafen, penthiopyrad, inpyrfluxam, isofetamid, pyrapropoyne, fluindapyr, fenpicoxamid, florylpicoxamid, acibenzolar-S-methyl, trinexepac-ethyl, fosetyl-aluminium, chlorothalonil, mancozeb, mandipropamid, oxathiapiprolin, fluazinam, fludioxonil, cyprodinil, metalaxyl-M, aminopyrifen, folpet, ipflufenquin, quinofumelin, tebufloquin, tolprocarb, tricyclazole, pyroquilon, cyflufenamid, metrafenone, N'-[2-chloro-4-(2-fluorophenoxy)-5-methyl-phenyl]-N-ethyl-N-methyl-formamidine, (this compound may be prepared from the methods described in WO 2016/202742); N'-[4-(2-bromophenoxy)-5-chloro-2-methyl-phenyl]-N-ethyl-N-methyl-formamidine, (this compound may be prepared from the methods described in WO 2016/202688); N-(1-benzyl-1,3-dimethyl-butyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3,3,3-trifluoro-1-methyl-propyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3-chloro-1-methyl-but-3-enyl)-8-fluoro-quinoline-3-carboxamide, (these compounds may be prepared from the methods described in WO 2017/153380); 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 4,4-difluoro-3,3-dimethyl-1-(7-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,6-trifluoro-3,3-dimethyl-isoquinoline, (these compounds may be prepared from the methods described in WO 2017/025510); 1-(4,5-dimethylbenzimidazol-1-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline, 6-chloro-4,4-difluoro-3,3-dimethyl-1-(4-methylbenzimidazol-1-yl)isoquinoline, (these compounds may be prepared from the methods described in

WO 2016/156085); N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine, N'-[5-chloro-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine, N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-isopropyl-N-methyl-formamidine, (these compounds may be prepared from the methods described in WO 2015/155075); N-isopropyl-N'-[5-methoxy-2-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-phenyl-ethyl)phenyl]-N-methyl-formamidine, (this compound may be prepared from the methods described in WO 2018/228896); N-methoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]cyclopropanecarboxamide, N,2-dimethoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, N-ethyl-2-methyl-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, 1-methoxy-3-methyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, 1,3-dimethoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, 3-ethyl-1-methoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, ethyl 1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]pyrazole-4-carboxylate, N,N-dimethyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-1,2,4-triazol-3-amine, (these compounds may be prepared from the methods described in WO 2017/055473, WO 2017/055469, WO 2017/093348 and WO 2017/118689); methyl (Z)-3-methoxy-2-[2-methyl-5-[3-(trifluoromethyl)pyrazol-1-yl]phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(3-propylpyrazol-1-yl)phenoxy]prop-2-enoate, methyl (Z)-2-[5-(3-isopropylpyrazol-1-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(4-propyltriazol-2-yl)phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-[4-(trifluoromethyl)triazol-2-yl]phenoxy]prop-2-enoate, (these compounds may be prepared from the methods described in WO 2020/079111); methyl (Z)-2-(5-cyclohexyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-(5-cyclopentyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(4-cyclohexylthiazol-2-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-[4-(ethoxymethyl)thiazol-2-yl]-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(4-bromothiazol-2-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-[5-(trifluoromethyl)thiazol-2-yl]phenoxy]prop-2-enoate, TAEGRO® (i.e., *Bacillus amyloliquefaciens* strain FZB24), Timorex Gold™ (plant extract comprising tea tree oil), and metarylpicoxamid.

In another embodiment to the present invention, there is provided a fungicidal composition comprising a mixture of component (A) and a component (B) as active ingredients, wherein component (A) is selected from a formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), and component (B) is a compound selected from the group consisting of azoxystrobin, trifloxystrobin, metyltetraprole, difenoconazole, hexaconazole, propiconazole, prothioconazole, mefentrifluconazole, fenpropidin, fenpropimorph, fluxapyroxad, fluopyram, isopyrazam, sedaxane, benzovindiflupyr, pydiflumetofen, isoflucypram, isofetamid, pyrapropoyne, fluindapyr, fempicoxamid, florylpicoxamid, acibenzolar-S-methyl, chlorothalonil, mancozeb, mandipropamid, oxathiapiprolin, fluazinam, fludioxonil, cyprodinil, metalaxyl-M, aminopyrifin, folpet, ipflufenquin, quinofumelin, tricyclazole, pyroquilon, cyflufenamid, metrafenone, N'-[2-chloro-4-(2-fluorophenoxy)-5-methyl-phenyl]-N-ethyl-N-methyl-formamidine, N'-[4-(2-bromophenoxy)-5-chloro-2-methyl-phenyl]-N-ethyl-N-methyl-formamidine, N-(1-benzyl-1,3-dimethyl-butyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3,3,3-trifluoro-1-methyl-propyl)-8-fluoro-quinoline-3-

carboxamide, N-(1-benzyl-3-chloro-1-methyl-but-3-enyl)-8-fluoro-quinoline-3-carboxamide, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 4,4-difluoro-3,3-dimethyl-1-(7-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,6-trifluoro-3,3-dimethyl-isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline, 6-chloro-4,4-difluoro-3,3-dimethyl-1-(4-methylbenzimidazol-1-yl)isoquinoline, N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine, N'-[5-chloro-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine, N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-isopropyl-N-methyl-formamidine, N-isopropyl-N'-[5-methoxy-2-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-phenyl-ethyl)phenyl]-N-methyl-formamidine, N-methoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]cyclopropanecarboxamide, N,2-dimethoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, N-ethyl-2-methyl-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, 1-methoxy-3-methyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, 1,3-dimethoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, 3-ethyl-1-methoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, ethyl 1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]pyrazole-4-carboxylate, N,N-dimethyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-1,2,4-triazol-3-amine, methyl (Z)-3-methoxy-2-[2-methyl-5-[3-(trifluoromethyl)pyrazol-1-yl]phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(3-propylpyrazol-1-yl)phenoxy]prop-2-enoate, methyl (Z)-2-[5-(3-isopropylpyrazol-1-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(4-propyltriazol-2-yl)phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-[4-(trifluoromethyl)triazol-2-yl]phenoxy]prop-2-enoate, methyl (Z)-2-[5-(5-cyclohexyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(5-cyclopentyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(4-cyclohexylthiazol-2-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-[4-(ethoxymethyl)thiazol-2-yl]-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(4-bromothiazol-2-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, and methyl (Z)-3-methoxy-2-[2-methyl-5-[5-(trifluoromethyl)thiazol-2-yl]phenoxy]prop-2-enoate.

Preferably, there is provided a fungicidal composition comprising a mixture of component (A) and a component (B) as active ingredients, wherein component (A) is selected from a compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), and component (B) is a compound selected from the group consisting of azoxystrobin, trifloxystrobin, metyltetraprole, difenoconazole, hexaconazole, propiconazole, prothioconazole, mefentrifluconazole, fenpropidin, fenpropimorph, fluxapyroxad, fluopyram, isopyrazam, sedaxane, benzovindiflupyr, pydiflumetofen, isoflucypram, isofetamid, pyrapropoyne, fluindapyr, fempicoxamid, florylpicoxamid, chlorothalonil, mancozeb, mandipropamid, oxathiapiprolin, fluazinam, fludioxonil, cyprodinil, metalaxyl-M, aminopyrifen, folpet, ipflufenquin, quinofumelin, tricyclazole, pyroquilon, N-(1-benzyl-1,3-dimethyl-butyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3,3,3-trifluoro-1-methyl-propyl)-8-fluoro-quinoline-3-carboxamide, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 4,4-difluoro-3,3-dimethyl-1-(7-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4,5-

trifluoro-3,3-dimethyl-isoquinoline, and 1-(4,5-dimethylbenzimidazol-1-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline.

In one set of embodiments, component (B) is a compound selected from the group consisting of azoxystrobin, trifloxystrobin, metyltetraprole, difenoconazole, hexaconazole, propiconazole, prothioconazole, 5 mefentrifluconazole, fenpropidin, fenpropimorph, fluxapyroxad, fluopyram, isopyrazam, sedaxane, benzovindiflupyr, pydiflumetofen, bixafen, isoflucypram, isofetamid, pyrapropoyne, fluindapyr, fencicoxamid, florylpicoxamid, metarylpicoxamid, chlorothalonil, mancozeb, mandipropamid, oxathiapiprolin, fluazinam, fludioxonil, cyprodinil, metalaxyl-M, aminopyrifin, folpet, ipflufenquin, quinofumelin, tricyclazole, pyroquilon, acibenzolar-S-methyl, cyflufenamid, metrafenone, fluazinam, fosetyl-aluminium, N-(1-benzyl-1,3-dimethyl-10 butyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3,3,3-trifluoro-1-methyl-propyl)-8-fluoro-quinoline-3-carboxamide, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 4,4-difluoro-3,3-dimethyl-1-(7-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline, TAEGRO®, and Timorex Gold™.

15 In a particularly preferred set of embodiments, component (B) is a compound selected from the group consisting of azoxystrobin, trifloxystrobin, metyltetraprole, difenoconazole, hexaconazole, propiconazole, prothioconazole, mefentrifluconazole, fenpropidin, fenpropimorph, fluxapyroxad, fluopyram, isopyrazam, sedaxane, benzovindiflupyr, pydiflumetofen, isoflucypram, isofetamid, pyrapropoyne, fluindapyr, fencicoxamid, florylpicoxamid, chlorothalonil, mancozeb, mandipropamid, oxathiapiprolin, fluazinam, 20 fludioxonil, cyprodinil, metalaxyl-M, aminopyrifin, folpet, ipflufenquin, quinofumelin, tricyclazole, pyroquilon, N-(1-benzyl-1,3-dimethyl-butyl)-8-fluoro-quinoline-3-carboxamide, N-(1-benzyl-3,3,3-trifluoro-1-methyl-propyl)-8-fluoro-quinoline-3-carboxamide, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 4,4-difluoro-3,3-dimethyl-1-(7-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline, 25 N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine, N-isopropyl-N'-[5-methoxy-2-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-phenyl-ethyl)phenyl]-N-methyl-formamidine, TAEGRO®, Timorex Gold™, acibenzolar-S-methyl, cyflufenamid, metrafenone, fosetyl-aluminium, metarylpicoxamid, methyl (Z)-3-methoxy-2-[2-methyl-5-[3-(trifluoromethyl)pyrazol-1-yl]phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(3-propylpyrazol-1-yl)phenoxy]prop-2-enoate, 30 methyl (Z)-2-(5-cyclohexyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-(5-cyclopentyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate, methyl (Z)-2-[5-(3-isopropylpyrazol-1-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-(4-propyltriazol-2-yl)phenoxy]prop-2-enoate, methyl (Z)-3-methoxy-2-[2-methyl-5-[4-(trifluoromethyl)triazol-2-yl]phenoxy]prop-2-enoate, N-methoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]cyclopropanecarboxamide, N,2-dimethoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, 35 (trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, N-ethyl-2-methyl-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide, 1-methoxy-3-methyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, 1,3-dimethoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea,

yl]phenyl]methyl]urea, 3-ethyl-1-methoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea, and ethyl 1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]pyrazole-4-carboxylate.

The component (B) compounds are referred to herein and above by a so-called "ISO common name" or another "common name" being used in individual cases or a trademark name. The component (B) compounds are known and are commercially available and/or can be prepared using procedures known in the art and/or procedures reported in the literature.

"TIMOREX Gold™" or "Timorex Gold®" as used herein, refers to melaleuca alternifolia oil, which is an extract of the tea tree plant *Melaleuca alternifolia*, commercially available as Timorex Gold®, which is a broad-spectrum botanical biofungicide.

TAEGRO™ or TAEGRO® as used herein, refers to a microorganism-based fungicide formulated as a wettable powder containing 130 g/kg *Bacillus amyloliquefaciens* strain FZB24, having Accession No. DSM 10271 (13% w/w minimum of 1×10^{13} cfu/kg), commercially available as TAEGRO®.

Throughout this document the expression "composition" stands for the various mixtures or combinations of component A, wherein said component A is selected from a compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), and components (B) (including the above-defined embodiments), for example in a single "ready-mix" form, in a combined spray mixture composed from separate formulations of the single active ingredient components, such as a "tank-mix", and in a combined use of the single active ingredients when applied in a sequential manner, i.e. one after the other with a reasonably short period, such as a few hours or days. The order of applying the component A, wherein said component A is selected from a compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), and component (B) is not essential for working the present invention.

In one embodiment of the present invention, there is provided a method for controlling harmful fungi, wherein the pest, their habitat, breeding grounds, their locus, or the plants to be protected against pest attack, the soil or plant propagation material (preferably seed) are treated with a pesticidally effective amount of a compound of formula (III), (VI), or (VII), according to the present invention.

In one embodiment of the present invention, there is provided a method for controlling harmful fungi, wherein the pest, their habitat, breeding grounds, their locus or the plants to be protected against pest attack, the soil or plant propagation material (preferably seed) are treated with a composition comprising a pesticidally effective amount of a compound of formula (III), (VI) or (VII), according to the present invention.

Preferably the compounds of the present invention and compositions comprising said compound of formula (III), (VI), or (VII), are suitable for controlling fungal plant diseases.

The compounds of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention may be used in unmodified form or, preferably, together with the adjuvants conventionally employed in the art of formulation. To this end they may

be conveniently formulated in known manner to emulsifiable concentrates, coatable pastes, directly sprayable or dilutable solutions or suspensions, dilute emulsions, wettable powders, soluble powders, dusts, granulates, and also encapsulations e.g., in polymeric substances. As with the type of the compositions, the methods of application, such as spraying, atomising, dusting, scattering, coating, or pouring, are chosen in accordance with the intended objectives and the prevailing circumstances. The compositions may also contain further adjuvants such as stabilizers, antifoams, viscosity regulators, binders or tackifiers as well as fertilizers, micronutrient donors or other formulations for obtaining special effects.

Suitable carriers and adjuvants, e.g., for agricultural use, can be solid or liquid and are substances useful in formulation technology, e.g., natural or regenerated mineral substances, solvents, dispersants, wetting agents, tackifiers, thickeners, binders, or fertilizers. Such carriers are for example described in WO 1997/33890.

Suspension concentrates are aqueous formulations in which finely divided solid particles of the active compound are suspended. Such formulations include anti-settling agents and dispersing agents and may further include a wetting agent to enhance activity as well an anti-foam and a crystal growth inhibitor. In use, these concentrates are diluted in water and normally applied as a spray to the area to be treated. The amount of active ingredient may range from 0.5% to 95% of the concentrate.

Wettable powders are in the form of finely divided particles which disperse readily in water or other liquid carriers. The particles contain the active ingredient retained in a solid matrix. Typical solid matrices include fuller's earth, kaolin clays, silicas and other readily wet organic or inorganic solids. Wettable powders normally contain from 5% to 95% of the active ingredient plus a small amount of wetting, dispersing or emulsifying agent.

Emulsifiable concentrates are homogeneous liquid compositions dispersible in water or other liquid and may consist entirely of the active compound with a liquid or solid emulsifying agent, or may also contain a liquid carrier, such as xylene, heavy aromatic naphthas, isophorone and other non-volatile organic solvents. In use, these concentrates are dispersed in water or other liquid and normally applied as a spray to the area to be treated. The amount of active ingredient may range from 0.5% to 95% of the concentrate.

Granular formulations include both extrudates and relatively coarse particles and are usually applied without dilution to the area in which treatment is required. Typical carriers for granular formulations include sand, fuller's earth, attapulgite clay, bentonite clays, montmorillonite clay, vermiculite, perlite, calcium carbonate, brick, pumice, pyrophyllite, kaolin, dolomite, plaster, wood flour, ground corn cobs, ground peanut hulls, sugars, sodium chloride, sodium sulphate, sodium silicate, sodium borate, magnesia, mica, iron oxide, zinc oxide, titanium oxide, antimony oxide, cryolite, gypsum, diatomaceous earth, calcium sulphate and other organic or inorganic materials which absorb or which can be coated with the active compound. Granular formulations normally contain 5% to 25% of active ingredients which may include surface-active agents such as heavy aromatic naphthas, kerosene and other petroleum fractions, or vegetable oils; and/or stickers such as dextrans, glue or synthetic resins.

Dusts are free-flowing admixtures of the active ingredient with finely divided solids such as talc, clays, flours, and other organic and inorganic solids which act as dispersants and carriers.

The active ingredients (compounds of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below)), and mixtures thereof with component (B) can also be contained in microcapsules. Microcapsules contain the active ingredients in a porous carrier. This enables the active ingredients to be released into the environment in controlled amounts (e.g., slow-release). Microcapsules usually have a diameter of from 0.1 to 500 microns. They contain active ingredients in an amount of about from 25 to 95 % by weight of the capsule weight. The active ingredients can be in the form of a monolithic solid, in the form of fine particles in solid or liquid dispersion or in the form of a suitable solution.

The encapsulating membranes can comprise, for example, natural or synthetic rubbers, cellulose, styrene/butadiene copolymers, polyacrylonitrile, polyacrylate, polyesters, polyamides, polyureas, polyurethane, or chemically modified polymers, and starch xanthates, or other polymers that are known to the person skilled in the art. Alternatively, very fine microcapsules can be formed in which the active ingredient is contained in the form of finely divided particles in a solid matrix of base substance, but the microcapsules are not themselves encapsulated.

Microcapsules are typically droplets or granules of the active ingredient enclosed in an inert porous shell which allows escape of the enclosed material to the surroundings at controlled rates. Encapsulated droplets are typically 1 to 50 microns in diameter. The enclosed liquid typically constitutes 50 to 95% of the weight of the capsule and may include solvent in addition to the active compound. Encapsulated granules are generally porous granules with porous membranes sealing the granule pore openings, retaining the active species in liquid form inside the granule pores. Granules typically range from 1 millimetre to 1 centimetre and preferably 1 to 2 millimetres in diameter. Granules are formed by extrusion, agglomeration or prilling, or are naturally occurring. Examples of such materials are vermiculite, sintered clay, kaolin, attapulgite clay, sawdust, and granular carbon. Shell or membrane materials include natural and synthetic rubbers, cellulosic materials, styrene-butadiene copolymers, polyacrylonitriles, polyacrylates, polyesters, polyamides, polyureas, polyurethanes and starch xanthates.

Other useful formulations for agrochemical applications include simple solutions of the active ingredient in a solvent in which it is completely soluble at the desired concentration, such as acetone, alkylated naphthalenes, xylene and other organic solvents. Pressurised sprayers, wherein the active ingredient is dispersed in finely divided form because of vaporisation of a low boiling dispersant solvent carrier, may also be used.

Suitable agricultural adjuvants and carriers that are useful in formulating the compositions of the invention in the formulation types described above are well known to a person skilled in the art.

Liquid carriers that can be employed include, for example, water, toluene, xylene, petroleum naphtha, crop oil, acetone, methyl ethyl ketone, cyclohexanone, acetic anhydride, acetonitrile, acetophenone, amyl acetate, 2-butanone, chlorobenzene, cyclohexane, cyclohexanol, alkyl acetates, diacetonalcohol, 1,2-dichloropropane, diethanolamine, p diethylbenzene, diethylene glycol, diethylene glycol abietate, diethylene glycol butyl ether,

diethylene glycol ethyl ether, diethylene glycol methyl ether, N,N-dimethyl formamide, dimethyl sulfoxide, 1,4-dioxane, dipropylene glycol, dipropylene glycol methyl ether, dipropylene glycol dibenzoate, diproxitol, alkyl pyrrolidinone, ethyl acetate, 2-ethyl hexanol, ethylene carbonate, 1,1,1-trichloroethane, 2-heptanone, alpha pinene, d-limonene, ethylene glycol, ethylene glycol butyl ether, ethylene glycol methyl ether, gamma-
 5 butyrolactone, glycerol, glycerol diacetate, glycerol monoacetate, glycerol triacetate, hexadecane, hexylene glycol, isoamyl acetate, isobornyl acetate, isooctane, isophorone, isopropyl benzene, isopropyl myristate, lactic acid, laurylamine, mesityl oxide, methoxy-propanol, methyl isoamyl ketone, methyl isobutyl ketone, methyl laurate, methyl octanoate, methyl oleate, methylene chloride, m-xylene, n-hexane, n-octylamine, octadecanoic
 10 acid, octyl amine acetate, oleic acid, oleylamine, o-xylene, phenol, polyethylene glycol (PEG400), propionic acid, propylene glycol, propylene glycol monomethyl ether, p-xylene, toluene, triethyl phosphate, triethylene glycol, xylene sulfonic acid, paraffin, mineral oil, trichloroethylene, perchloroethylene, ethyl acetate, amyl acetate, butyl acetate, methanol, ethanol, isopropanol, and higher molecular weight alcohols such as amyl alcohol, tetrahydrofurfuryl alcohol, hexanol, octanol, etc., ethylene glycol, propylene glycol, glycerine and N-methyl-2-pyrrolidinone. Water is generally the carrier of choice for the dilution of concentrates.

15 Suitable solid carriers include, for example, talc, titanium dioxide, pyrophyllite clay, silica, attapulgite clay, kieselguhr, chalk, diatomaceous earth, lime, calcium carbonate, bentonite clay, fuller's earth, cotton seed hulls, wheat flour, soybean flour, pumice, wood flour, walnut shell flour and lignin.

A broad range of surface-active agents are advantageously employed in both said liquid and solid compositions, especially those designed to be diluted with carrier before application. These agents, when
 20 used, normally comprise from 0.1% to 15% by weight of the formulation. They can be anionic, cationic, non-ionic or polymeric in character and can be employed as emulsifying agents, wetting agents, suspending agents or for other purposes. Typical surface-active agents include salts of alkyl sulfates, such as diethanolammonium lauryl sulphate; alkylarylsulfonate salts, such as calcium dodecylbenzenesulfonate; alkylphenol-alkylene oxide addition products, such as nonylphenol-C.sub. 18 ethoxylate; alcohol-alkylene oxide addition products, such
 25 as tridecyl alcohol-C.sub. 16 ethoxylate; soaps, such as sodium stearate; alkyl naphthalenesulfonate salts, such as sodium dibutyl naphthalenesulfonate; dialkyl esters of sulfosuccinate salts, such as sodium di(2-ethylhexyl) sulfosuccinate; sorbitol esters, such as sorbitol oleate; quaternary amines, such as lauryl trimethylammonium chloride; polyethylene glycol esters of fatty acids, such as polyethylene glycol stearate; block copolymers of ethylene oxide and propylene oxide; and salts of mono and dialkyl phosphate esters.

30 Other adjuvants commonly utilized in agricultural compositions include crystallisation inhibitors, viscosity modifiers, suspending agents, spray droplet modifiers, pigments, antioxidants, foaming agents, anti-foaming agents, light-blocking agents, compatibilizing agents, antifoam agents, sequestering agents, neutralising agents and buffers, corrosion inhibitors, dyes, odorants, spreading agents, penetration aids, micronutrients, emollients, lubricants and sticking agents.

35 In addition, further, other biocidal active ingredients or compositions may be combined with the compounds or compositions of the invention and used in the methods of the invention and applied simultaneously or sequentially with the compounds or compositions of the invention. When applied simultaneously, these further

active ingredients may be formulated together with the compounds or compositions of the invention or mixed in, for example, the spray tank. These further biocidal active ingredients may be fungicides, herbicides, insecticides, bactericides, acaricides, nematocides and/or plant growth regulators.

Pesticidal agents are referred to herein using their common name are known, for example, from "The Pesticide Manual", 15th Ed., British Crop Protection Council 2009.

In addition, the compositions of the invention may also be applied with one or more systemically acquired resistance inducers ("SAR" inducer). SAR inducers are known and described in, for example, United States Patent No. US 6,919,298 and include, for example, salicylates and the commercial SAR inducer acibenzolar-S-methyl.

The compounds of formula (III), (VI), or (VII), according to the invention are normally used in the form of agrochemical compositions and can be applied to the crop area or plant to be treated, simultaneously or in succession with further compounds. These further compounds can be e.g., fertilizers or micronutrient donors or other preparations, which influence the growth of plants. They can also be selective herbicides or non-selective herbicides as well as insecticides, fungicides, bactericides, nematocides, molluscicides or mixtures of several of these preparations, if desired together with further carriers, surfactants or application promoting adjuvants customarily employed in the art of formulation.

The compounds of formula (III), (VI), or (VII), according to the invention may be used in the form of (fungicidal) compositions for controlling or protecting against phytopathogenic microorganisms, comprising as active ingredient a compound as defined herein, in free form or in agrochemical usable salt form, and at least one of the above-mentioned adjuvants.

The invention therefore provides a composition, preferably a fungicidal composition, comprising a compound of formula (III), (VI), or (VII), according to the invention, an agriculturally acceptable carrier and optionally an adjuvant. An agricultural acceptable carrier is for example a carrier that is suitable for agricultural use. Agricultural carriers are well known in the art. Preferably, said composition may comprise at least one or more pesticidal-active compounds, for example an additional fungicidal active ingredient in addition to a compound of formula formula (III), (VI), or (VII).

The compound of formula (III), (VI), or (VII), according to the invention may be the sole active ingredient of a composition or it may be admixed with one or more additional active ingredients such as a pesticide, including fungicides, herbicide, insecticide, synergist, or plant growth regulator where appropriate. An additional active ingredient may, in some cases, result in unexpected synergistic activities.

Examples of suitable additional active ingredients include the following: acycloamino acid fungicides, aliphatic nitrogen fungicides, amide fungicides, anilide fungicides, antibiotic fungicides, aromatic fungicides, arsenical fungicides, aryl phenyl ketone fungicides, benzamide fungicides, benzanilide fungicides, benzimidazole fungicides, benzothiazole fungicides, botanical fungicides, bridged diphenyl fungicides, carbamate fungicides, carbanilate fungicides, conazole fungicides, copper fungicides, dicarboximide fungicides, dinitrophenol fungicides, dithiocarbamate fungicides, dithiolane fungicides, furamide fungicides, furanilide fungicides,

hydrazide fungicides, imidazole fungicides, mercury fungicides, morpholine fungicides, organophosphorous fungicides, organotin fungicides, oxathiin fungicides, oxazole fungicides, phenylsulfamide fungicides, polysulfide fungicides, pyrazole fungicides, pyridine fungicides, pyrimidine fungicides, pyrrole fungicides, quaternary ammonium fungicides, quinoline fungicides, quinone fungicides, quinoxaline fungicides, strobilurin fungicides, sulfonanilide fungicides, thiadiazole fungicides, thiazole fungicides, thiazolidine fungicides, thiocarbamate fungicides, thiophene fungicides, triazine fungicides, triazole fungicides, triazolopyrimidine fungicides, urea fungicides, valinamide fungicides, and zinc fungicides.

A further aspect of the present invention is a method of controlling diseases on useful plants or on propagation material thereof caused by phytopathogens, which comprises applying to the useful plants, the locus thereof or propagation material thereof a composition according to the invention. Preferred is a method, which comprises applying to the useful plants or to the locus thereof a composition according to the invention, more preferably to the useful plants. Further preferred is a method, which comprises applying to the propagation material of the useful plants a composition according to the invention.

Throughout this document the expression "composition" refers to the various mixtures or combinations of components (A) and (B), for example in a single "ready-mix" form, in a combined spray mixture composed from separate formulations of the single active ingredient components, such as a "tank-mix", and in a combined use of the single active ingredients when applied in a sequential manner, i.e. one after the other with a reasonably short period, such as a few hours or days. The order of applying the components (A) and (B) is not essential for working the present invention.

The compositions according to the invention are effective against harmful microorganisms, such as microorganisms, that cause phytopathogenic diseases, in particular against phytopathogenic fungi and bacteria.

Preferably, the formulation comprising a composition according to the invention may comprise of from 0.01 to 90% by weight of the composition comprising components (A) and (B), and of from 0 to 20% of an agriculturally acceptable surfactant. Preferably, the formulation further comprises other active agents, in particular microbiocides and pesticides, more generally.

Advantageously, the formulation further comprises of from 10 to 99.99% solid or liquid formulation inerts, conservatives and/or adjuvants.

The present invention preferably also relates to a concentrated composition for dilution by the user, comprising a composition according to the invention, comprising of from 2 to 80% by weight, preferably between 5 and 70% by weight, of active agents comprising at least a composition comprising (A) and (B), and optionally, other active agents.

The present invention preferably also relates to a seed dressing formulation for application to plant propagation materials, comprising a composition according to the invention, and further comprising a dilutant. Preferably, the seed dressing formulation is in the form of an aqueous suspension or in a dry powder form having good

adherence to the plant propagation materials. Preferably, the seed dressing formulation may comprise the active agents in an encapsulated form, preferably a slow-release capsules and/or microcapsules.

The present invention preferably also relates to a method of combating and controlling phytopathogens, comprising applying a fungicidally effective amount of a composition according to the invention to a pest, a
5 locus of pest, or to a plant susceptible to attack by a pest, with the exception of a method for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body.

Application according to the methods or uses according to any one of embodiments according to the invention is preferably to a crop of plants, the locus thereof or propagation material thereof. Preferably application is to the phytopathogen, to the locus of the phytopathogen, or to a plant susceptible to attack by the phytopathogen,
10 or to a propagation material thereof. Application of the compounds as defined in any one of embodiments 1 to 13 can be performed according to any of the usual modes of application, e.g., foliar, drench, soil, in furrow etc.

The compounds as defined in any one of embodiments according to the invention are preferably used for pest control at rates of 1 to 500 g/ha, preferably 50-300 g/ha.

The compounds as defined in any one of embodiments according to the invention are suitable for use on any
15 plant, including those that have been genetically modified to be resistant to active ingredients such as herbicides, or to produce biologically active compounds that control infestation by plant pests.

Generally, a compound as defined in any one of embodiments according to the invention is used in the form of a composition (e.g., formulation) containing a carrier. A compound as defined in any one of embodiments according to the invention and compositions thereof can be used in various forms such as aerosol dispenser,
20 capsule suspension, cold fogging concentrate, dustable powder, emulsifiable concentrate, emulsion oil in water, emulsion water in oil, encapsulated granule, fine granule, flowable concentrate for seed treatment, gas (under pressure), gas generating product, granule, hot fogging concentrate, macrogranule, microgranule, oil dispersible powder, oil miscible flowable concentrate, oil miscible liquid, paste, plant rodlet, powder for dry seed treatment, seed coated with a pesticide, soluble concentrate, soluble powder, solution for seed treatment,
25 suspension concentrate (flowable concentrate), ultra-low volume (ulv) liquid, ultra-low volume (ulv) suspension, water dispersible granules or tablets, water dispersible powder for slurry treatment, water soluble granules or tablets, water soluble powder for seed treatment and wettable powder.

Compositions of this invention, including all of the above disclosed embodiments and preferred examples thereof, can be mixed with one or more further pesticides including further fungicides, insecticides,
30 nematocides, bactericides, acaricides, growth regulators, chemosterilants, semiochemicals, repellents, attractants, pheromones, feeding stimulants or other biologically active compounds to form a multi-component pesticide giving an even broader spectrum of agricultural protection.

A formulation typically comprises a liquid or solid carrier and optionally one or more customary formulation auxiliaries, which may be solid or liquid auxiliaries, for example unepoxidized or epoxidized vegetable oils (for
35 example epoxidized coconut oil, rapeseed oil or soya oil), antifoams, for example silicone oil, preservatives, clays, inorganic compounds, viscosity regulators, surfactant, binders and/or tackifiers. The composition may

also further comprise a fertilizer, a micronutrient donor or other preparations which influence the growth of plants as well as comprising a combination containing the compound of the invention with one or more other biologically active agents, such as bactericides, fungicides, nematicides, plant activators, acaricides, and insecticides.

- 5 The compositions are prepared in a manner known per se, in the absence of auxiliaries for example by grinding, screening and/or compressing a solid compound of the present invention and in the presence of at least one auxiliary for example by intimately mixing and/or grinding the compound of the present invention with the auxiliary (auxiliaries). In the case of solid compounds of the invention, the grinding/milling of the compounds is to ensure specific particle size.
- 10 Examples of compositions for use in agriculture are emulsifiable concentrates, suspension concentrates, microemulsions, oil dispersibles, directly sprayable or dilutable solutions, spreadable pastes, dilute emulsions, soluble powders, dispersible powders, wettable powders, dusts, granules or encapsulations in polymeric substances, which comprise - at least – a compound of formula (III), (VI) or (VII), as defined herein and the type of composition is to be selected to suit the intended aims and the prevailing circumstances.
- 15 As a rule, the compositions comprise 0.1 to 99 %, especially 0.1 to 95 %, of a compound (A), wherein said component (A) can be selected from a compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below); and optionally compound (B), as defined in any one of embodiments according to the invention and 1 to 99.9 %, especially 5 to 99.9 %, of at least one solid or liquid carrier, it being possible as a rule for 0 to 25 %, especially 0.1 to 20%, of the composition to be surfactants (% in each case meaning percent by weight). Whereas concentrated
- 20 compositions tend to be preferred for commercial goods, the end consumer as a rule uses dilute compositions which have substantially lower concentrations of active ingredient.

With respect to compositions comprising component (A) and component (B); in general, the weight ratio of component (A) to component (B) is from 2000 : 1 to 1 : 1000. The weight ratio of component (A) to component

25 (B) is preferably from 100 : 1 to 1 : 100; more preferably from 20 : 1 to 1 : 50, yet more preferably from 12 : 1 to 1 : 25; yet more preferably from 10 : 1 to 1 : 10, again more preferably from 5 : 1 to 1 : 15; and most preferably from 2 : 1 to 1 : 5.

Besides a potential synergistic action with respect to fungicidal activity, the compositions according to the invention can also have further surprising advantageous properties. Examples of such advantageous

30 properties that may be mentioned are: more advantageous degradability; improved toxicological and/or ecotoxicological behaviour; or improved characteristics of the useful plants including: emergence, crop yields, more developed root system, tillering increase, increase in plant height, bigger leaf blade, less dead basal leaves, stronger tillers, greener leaf colour, less fertilizers needed, less seeds needed, more productive tillers, earlier flowering, early grain maturity, less plant verse (lodging), increased shoot growth, improved plant vigour,

35 and early germination.

Additional beneficial effects can be the suppression or reduction of development of resistance against a certain active ingredient, by combinations that may have one or more different modes of action may in particular be beneficial.

Some compositions according to the invention have a systemic action and can be used as foliar, soil and seed treatment fungicides.

With the compositions according to the invention it is possible to inhibit or destroy the phytopathogenic microorganisms which occur in plants or in parts of plants (fruit, blossoms, leaves, stems, tubers, roots) in different useful plants, while at the same time the parts of plants which grow later are also protected from attack by phytopathogenic microorganisms.

The compositions according to the invention can be applied to the phytopathogenic microorganisms, the useful plants, the locus thereof, the propagation material thereof, storage goods or technical materials threatened by microorganism attack.

The compositions according to the invention may be applied before or after infection of the useful plants, the propagation material thereof, storage goods or technical materials by the microorganisms.

The amount of a composition according to the invention to be applied, will depend on various factors, such as the compounds employed; the subject of the treatment, such as, for example plants, soil or seeds; the type of treatment, such as, for example spraying, dusting or seed dressing; the purpose of the treatment, such as, for example prophylactic or therapeutic; the type of fungi to be controlled or the application time.

When applied to the useful plants component (A) is typically applied at a rate of 5 to 2000 g a.i./ha, particularly 10 to 1000 g a.i./ha, e.g., 50, 75, 100 or 200 g a.i./ha, preferably in association with 1 to 5000 g a.i./ha, particularly 2 to 2000 g a.i./ha, e.g., 100, 250, 500, 800, 1000, 1500 g a.i./ha of component (B).

The term "g a.i./ha" as used herein refer to the application rate given in gram [g] of active ingredient [a.i.] per unit of surface [ha]. The unit hectare (symbol ha) is the metric unit of area that equals a square with 100 m side (1 hm²) or 10,000 square meters. Hectare is a commonly used unit of area in the metric system.

In agricultural practice the application rates of the compositions according to the invention depend on the type of effect desired, and typically range from 20 to 4000 g of total composition per hectare.

When the compositions according to the invention are used for treating seed, rates of 0.001 to 50 g of a compound of component (A) per kg of seed, preferably from 0.01 to 10g per kg of seed, and preferably 0.001 to 50 g of a compound of component (B), per kg of seed, preferably from 0.01 to 10g per kg of seed, are generally sufficient.

Examples of foliar formulation types for pre-mix compositions are:

GR: Granules

WP: wettable powders

WG: water dispersible granules (powders)

SG: water soluble granules

SL: soluble concentrates

EC: emulsifiable concentrate

DC: dispersible concentrate

5 EW: emulsions, oil in water

ME: micro-emulsion

SC: aqueous suspension concentrate

CS: aqueous capsule suspension

OD: oil-based suspension concentrate, and

10 SE: aqueous suspo-emulsion.

Whereas examples of seed treatment formulation types for pre-mix compositions are:

WS: wettable powders for seed treatment slurry

LS: solution for seed treatment

ES: emulsions for seed treatment

15 FS: suspension concentrate for seed treatment

WG: water dispersible granules, and

CS: aqueous capsule suspension.

Examples of formulation types suitable for tank-mix compositions are solutions, dilute emulsions, suspensions, or a mixture thereof, and dusts.

20 As with the nature of the formulations, the methods of application, such as foliar, drench, spraying, atomizing, dusting, scattering, coating, or pouring, are chosen in accordance with the intended objectives and the prevailing circumstances.

The tank-mix compositions are generally prepared by diluting with a solvent (for example, water) the one or more pre-mix compositions containing different pesticides, and optionally further auxiliaries.

25 Suitable carriers and adjuvants can be solid or liquid and are the substances ordinarily employed in formulation technology, e.g., natural or regenerated mineral substances, solvents, dispersants, wetting agents, tackifiers, thickeners, binders, or fertilizers.

30 Generally, a tank-mix formulation for foliar or soil application comprises 0.1 to 20%, especially 0.1 to 15 %, of the desired ingredients, and 99.9 to 80 %, especially 99.9 to 85 %, of a solid or liquid auxiliaries (including, for example, a dilutant or solvent such as water), where the auxiliaries can be a surfactant in an amount of 0 to 20 %, especially 0.1 to 15 %, based on the tank-mix formulation.

Typically, a pre-mix formulation for foliar application comprises 0.1 to 99.9 %, especially 1 to 95 %, of the desired ingredients, and 99.9 to 0.1 %, especially 99 to 5 %, of a solid or liquid adjuvant (including, for example, a solvent such as water), where the auxiliaries can be a surfactant in an amount of 0 to 50 %, especially 0.5
35 to 40 %, based on the pre-mix formulation.

Normally, a tank-mix formulation for seed treatment application comprises 0.25 to 80%, especially 1 to 75 %, of the desired ingredients, and 99.75 to 20 %, especially 99 to 25 %, of a solid or liquid auxiliaries (including, for example, a solvent such as water), where the auxiliaries can be a surfactant in an amount of 0 to 40 %, especially 0.5 to 30 %, based on the tank-mix formulation.

- 5 Typically, a pre-mix formulation for seed treatment application comprises 0.5 to 99.9 %, especially 1 to 95 %, of the desired ingredients, and 99.5 to 0.1 %, especially 99 to 5 %, of a solid or liquid adjuvant (including, for example, a solvent such as water), where the auxiliaries can be a surfactant in an amount of 0 to 50 %, especially 0.5 to 40 %, based on the pre-mix formulation.

Whereas commercial products will preferably be formulated as concentrates (e.g., pre-mix composition
10 (formulation)), the end user will normally employ dilute formulations (e.g., tank mix composition).

Preferred seed treatment pre-mix formulations are aqueous suspension concentrates. The formulation can be applied to the seeds using conventional treating techniques and machines, such as fluidized bed techniques, the roller mill method, rotostatic seed treaters, and drum coaters. Other methods, such as spouted beds may also be useful. The seeds may be presized before coating. After coating, the seeds are typically dried and then
15 transferred to a sizing machine for sizing. Such procedures are known in the art. The compounds of the present invention are particularly suited for use in soil and seed treatment applications. In general, the pre-mix compositions of the invention contain 0.5 to 99.9 especially 1 to 95, advantageously 1 to 50 % by mass of the desired ingredients, and 99.5 to 0.1, especially 99 to 5 % by mass of a solid or liquid adjuvant (including, for example, a solvent such as water), where the auxiliaries (or adjuvant) can be a surfactant in an amount of 0 to
20 50, especially 0.5 to 40 % by mass based on the mass of the pre-mix formulation.

In addition, further, other biocidally active ingredients or compositions may be combined with the compositions of the invention and used in the methods of the invention and applied simultaneously or sequentially with the compositions of the invention. When applied simultaneously, these further active ingredients may be formulated together with the compositions of the invention or mixed in, for example, the spray tank. These
25 further biocidally active ingredients may be fungicides, herbicides, insecticides, bactericides, acaricides, nematocides and/or plant growth regulators.

In addition, the compositions of the invention may also be applied with one or more systemically acquired resistance inducers ("SAR" inducer). SAR inducers are known and described in, for example, United States Patent No. US6,919,298 and include, for example, salicylates and the commercial SAR inducer acibenzolar-S-methyl.
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The compounds as defined in any one of embodiments according to the invention are normally used in the form of compositions and can be applied to the crop area or plant to be treated, simultaneously or in succession with further compounds. These further compounds can be e.g., fertilizers or micronutrient donors or other preparations, which influence the growth of plants. They can also be selective herbicides or non-selective
35 herbicides as well as insecticides, fungicides, bactericides, nematocides, molluscicides or mixtures of several

of these preparations, if desired together with further carriers, surfactants or application promoting adjuvants customarily employed in the art of formulation.

The compounds of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), may be used in the form of (fungicidal) compositions for controlling or protecting against phytopathogenic fungi comprising as active ingredient at least one compound of formula (III), (VI), or (VII), according to the invention, in free form or in agrochemically usable salt form, and at least one of the above-mentioned adjuvants.

The plants and / or target crops in accordance with the invention include conventional as well as genetically enhanced or engineered varieties such as, for example, insect resistant (e.g., Bt. and VIP varieties) as well as disease resistant, herbicide tolerant (e.g., glyphosate- and glufosinate-resistant maize varieties commercially available under the trade names RoundupReady® and LibertyLink®) and nematode tolerant varieties. By way of example, suitable genetically enhanced or engineered crop varieties include the Stoneville 5599BR cotton and Stoneville 4892BR cotton varieties.

The term "plants" and/or "target crops" is to be understood as including also plants that have been rendered tolerant to herbicides like bromoxynil or classes of herbicides (such as, for example, HPPD inhibitors, ALS inhibitors, for example primisulfuron, prosulfuron and trifloxysulfuron, EPSPS (5-enol-pyrovyl-shikimate-3-phosphate-synthase) inhibitors, GS (glutamine synthetase) inhibitors or PPO (protoporphyrinogen-oxidase) inhibitors) as a result of conventional methods of breeding or genetic engineering. An example of a crop that has been rendered tolerant to imidazolinones, e.g., imazamox, by conventional methods of breeding (mutagenesis) is Clearfield® summer rape (Canola). Examples of crops that have been rendered tolerant to herbicides or classes of herbicides by genetic engineering methods include glyphosate- and glufosinate-resistant maize varieties commercially available under the trade names RoundupReady®, Herculex I® and LibertyLink®.

The term "plants" and/or "target crops" is to be understood as including those which naturally are or have been rendered resistant to harmful insects. This includes plants transformed by the use of recombinant DNA techniques, for example, to be capable of synthesizing one or more selectively acting toxins, such as are known, for example, from toxin-producing bacteria. Examples of toxins which can be expressed include δ -endotoxins, vegetative insecticidal proteins (Vip), insecticidal proteins of bacteria colonizing nematodes, and toxins produced by scorpions, arachnids, wasps, and fungi. An example of a crop that has been modified to express the *Bacillus thuringiensis* toxin is the Bt maize KnockOut® (Syngenta Seeds). An example of a crop comprising more than one gene that codes for insecticidal resistance and thus expresses more than one toxin is VipCot® (Syngenta Seeds). Crops or seed material thereof can also be resistant to multiple types of pests (so-called stacked transgenic events when created by genetic modification). For example, a plant can have the ability to express an insecticidal protein while at the same time being herbicide tolerant, for example Herculex I® (Dow AgroSciences, Pioneer Hi-Bred International).

The term "plants" and/or "target crops" is to be understood as also including plants which have been so transformed by the use of recombinant DNA techniques that they are capable of synthesising antipathogenic substances having a selective action, such as, for example, the so-called "pathogenesis-related proteins" (PRPs, see e.g., EP0392225A). Examples of such antipathogenic substances and transgenic plants capable of synthesising such antipathogenic substances are known, for example, from EP0392225A, WO95/33818, and EP0353191A. The methods of producing such transgenic plants are generally known to the person skilled in the art and are described, for example, in the publications mentioned above.

The compound of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention can be used in the agricultural sector and related fields of use, e.g., as active ingredients for controlling plant pests or on non-living materials for the control of spoilage microorganisms or organisms potentially harmful to man. The novel compounds are distinguished by excellent activity at low rates of application, by being well tolerated by plants and by being environmentally safe. They have very useful curative, preventive and systemic properties and can be used for protecting numerous cultivated plants. The of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), can be used to inhibit or destroy the pests that occur on plants or parts of plants (fruit, blossoms, leaves, stems, tubers, roots) of different crops of useful plants, while at the same time also protecting those parts of the plants that grow later, e.g., from phytopathogenic microorganisms.

The present invention further relates to a method for controlling or preventing infestation of plants or plant propagation material and/or harvested food crops susceptible to microbial attack by treating plants or plant propagation material and/or harvested food crops wherein an effective amount a compound of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention is applied to the plants, to parts thereof or the locus thereof.

It is also possible to use a compound of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention as a fungicide. The term "fungicide" as used herein means a compound that controls, modifies, or prevents the growth of fungi. The term "fungicidally effective amount" where used means the quantity of such a compound or combination of such compounds that is capable of producing an effect on the growth of fungi. Controlling or modifying effects include all deviation from natural development, such as killing, retardation and the like, and prevention includes barrier or other defensive formation in or on a plant to prevent fungal infection.

It may also be possible to use compound of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention as dressing agents for the treatment of plant propagation material, e.g., seed, such as fruits, tubers or grains, or plant cuttings, for the protection against fungal infections as well as against phytopathogenic fungi occurring in the soil. The propagation material can be treated with a composition comprising a of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), before planting: seed, for example, can be dressed before being sown. The active of

compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), can also be applied to grains (coating), either by impregnating the seeds in a liquid formulation or by coating them with a solid formulation. The composition can also be applied to the planting site when the propagation material is being planted, for example, to the seed furrow during sowing.

5 The invention relates also to such methods of treating plant propagation material and to the plant propagation material so treated.

Furthermore, the compound of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention can be used for controlling fungi in related areas, for example in the protection of technical materials, including wood and wood
10 related technical products, in food storage, in hygiene management.

In addition, the invention could be used to protect non-living materials from fungal attack, e.g., lumber, wall boards, and paint.

The compound of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention are for example, effective
15 against fungi and fungal vectors of disease as well as phytopathogenic bacteria and viruses. These fungi and fungal vectors of disease as well as phytopathogenic bacteria and viruses are for example: *Absidia corymbifera*, *Alternaria* spp., *Aphanomyces* spp., *Ascochyta* spp., *Aspergillus* spp. including *A. flavus*, *A. fumigatus*, *A. nidulans*, *A. niger*, *A. terreus*, *Aureobasidium* spp. including *A. pullulans*, *Blastomyces dermatitidis*, *Blumeria graminis*, *Bremia lactucae*, *Botryosphaeria* spp. including *B. dothidea*, *B. obtusa*, *Botrytis* spp.
20 including *B. cinerea*, *Candida* spp. including *C. albicans*, *C. glabrata*, *C. krusei*, *C. lusitanae*, *C. parapsilosis*, *C. tropicalis*, *Cephalosporium fragrans*, *Ceratocystis* spp., *Cercospora* spp. including *C. arachidicola*, *Cercosporidium personatum*, *Cladosporium* spp., *Claviceps purpurea*, *Coccidioides immitis*, *Cochliobolus* spp., *Colletotrichum* spp. including *C. musae*, *Corynespora* spp. including *Corynespora cassiicola*, *Cryptococcus neoformans*, *Diaporthe* spp. including *Diaporthe miricariae* (also known as *Diaporthe ueckeri* or
25 *Diaporthe ueckerae*), *Didymella* spp., *Drechslera* spp., *Elsinoe* spp., *Epidermophyton* spp., *Erwinia amylovora*, *Erysiphe* spp. including *E. cichoracearum*, *Eutypa lata*, *Fusarium* spp. including *F. culmorum*, *F. graminearum*, *F. langsethiae*, *F. moniliforme*, *F. oxysporum*, *F. proliferatum*, *F. subglutinans*, *F. solani*, *Gaeumannomyces graminis*, *Gibberella fujikuroi*, *Gloeodes pomigena*, *Gloeosporium musarum*, *Glomerella cingulate*, *Guignardia bidwellii*, *Gymnosporangium juniperi-virginianae*, *Helminthosporium* spp., *Hemileia* spp., *Histoplasma* spp.
30 including *H. capsulatum*, *Laetisaria fuciformis*, *Leptographium lindbergi*, *Leveillula taurica*, *Lophodermium seditiosum*, *Microdochium nivale*, *Microsporum* spp., *Monilinia* spp., *Mucor* spp., *Mycosphaerella* spp. including *M. graminicola*, *M. pomi*, *Oncobasidium theobromaeon*, *Ophiostoma piceae*, *Paracoccidioides* spp., *Penicillium* spp. including *P. digitatum*, *P. italicum*, *Petriellidium* spp., *Peronosclerospora* spp. including *P. maydis*, *P. philippinensis* and *P. sorghi*, *Peronospora* spp., *Phaeosphaeria nodorum*, *Phakopsora pachyrhizi*,
35 *Phellinus igniarius*, *Phialophora* spp., *Phoma* spp., *Phomopsis viticola*, *Phytophthora* spp. including *P. infestans*, *Plasmopara* spp. including *P. halstedii*, *P. viticola*, *Pleospora* spp., *Podosphaera* spp. including *P. leucotricha*, *Polymyxa graminis*, *Polymyxa betae*, *Pseudocercospora herpotrichoides*, *Pseudomonas* spp.,

Pseudoperonospora spp. including *P. cubensis*, *P. humuli*, *Pseudopeziza tracheiphila*, *Puccinia* spp. including *P. hordei*, *P. recondita*, *P. striiformis*, *P. triticina*, *Pyrenopeziza* spp., *Pyrenophora* spp., *Pyricularia* spp. including *P. oryzae*, *Pythium* spp. including *P. ultimum*, *Ramularia* spp., *Rhizoctonia* spp., *Rhizomucor pusillus*, *Rhizopus arrhizus*, *Rhynchosporium* spp., *Scedosporium* spp. including *S. apiospermum* and *S. prolificans*,
 5 *Schizothyrium pomi*, *Sclerotinia* spp., *Sclerotium* spp., *Septoria* spp., including *S. nodorum*, *S. tritici*, *Sphaerotheca macularis*, *Sphaerotheca fusca* (*Sphaerotheca fuliginea*), *Sporothrix* spp., *Stagonospora nodorum*, *Stemphylium* spp., *Stereum hirsutum*, *Thanatephorus cucumeris*, *Thielaviopsis basicola*, *Tilletia* spp., *Trichoderma* spp. including *T. harzianum*, *T. pseudokoningii*, *T. viride*, *Trichophyton* spp., *Typhula* spp., *Uncinula necator*, *Urocystis* spp., *Ustilago* spp., *Venturia* spp. including *V. inaequalis*, *Verticillium* spp., and
 10 *Xanthomonas* spp..

The of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), according to the invention may be used for example on turf, ornamentals, such as flowers, shrubs, broad-leaved trees, or evergreens, for example conifers, as well as for tree injection, pest management and the like.

15 Within the scope of present invention, target crops and/or useful plants to be protected typically comprise perennial and annual crops, such as berry plants for example blackberries, blueberries, cranberries, raspberries and strawberries; cereals for example barley, maize (corn), millet, oats, rice, rye, sorghum triticate and wheat; fibre plants for example cotton, flax, hemp, jute and sisal; field crops for example sugar and fodder beet, coffee, hops, mustard, oilseed rape (canola), poppy, sugar cane, sunflower, tea and tobacco; fruit trees
 20 for example apple, apricot, avocado, banana, cherry, citrus, nectarine, peach, pear and plum; grasses for example Bermuda grass, bluegrass, bentgrass, centipede grass, fescue, ryegrass, St. Augustine grass and Zoysia grass; herbs such as basil, borage, chives, coriander, lavender, lovage, mint, oregano, parsley, rosemary, sage and thyme; legumes for example beans, lentils, peas and soya beans; nuts for example almond, cashew, ground nut, hazelnut, peanut, pecan, pistachio and walnut; palms for example oil palm;
 25 ornamentals for example flowers, shrubs and trees; other trees, for example cacao, coconut, olive and rubber; vegetables for example asparagus, aubergine, broccoli, cabbage, carrot, cucumber, garlic, lettuce, marrow, melon, okra, onion, pepper, potato, pumpkin, rhubarb, spinach and tomato; and vines for example grapes.

The term "useful plants" is to be understood as also including useful plants that have been rendered tolerant to herbicides like bromoxynil or classes of herbicides (such as, for example, HPPD inhibitors, ALS inhibitors,
 30 for example primisulfuron, prosulfuron and trifloxysulfuron, EPSPS (5-enol-pyrovyl-shikimate-3-phosphate-synthase) inhibitors, GS (glutamine synthetase) inhibitors or PPO (protoporphyrinogen-oxidase) inhibitors) as a result of conventional methods of breeding or genetic engineering. An example of a crop that has been rendered tolerant to imidazolinones, e.g., imazamox, by conventional methods of breeding (mutagenesis) is Clearfield® summer rape (Canola). Examples of crops that have been rendered tolerant to herbicides or
 35 classes of herbicides by genetic engineering methods include glyphosate- and glufosinate-resistant maize varieties commercially available under the trade names RoundupReady®, Herculex I® and LibertyLink®.

The term "useful plants" is to be understood as also including useful plants which have been so transformed using recombinant DNA techniques that they are capable of synthesizing one or more selectively acting toxins, such as are known, for example, from toxin-producing bacteria, especially those of the genus *Bacillus*.

Examples of such plants are: YieldGard® (maize variety that expresses a CryIA(b) toxin); YieldGard Rootworm® (maize variety that expresses a CryIIIB(b1) toxin); YieldGard Plus® (maize variety that expresses a CryIA(b) and a CryIIIB(b1) toxin); Starlink® (maize variety that expresses a Cry9(c) toxin); Herculex I® (maize variety that expresses a CryIF(a2) toxin and the enzyme phosphinothricin N-acetyltransferase (PAT) to achieve tolerance to the herbicide glufosinate ammonium); NuCOTN 33B® (cotton variety that expresses a CryIA(c) toxin); Bollgard I® (cotton variety that expresses a CryIA(c) toxin); Bollgard II® (cotton variety that expresses a CryIA(c) and a CryIIA(b) toxin); VIPCOT® (cotton variety that expresses a VIP toxin); NewLeaf® (potato variety that expresses a CryIIIA toxin); Nature-Gard® Agrisure® GT Advantage (GA21 glyphosate-tolerant trait), Agrisure® CB Advantage (Bt11 corn borer (CB) trait), Agrisure® RW (corn rootworm trait) and Protecta®.

The term "crops" is to be understood as including also crop plants which have been so transformed using recombinant DNA techniques that they are capable of synthesizing one or more selectively acting toxins, such as are known, for example, from toxin-producing bacteria, especially those of the genus *Bacillus*.

Toxins that can be expressed by transgenic plants include, for example, insecticidal proteins from *Bacillus cereus* or *Bacillus popilliae*; or insecticidal proteins from *Bacillus thuringiensis*, such as δ -endotoxins, e.g. Cry1Ab, Cry1Ac, Cry1F, Cry1Fa2, Cry2Ab, Cry3A, Cry3Bb1 or Cry9C, or vegetative insecticidal proteins (Vip), e.g. Vip1, Vip2, Vip3 or Vip3A; or insecticidal proteins of bacteria colonising nematodes, for example *Photorhabdus* spp. or *Xenorhabdus* spp., such as *Photorhabdus luminescens*, *Xenorhabdus nematophilus*; toxins produced by animals, such as scorpion toxins, arachnid toxins, wasp toxins and other insect-specific neurotoxins; toxins produced by fungi, such as *Streptomyces* toxins, plant lectins, such as pea lectins, barley lectins or snowdrop lectins; agglutinins; proteinase inhibitors, such as trypsin inhibitors, serine protease inhibitors, patatin, cystatin, papain inhibitors; ribosome-inactivating proteins (RIP), such as ricin, maize-RIP, abrin, luffin, saporin or bryodin; steroid metabolism enzymes, such as 3-hydroxysteroidoxidase, ecdysteroid-UDP-glycosyl-transferase, cholesterol oxidases, ecdysone inhibitors, HMG-COA-reductase, ion channel blockers, such as blockers of sodium or calcium channels, juvenile hormone esterase, diuretic hormone receptors, stilbene synthase, bibenzyl synthase, chitinases and glucanases.

Further, in the context of the present invention there are to be understood by δ -endotoxins, for example Cry1Ab, Cry1Ac, Cry1F, Cry1Fa2, Cry2Ab, Cry3A, Cry3Bb1 or Cry9C, or vegetative insecticidal proteins (Vip), for example Vip1, Vip2, Vip3 or Vip3A, expressly also hybrid toxins, truncated toxins and modified toxins. Hybrid toxins are produced recombinantly by a new combination of different domains of those proteins (see, for example, WO 02/15701). Truncated toxins, for example a truncated Cry1Ab, are known. In the case of modified toxins, one or more amino acids of the naturally occurring toxin are replaced. In such amino acid replacements, preferably non-naturally present protease recognition sequences are inserted into the toxin, such as, for example, in the case of Cry3A055, a cathepsin-G-recognition sequence is inserted into a Cry3A toxin (see WO03/018810).

More examples of such toxins or transgenic plants capable of synthesising such toxins are disclosed, for example, in EP-A-0 374 753, WO93/07278, WO95/34656, EP-A-0 427 529, EP-A-451 878 and WO03/052073.

The processes for the preparation of such transgenic plants are generally known to the person skilled in the art and are described, for example, in the publications mentioned above. CryI-type deoxyribonucleic acids and their preparation are known, for example, from WO 95/34656, EP-A-0 367 474, EP-A-0 401 979 and WO 90/13651.

The toxin contained in the transgenic plants imparts to the plants tolerance to harmful insects. Such insects can occur in any taxonomic group of insects but are especially commonly found in the beetles (Coleoptera), two-winged insects (Diptera) and butterflies (Lepidoptera).

Transgenic plants containing one or more genes that code for an insecticidal resistance and express one or more toxins are known and some of them are commercially available. Examples of such plants are: YieldGard® (maize variety that expresses a Cry1Ab toxin); YieldGard Rootworm® (maize variety that expresses a Cry3Bb1 toxin); YieldGard Plus® (maize variety that expresses a Cry1Ab and a Cry3Bb1 toxin); Starlink® (maize variety that expresses a Cry9C toxin); Herculex I® (maize variety that expresses a Cry1Fa2 toxin and the enzyme phosphinothricine N-acetyltransferase (PAT) to achieve tolerance to the herbicide glufosinate ammonium); NuCOTN 33B® (cotton variety that expresses a Cry1Ac toxin); Bollgard I® (cotton variety that expresses a Cry1Ac toxin); Bollgard II® (cotton variety that expresses a Cry1Ac and a Cry2Ab toxin); VipCot® (cotton variety that expresses a Vip3A and a Cry1Ab toxin); NewLeaf® (potato variety that expresses a Cry3A toxin); NatureGard®, Agrisure® GT Advantage (GA21 glyphosate-tolerant trait), Agrisure® CB Advantage (Bt11 corn borer (CB) trait) and Protecta®.

Further examples of such transgenic crops are:

1. Bt11 Maize from Syngenta Seeds SAS, Chemin de l'Hobit 27, F-31 790 St. Sauveur, France, registration number C/FR/96/05/10. Genetically modified *Zea mays* which has been rendered resistant to attack by the European corn borer (*Ostrinia nubilalis* and *Sesamia nonagrioides*) by transgenic expression of a truncated Cry1Ab toxin. Bt11 maize also transgenically expresses the enzyme PAT to achieve tolerance to the herbicide glufosinate ammonium.

2. Bt176 Maize from Syngenta Seeds SAS, Chemin de l'Hobit 27, F-31 790 St. Sauveur, France, registration number C/FR/96/05/10. Genetically modified *Zea mays* which has been rendered resistant to attack by the European corn borer (*Ostrinia nubilalis* and *Sesamia nonagrioides*) by transgenic expression of a Cry1Ab toxin. Bt176 maize also transgenically expresses the enzyme PAT to achieve tolerance to the herbicide glufosinate ammonium.

3. MIR604 Maize from Syngenta Seeds SAS, Chemin de l'Hobit 27, F-31 790 St. Sauveur, France, registration number C/FR/96/05/10. Maize which has been rendered insect-resistant by transgenic expression of a modified Cry3A toxin. This toxin is Cry3A055 modified by insertion of a cathepsin-G-protease recognition sequence. The preparation of such transgenic maize plants is described in WO 03/018810.

4. MON 863 Maize from Monsanto Europe S.A. 270-272 Avenue de Tervuren, B-1150 Brussels, Belgium, registration number C/DE/02/9. MON 863 expresses a Cry3Bb1 toxin and has resistance to certain Coleoptera insects.

5. IPC 531 Cotton from Monsanto Europe S.A. 270-272 Avenue de Tervuren, B-1150 Brussels, Belgium, registration number C/ES/96/02.

6. 1507 Maize from Pioneer Overseas Corporation, Avenue Tedesco, 7 B-1160 Brussels, Belgium, registration number C/NL/00/10. Genetically modified maize for the expression of the protein Cry1F for achieving resistance to certain Lepidoptera insects and of the PAT protein for achieving tolerance to the herbicide glufosinate ammonium.

10 7. NK603 × MON 810 Maize from Monsanto Europe S.A. 270-272 Avenue de Tervuren, B-1150 Brussels, Belgium, registration number C/GB/02/M3/03. Consists of conventionally bred hybrid maize varieties by crossing the genetically modified varieties NK603 and MON 810. NK603 × MON 810 Maize transgenically expresses the protein CP4 EPSPS, obtained from *Agrobacterium sp.* strain CP4, which imparts tolerance to the herbicide Roundup® (contains glyphosate), and also a Cry1Ab toxin obtained from *Bacillus thuringiensis* subsp. *kurstaki* which brings about tolerance to certain Lepidoptera, include the European corn borer.

15 The term “locus” as used herein means fields in or on which plants are growing, or where seeds of cultivated plants are sown, or where seed will be placed into the soil. It includes soil, seeds, and seedlings, as well as established vegetation.

The term “plants” refers to all physical parts of a plant, including seeds, seedlings, saplings, roots, tubers, stems, stalks, foliage, and fruits.

20 The term “plant propagation material” is understood to denote generative parts of the plant, such as seeds, which can be used for the multiplication of the latter, and vegetative material, such as cuttings or tubers, for example potatoes. There may be mentioned for example seeds (in the strict sense), roots, fruits, tubers, bulbs, rhizomes and parts of plants. Germinated plants and young plants which are to be transplanted after germination or after emergence from the soil, may also be mentioned. These young plants may be protected before transplantation by a total or partial treatment by immersion. Preferably “plant propagation material” is understood to denote seeds.

Pesticidal agents referred to herein using their common name are known, for example, from "The Pesticide Manual", 15th Ed., British Crop Protection Council 2009.

30 The compounds as defined in any one of embodiments according to the invention for use in the inventive methods may be the sole active ingredient of a composition or it may be admixed with one or more additional active ingredients such as a pesticide, fungicide, synergist, herbicide, or plant growth regulator where appropriate. An additional active ingredient may, in some cases, result in unexpected synergistic activities.

35 The following mixtures of the compound according to the present invention with active ingredients are preferred. The abbreviation “TX” means one compound selected from compound of formula (III), (VI) or (VII),

or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), and a compound selected from the group of substances consisting of (4E,10Z)-tetradeca-4,10-dienyl acetate + TX; (7E,9Z)-dodeca-7,9-dien-1-yl acetate + TX; (E)-6-methylhept-2-en-4-ol + TX; (E)-dec-5-en-1-yl acetate with (E)-dec-5-en-1-ol + TX; (E)-tridec-4-en-1-yl acetate + TX; (S)-bioallethrin + TX; (Z)-dodec-7-en-1-yl acetate + TX; (Z)-hexadec-11-en-1-yl acetate + TX; (Z)-hexadec-11-enal + TX; (Z)-hexadec-13-en-11-yn-1-yl acetate + TX; (Z)-icos-13-en-10-one + TX; (Z)-tetradec-7-en-1-al + TX; (Z)-tetradec-9-en-1-ol + TX; (Z)-tetradec-9-en-1-yl acetate + TX; 1,1-bis(4-chlorophenyl)-2-ethoxyethanol + TX; 1-(2-chlorophenyl)-3,3-dimethyl-2-(1,2,4-triazol-1-ylmethyl)butan-2-ol + TX; 1-(5-bromo-2-pyridyl)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1,2,4-triazol-1-yl)propan-2-ol + TX; 1-hydroxy-1H-pyridine-2-thione + TX; 1-methylcyclopropene + TX; 1-naphthaleneacetamide + TX; 1-naphthylacetic acid + TX; 2,2-dichlorovinyl 2-ethylsulfinyethyl methyl phosphate + TX; 2,4-D + TX; 2,4-DB + TX; 2,6-dichloro-N-(4-trifluormethylbenzyl)benzamide + TX; 2-(1,3-dithiolan-2-yl)phenyl dimethylcarbamate + TX; 2-(2-butoxyethoxy)ethyl piperonylate + TX; 2-(4,5-dimethyl-1,3-dioxolan-2-yl)phenyl methylcarbamate + TX; 2-(difluoromethyl)-N-((3R)-1,1,3-trimethylindan-4-yl) pyridine-3-carboxamide + TX; 2-(octylthio)-ethanol + TX; 2-bromo-2-bromomethyl-pentanedinitrile + TX; 2-chlorovinyl diethyl phosphate + TX; 2-imidazolidone + TX; 2-methyl(prop-2-ynyl)aminophenyl methylcarbamate + TX; 2-thiocyanatoethyl laurate + TX; 3-(4-chlorophenyl)-5-methylrhodanine + TX; 3-(difluoromethyl)-1-methyl-N-[1,1,3-trimethylindan-4-yl]pyrazole-4-carboxamide + TX; 3-(difluoromethyl)-N-(7-fluoro-1,1,3,3-tetramethylindan-4-yl)-1-methyl-pyrazole-4-carboxamide + TX; 3-(difluoromethyl)-N-(7-fluoro-1,1,3,3-tetramethylindan-4-yl)-1-methyl-pyrazole-4-carboxamide + TX; 3-chloro-6-methyl-5-phenyl-4-(2,4,6-trifluorophenyl)pyridazine + TX; 3-methyl-1-phenylpyrazol-5-yl dimethyl-carbamate + TX; 3-phenylphenol + TX; 4,5-dichlorodithiol-3-one + TX; 4-(2,6-difluorophenyl)-6-methyl-5-phenyl-pyridazine-3-carbonitrile + TX; 4-(2-bromo-4-fluoro-phenyl)-N-(2-chloro-6-fluoro-phenyl)-2,5-dimethyl-pyrazol-3-amine + TX; 4-(quinoxalin-2-ylamino)benzenesulfonamide + TX; 4-[[6-[2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-(1,2,4-triazol-1-yl)propyl]-3-pyridyl]oxy]benzonitrile + TX; 4-chloro-2-(2-chloro-2-methyl-propyl)-5-[(6-iodo-3-pyridyl)methoxy]pyridazin-3-one + TX; 4-CPA + TX; 4-methyl(prop-2-ynyl)amino-3,5-xylyl methylcarbamate + TX; 4-methylnonan-5-ol with 4-methylnonan-5-one + TX; 4-phenylphenol + TX; 5-(1,3-benzodioxol-5-yl)-3-hexylcyclohex-2-enone + TX; 5-amino-1,3,4-thiadiazole-2-thiol + TX; 5-fluoro-2-(p-tolylmethoxy)pyrimidin-4-amine + TX; 5-hydroxy-6-methyl-4-(((E)-pyridin-3-ylmethylene)amino)-4,5-dihydro-1,2,4-triazin-3(2H)-one + TX; 5-methyl-6-thioxo-1,3,5-thiadiazinan-3-ylacetic acid + TX; 8-hydroxyquinoline sulfate + TX; 11-ethyl-10,12-dioxo-2,5,8-trithia-4,11-diazatricyclo[7.3.0.0.3,7]dodeca-1(9),3,6-triene-6-carbonitrile + TX; 14-methyloctadec-1-ene + TX; [(9Z,11E)-tetradeca-9,11-dienyl] acetate + TX; [(Z)-dodec-9-enyl] acetate + TX; abamectin + TX; acephate + TX; acequinocyl + TX; acetamiprid + TX; acethion + TX; acetoprole + TX; acibenzolar + TX; acibenzolar-S-methyl + TX; acrinathrin + TX; Adoxophyes orana GV + TX; Agrobacterium radiobacter + TX; alanycarb + TX; albendazole + TX; aldicarb + TX; allethrin + TX; allosamidin + TX; allyl alcohol + TX; allyxycarb + TX; alpha-ecdysone + TX; alpha-multistriatin + TX; Amblyseius spp. + TX; ametocetradin + TX; amidithion + TX; amidoflumet + TX; amidothioate + TX; aminocarb + TX; amisulbrom + TX; amiton + TX; amiton hydrogen oxalate + TX; amitraz + TX; anabasin + TX; Anagrapta falcifera NPV + TX; Anagrus atomus + TX; ancymidol + TX; anilazine + TX; anisiflupurin + TX; anthraquinone + TX; antu + TX; Aphelinus abdominalis + TX; Aphidius

colemani + TX; Aphidoletes aphidimyza + TX; athidathion + TX; aureofungin + TX; Autographa californica NPV + TX; avermectin B1a + TX; azaconazole + TX; azadirachtin A + TX; azafenidin + TX; azamethiphos + TX; azinphos-ethyl + TX; azinphos-methyl + TX; azithiram + TX; azoxystrobin + TX; Bacillus sphaericus (Neide) + TX; Bacillus thuringiensis + TX; Bacillus thuringiensis delta endotoxin + TX; Bacillus thuringiensis ssp. aizawai + TX; baculovirus + TX; barthrin + TX; Beauveria brongniartii + TX; benalaxyl + TX; benalaxyl-M + TX; benazepril + TX; benclotiaz + TX; benfuracarb + TX; benomyl + TX; bensultap + TX; benthiavalicarb + TX; benzalkonium chloride + TX; benzamorf + TX; benzothiostrubin + TX; benzovindiflupyr + TX; beta-cyfluthrin + TX; beta-cypermethrin + TX; bethoxazin + TX; bifenazate + TX; bifenthrin + TX; binapacryl + TX; bioallethrin + TX; bioethanomethrin + TX; biopermethrin + TX; bioresmethrin + TX; bisthiosemi + TX; bistrifluron + TX; bitertanol + TX; bixafen + TX; blasticidin-S + TX; borax + TX; bordeaux mixture + TX; boscalid + TX; brodifacoum + TX; brofenvalerate + TX; brofluthrin + TX; bromadiolone + TX; bromfenvinfos + TX; bromophos + TX; bromophos-ethyl + TX; bromuconazole + TX; bufencarb + TX; bupirimate + TX; buprofezin + TX; buserelin + TX; busulfan + TX; but-3-ynyl N-[6-[[[(Z)-[(1-methyltetrazol-5-yl)-phenyl-methylene]amino]oxymethyl]-2-pyridyl]carbamate + TX; butacarb + TX; butathiofos + TX; butocarboxim + TX; butonate + TX; butopyronoxyl + TX; butoxy(polypropylene glycol) + TX; butoxycarboxim + TX; butylamine + TX; cadusafos + TX; calciferol + TX; calcium phosphate + TX; calcium polysulfide + TX; cambendazole + TX; captafol + TX; captan + TX; carbanolate + TX; carbaryl + TX; carbendazim + TX; carbendazim hydrochloride + TX; carbofuran + TX; carbosulfan + TX; carboxin + TX; carprofen + TX; carpropamid + TX; cartap + TX; cartap hydrochloride + TX; cefalexin + TX; cefovecin + TX; cefquinome + TX; ceftiour + TX; cestex + TX; cevadine + TX; chinomethionat + TX; chitosan + TX; chlobenthiazone + TX; chloralose + TX; chlorantraniliprole + TX; chlorbenside + TX; chlordimeform + TX; chlorethephon + TX; chlorethoxyfos + TX; chlorfenapyr + TX; chlorfenazole + TX; chlorfentazine + TX; chlorfenvinphos + TX; chlorfluazuron + TX; chlormephos + TX; chlormequat + TX; chlorodimeform hydrochloride + TX; chloroinconazide + TX; chloromebuform + TX; chloromethiuron + TX; chloroneb + TX; chlorothalonil + TX; chlorphoxim + TX; chlorprazophos + TX; chlorpyrifos + TX; chlorpyrifos-methyl + TX; chlortetracycline + TX; chlorthiophos + TX; chlozolate + TX; cholecalciferol + TX; chromafenozide + TX; Chrysoperla carnea + TX; cinerin + TX; cinerin I + TX; cinerin II + TX; cis-jasmone + TX; cis-resmethrin + TX; cismethrin + TX; clenbuterol + TX; climbazole + TX; cloethocarb + TX; clofencet + TX; clorsulon + TX; clothianidin + TX; clozylacon (acetamide) + TX; codlure + TX; copper acetate + TX; copper hydroxide + TX; copper naphthenate + TX; copper octanoate + TX; copper oleate + TX; copper oxide + TX; copper oxychloride + TX; copper silicate + TX; copper sulfate + TX; copper(II) carbonate + TX; coumachlor + TX; coumafene + TX; coumafuryl + TX; Coumatetralyl + TX; coumethoxystrobin (jiaxiangjunzhi) + TX; coumithoate + TX; coumoxystrobin + TX; cryolite + TX; Cryptolaemus montrouzieri + TX; cuelure + TX; cufraneb + TX; cuprous(I) oxide + TX; cyanofenphos + TX; cyanthoate + TX; cyazofamid + TX; cybutryne + TX; cyclafuramid + TX; cyclethrin + TX; cyclobutrifluram + TX; Cydia pomonella GV + TX; cyenopyrafen + TX; cyflufenamid + TX; cyflumetofen + TX; cyfluthrin + TX; cyhalothrin + TX; cymiazole + TX; cymoxanil + TX; cypermethrin (alphametrin) + TX; cyphenothrin + TX; cyproconazole + TX; cyprodinil + TX; cyprodinil + TX; cyromazine + TX; cytokinins + TX; D-tetramethrin + TX; Dacnusa sibirica + TX; DAEP + TX; dazomet + TX; DCPM + TX; debacarb + TX; decarbofuran + TX; deltamethrin + TX; demephion-O + TX;

demephion-S + TX; demeton-O + TX; demeton-S + TX; demeton-S-methyl + TX; demeton-S-methylsulphon + TX; diafenthiuron + TX; dialifos + TX; diazinon + TX; dibutyl adipate + TX; dibutyl phthalate + TX; dibutyl succinate + TX; dicapthon + TX; dichlobentiazox + TX; dichlofluanid + TX; dichlone + TX; dichlorprop + TX; dichlorvos + TX; dichlozoline + TX; diclocymet + TX; diclomezine + TX; dicloran + TX; dicofol + TX; dicresyl + TX; dicrotophos + TX; dicyclanil + TX; dicyclopentadiene + TX; diethofencarb + TX; diethyltoluamide + TX; difenacoum + TX; difenoconazole + TX; difenzoquat + TX; difethialone + TX; diflovidazin + TX; diflubenzuron + TX; diflumetorim + TX; Diglyphus isaea + TX; dimatif + TX; dimefluthrin + TX; dimetan + TX; dimethachlon + TX; dimethipin + TX; dimethirimol + TX; dimethoate + TX; dimethomorph + TX; dimethrin + TX; dimethyl disulfide + TX; dimethyl phthalate + TX; dimetilan + TX; dimoxystrobin + TX; dinactin + TX; diniconazole + TX; diniconazole-M + TX; dinobuton + TX; dinocap + TX; dinocton + TX; dinoseb + TX; dinotefuran + TX; diofenolan + TX; dioxabenzofos + TX; diphenylamine + TX; dipyrithione + TX; disparlure + TX; disulfiram + TX; disulfoton + TX; ditalimfos + TX; dithianon + TX; dithicrofos + TX; dithiocarbamate + TX; dodec-8-en-1-yl acetate + TX; dodemorph + TX; dodicin + TX; dodine + TX; dofenapyn + TX; dominicalure + TX; doramectin + TX; drazoxolon + TX; DSP + TX; ecdysterone + TX; edifenphos + TX; emamectin benzoate + TX; EMPC + TX; empenthrin + TX; Encarsia formosa + TX; endosulfan + TX; endothal + TX; endothion + TX; enestroburin (enoxastrobin) + TX; enrofloxacin + TX; entomopathogenic bacteria + TX; entomopathogenic fungi + TX; entomopathogenic virus + TX; EPBP + TX; epoxiconazole + TX; eprinomectin + TX; Eretmocerus eremicus + TX; esfenvaterate + TX; etaconazole + TX; ethaboxam + TX; ethiofencarb + TX; ethion + TX; ethiprole + TX; ethirimol + TX; ethoate-methyl + TX; ethoprophos + TX; ethoxyquin + TX; ethyl 4-methyloctanoate + TX; ethyl formate + TX; ethyl hexanediol + TX; etofenprox + TX; etoxazole + TX; etridiazole + TX; etrimfos + TX; eugenol + TX; eurax + TX; EXD + TX; exo-brevicommin + TX; famoxadone + TX; famphur + TX; farnesol with nerolidol + TX; febantel + TX; fenamidone + TX; fenaminstrobin + TX; fenamiphos + TX; fenarimol + TX; fenazaquin + TX; fenbendazole + TX; fenbuconazole + TX; fenbutatin oxide + TX; fenepitramidoquin + TX; fenethacarb + TX; fenfluthrin + TX; fenfuram + TX; fenhexamid + TX; fenitrothion + TX; fenobucarb + TX; fenopyramid + TX; fenothiocarb + TX; fenoxacrim + TX; fenoxanil + TX; fenoxycarb + TX; fempiclonil + TX; fempicoxamid + TX; fempirithrin + TX; fenpropathrin + TX; fenpropidin + TX; fenpropimorph + TX; fenpyrazamine + TX; fenpyroximate + TX; fensulfothion + TX; fenthion + TX; fenthion-ethyl + TX; fentin + TX; fentin acetate + TX; fentin chloride + TX; fentin hydroxide + TX; fenvalerate + TX; ferbam + TX; ferimzone + TX; ferric phosphate + TX; fipronil + TX; flocoumafen + TX; flonicamid + TX; florfenicol + TX; florylpicoxamid + TX; fluacrypyrim + TX; fluazinam + TX; fluazuron + TX; flubendazole + TX; flubendiamide + TX; flubeneteram + TX; flubenzimin + TX; flucycloxuron + TX; flucycloxuron + TX; flucythrinate + TX; fludioxonil + TX; fluenetil + TX; flufenerim + TX; flufenoxuron + TX; flufenoxystrobin + TX; flufenprox + TX; fluindapyr + TX; flumetralin + TX; flumetylsulforim + TX; flumorph + TX; fluopicolide + TX; fluopimomide + TX; fluopyram + TX; fluoroimide + TX; fluoxapiprolin + TX; fluoxastrobin + TX; fluoxytioconazole + TX; flupyrazofos + TX; fluquinconazole + TX; flusilazole + TX; flusulfamide + TX; flutianil + TX; flutolanil + TX; flutriafol + TX; fluxapyroxad + TX; folpet + TX; fonofos + TX; forchlorfenuron + TX; formaldehyde + TX; formetanate + TX; formetanate hydrochloride + TX; formothion + TX; formparanate + TX; fosetyl + TX; fosetyl-aluminium + TX; fosmethilan + TX; fosthiazate + TX; fosthietan + TX; frontalinal + TX; fuberidazole + TX; furalaxyl + TX; furametpyr + TX; furathiocarb + TX; furethrin

+ TX; furfural + TX; gibberellic acid + TX; glyodin + TX; glyphosate + TX; grandlure I + TX; grandlure II + TX; grandlure III + TX; grandlure IV + TX; guazatine triacetate + TX; halfenprox + TX; halofenozide + TX; hemel + TX; heptenophos + TX; Heterorhabditis bacteriophora and H. megidis + TX; hexaconazole + TX; hexadecyl cyclopropanecarboxylate + TX; hexaflumuron + TX; hexalure + TX; hexamide + TX; hexythiazox + TX;

5 Hippodamia convergens + TX; huanjunzuo (rac-(1S,2S)-1-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)cycloheptanol) + TX; hydramethylnon + TX; hydrated lime (calcium hydroxide) + TX; hymexazol + TX; hyquincarb + TX; icaridin + TX; imanin (hypericin) + TX; imazalil + TX; imazalil sulfate + TX; imibenconazole + TX; imibenconazole + TX; imidacloprid + TX; iminoctadine + TX; indoxacarb + TX; inpyrfluxam + TX; iodocarb + TX; ipconazole + TX; ipfentrifluconazole + TX; ipflufenquin + TX; iprobenfos (IBP) + TX; iprodione + TX;

10 iprovalicarb + TX; ipsdienol + TX; ipsenol + TX; IPSP + TX; isamidofos + TX; isazofos + TX; isocarbophos + TX; isofetamid + TX; isoflucypram + TX; isolan + TX; isoprocab + TX; isoprothiolane + TX; isopyrazam + TX; isothioate + TX; isotianil + TX; isoxathion + TX; ivermectin + TX; japonilure + TX; jasmodin I + TX; jasmodin II + TX; juvenile hormone I + TX; juvenile hormone II + TX; juvenile hormone III + TX; kadethrin + TX; kanamycin + TX; kasugamycin + TX; kasugamycin hydrochloride hydrate + TX; kinetin + TX; kinoprene + TX; kresoxim-

15 methyl + TX; kurstaki + TX; lambda-cyhalothrin + TX; Leptomastix dactylopii + TX; leptophos + TX; levamisole + TX; lineatin + TX; lirimfos + TX; looplure + TX; lufenuron + TX; lvbenmixianan + TX; lythidathion + TX; m-cumenyl methylcarbamate + TX; Macrolophus caliginosus + TX; magnesium phosphide + TX; malathion + TX; maleic hydrazide + TX; malonoben + TX; Mamestra brassicae NPV + TX; mancopper + TX; mancozeb + TX; mandestrobil + TX; mandipropamid + TX; maneb + TX; mazidox + TX; mebendazole + TX; mecarbam + TX;

20 mecarphon + TX; medlure + TX; mefentrifluconazole + TX; megatomoic acid + TX; meloxicam + TX; menazon + TX; mepanipyrim + TX; meperfluthrin + TX; mephosfolan + TX; mepiquat + TX; mepronil + TX; meptyldinocap + TX; mesulfenfos + TX; metaflumizone + TX; metalaxyl + TX; metalaxyl-M + TX; metaldehyde + TX; metam + TX; metam-potassium + TX; metam-sodium + TX; Metaphycus helvolus + TX; Metarhizium anisopliae var. acridum + TX; Metarhizium anisopliae var. anisopliae + TX; metarylpicoxamid + TX; metconazole + TX;

25 methacrifos + TX; methamidophos + TX; methasulfocarb + TX; methidathion + TX; methiocarb + TX; methiotepa + TX; methocrotophos + TX; methomyl + TX; methoprene + TX; methoquin-butyl + TX; methothrin + TX; methoxyfenozide + TX; methyl apholate + TX; methyl eugenol + TX; methyl iodide + TX; methyl neodecanamide + TX; metiram + TX; metofluthrin + TX; metolcarb + TX; metominostrobin + TX; metoxadiazone + TX; metrafenone + TX; metyltetraprole + TX; mevinphos + TX; mexacarbate + TX; MGK 264

30 + TX; milbemycin + TX; milbemycin oxime + TX; monocrotophos + TX; morantel tartrate + TX; morzid + TX; moxidectin + TX; muscalure + TX; myclobutanil + TX; myclozolin + TX; Myrothecium verrucaria composition + TX; N-[2-[2,4-dichloro-phenoxy]phenyl]-3-(difluoromethyl)-1-methyl-pyrazole-4-carboxamide + TX; N-cyclopropyl-3-(difluoromethyl)-5-fluoro-N-[(2-isopropylphenyl)methyl]-1-methyl-pyrazole-4-carboxamide + TX;

35 nabam + TX; naled + TX; NC-170 + TX; nemadectin + TX; Neodiprion sertifer NPV and N. lecontei NPV + TX; niclosamide-olamine + TX; nicotine + TX; nicotine sulfate + TX; nikkomycins + TX; nitenpyram + TX; nithiazine + TX; nitrapyrin + TX; nitrilacarb + TX; nitrothal-isopropyl + TX; norbormide + TX; normicotine + TX; novaluron + TX; noviflumuron + TX; nuarimol + TX; O,O,O',O'-tetrapropyl dithiopyrophosphate + TX; octadeca-2,13-dien-1-yl acetate + TX; octadeca-2,13-dien-1-yl acetate + TX; octhilinone + TX; ofurace + TX; oleic acid + TX;

omethoate + TX; orfuralure + TX; Orius spp. + TX; orysastrobin + TX; osthol + TX; ostramone + TX; oxadixyl + TX; oxamate + TX; oxamyl + TX; oxantel pamoate + TX; oxasulfuron + TX; oxathiapiprolin + TX; oxfendazole + TX; oxibendazole + TX; oxine copper + TX; oxolinic acid + TX; oxpoconazole + TX; oxycarboxin + TX; oxydemeton-methyl + TX; oxydeprofos + TX; oxydisulfoton + TX; oxytetracycline + TX; oxytetracycline dihydrate + TX; paclobutrazole + TX; Paecilomyces fumosoroseus + TX; paraoxon + TX; parathion + TX; parathion-methyl + TX; parbendazole + TX; pefurazoate + TX; penconazole + TX; pencycuron + TX; penethamate + TX; penflufen + TX; pen thiopyrad + TX; permethrin + TX; petroleum oils + TX; PH 60-38 + TX; phenamacril + TX; phenthoate + TX; phorate + TX; phosacetim + TX; phosalone + TX; phosfolan + TX; phosglycin + TX; phosmet + TX; phosnichlor + TX; phosphamidon + TX; phosphocarb + TX; phosphonic acid + TX; phosphorus + TX; phoxim + TX; phoxim-methyl + TX; phthalide + TX; Phytoseiulus persimilis + TX; picarbutrazox + TX; picoxystrobin + TX; pimobendan + TX; pindone + TX; piperalin + TX; piperonyl butoxide + TX; piprotal + TX; pirimetaphos + TX; pirimicarb + TX; pirimiphos-methyl + TX; polycarbamate + TX; polynactin + TX; polyoxin B + TX; polyoxin d + TX; potassium ethylxanthate + TX; potassium hydroxyquinoline sulfate + TX; praziquantel + TX; precocene I + TX; precocene II + TX; precocene III + TX; primidophos + TX; probenazole + TX; prochloraz + TX; procymidone + TX; profenofos + TX; profluthrin + TX; prohexadione + TX; prohexadione-calcium + TX; promacyl + TX; promecarb + TX; propamidine + TX; propamocarb + TX; propaphos + TX; propargite + TX; propetamphos + TX; propiconazole + TX; propineb + TX; propionic acid + TX; propoxur + TX; propyl isomer + TX; proquinazid + TX; prothidathion + TX; prothioconazole + TX; prothiofos + TX; prothoate + TX; protrifenbute + TX; pydiflumetofen + TX; pymetrozine + TX; pyraclofos + TX; pyraclostrobin + TX; pyrafluprole + TX; pyrametostrobin + TX; pyrantel pamoate + TX; pyraoxystrobin + TX; pyrapropoyne + TX; pyraziflumid + TX; pyrazophos + TX; pyrazoxone + TX; pyresmethrin + TX; pyrethrin I + TX; pyrethrin II + TX; pyrethrins (natural products) + TX; pyrethroids (natural products) + TX; pyribencarb + TX; pyridaben + TX; pyridachlometyl + TX; pyridalyl + TX; pyridaphenthion + TX; pyridin-4-amine + TX; pyrifenox + TX; pyrifluquinazon + TX; pyrimethanil + TX; pyrimidifen + TX; pyrimorph + TX; pyriofenone + TX; pyriprole + TX; pyriproxyfen + TX; pyrisoxazole + TX; pyroquilon + TX; quassia + TX; quinalphos + TX; quinalphos-methyl + TX; quinoxaline + TX; quinoclamine + TX; quinofumelin + TX; quinonamid + TX; quinothion + TX; quinoxifen + TX; quintozone + TX; R-1492 + TX; R-metalaxyl + TX; Reynoutria sachalinensis extract + TX; ribavirin + TX; rotenone + TX; ryanodine (ryania) + TX; sabadilla + TX; schradan + TX; scilliroside + TX; seboctylamine + TX; sedaxane + TX; selamectin + TX; sesamex + TX; sesamolin + TX; siglure + TX; silafluofen + TX; silthiofam + TX; simeconazole + TX; sodium tetrathiocarbonate + TX; sophamide + TX; sordidin + TX; spinetoram + TX; spinosad + TX; spiroadiclofen + TX; spiromesifen + TX; spirotetramat + TX; spiroxamine + TX; Steinernema bibionis + TX; Steinernema carpocapsae + TX; Steinernema feltiae + TX; Steinernema glaseri + TX; Steinernema riobrave + TX; Steinernema riobrave + TX; Steinernema scapterisci + TX; Steinernema spp. + TX; streptomycin + TX; streptomycin sesquisulfate + TX; sulcatol + TX; sulcofuron + TX; sulfiram + TX; sulfur + TX; sulprofos + TX; tar oils + TX; tau-fluvalinate + TX; TCMTB + TX; TDE + TX; tebuconazole + TX; tebufenozide + TX; tebufenpyrad + TX; tebufloquin + TX; tebupirimfos + TX; tecnazene + TX; teflubenzuron + TX; tefluthrin + TX; temephos + TX; terallethrin + TX; terbam + TX; terbufos + TX; tetrachlorvinphos + TX; tetraconazole + TX; tetradec-11-en-1-yl acetate + TX; tetradifon + TX; tetramethrin + TX; tetramethylfluthrin +

TX; tetranactin + TX; thiabendazole + TX; thiachlopid + TX; thiadiazole copper + TX; thiamethoxam + TX; thiapronil + TX; thicofos + TX; thicyofen + TX; thidiazuron + TX; thifluzamide + TX; thiocarboxime + TX; thiocyclam + TX; thiocyclam hydrogen oxalate + TX; thiodicarb + TX; thiofanox + TX; thiometon + TX; thiophanate + TX; thiophanate-methyl + TX; thioquinox + TX; thiosultap + TX; thiosultap-disodium + TX; thiram + TX; thuringiensin + TX; tiadinil + TX; tiamulin + TX; tioxyimid + TX; tolclofos-methyl + TX; tolfenpyrad + TX; tolprocarb + TX; tolylfluanid + TX; tralomethrin + TX; transpermethrin + TX; tretamine + TX; triadimefon + TX; triadimenol + TX; triarathene + TX; triazamate + TX; triazophos + TX; triazoxide + TX; tribufos + TX; trichlorfon + TX; trichlormetaphos-3 + TX; trichloronat + TX; Trichogramma spp. + TX; triclabendazole + TX; triclopyricarb + TX; tricyclazole + TX; tridemorph + TX; trifenmorph + TX; trifloxystrobin + TX; triflumizole + TX; triflumuron + TX; triforine + TX; trimedlure + TX; trimedlure A + TX; trimedlure B1 + TX; trimedlure B2 + TX; trimedlure C + TX; trimethacarb + TX; trinactin + TX; trinexapac + TX; trinexapac-ethyl + TX; triprene + TX; triticonazole + TX; trunc-call + TX; tulathromycin + TX; Typhlodromus occidentalis + TX; uniconazole + TX; uredepa + TX; validamycin + TX; valifenalate + TX; vamidothion + TX; vaniliprole + TX; veratridine + TX; veratrine + TX; verbutin + TX; Verticillium lecanii + TX; vinclozolin + TX; XMC + TX; xlenols + TX; zeatin + TX; zeta-cypermethrin + TX; zhongshengmycin + TX; zinc naphthenate + TX; zinc thiazole + TX; zineb + TX; ziram + TX; zolaprofos + TX; zoxamide + TX; 2-(difluoromethyl)-N-[(3S)-3-ethyl-1,1-dimethyl-indan-4-yl]pyridine-3-carboxamide (this compound may be prepared from the methods described in WO 2014/095675) + TX; methyl 3-[(4-chlorophenyl)methyl]-2-hydroxy-1-methyl-2-(1,2,4-triazol-1-ylmethyl)cyclopentanecarboxylate (this compound may be prepared from the methods described in WO 2019/093522) + TX; methyl (2R)-2-[2-chloro-4-(4-chlorophenoxy)phenyl]-2-hydroxy-3-(1,2,4-triazol-1-yl)propanoate (this compound may be prepared from the methods described in WO 2019/093522) + TX; 5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-N-[1-(2,6-difluorophenyl)cyclopropyl]pyrimidin-2-amine (this compound may be prepared from the methods described in WO 2021/255093) + TX; aminopyrifin (this compound may be prepared from the methods described in WO 2014/006945) + TX; dipymetitrone (this compound may be prepared from the methods described in WO 2011/138281) + TX; 1-[6-(difluoromethyl)-5-methyl-3-pyridyl]-4,4-difluoro-3,3-dimethyl-isoquinoline (this compound may be prepared from the methods described in WO 2017/016915) + TX; 1-[4-(difluoromethoxy)-2-methyl-phenyl]-2-(1,2,4-triazol-1-yl)-1-[1-(trifluoromethyl)cyclopropyl]ethanol (this compound may be prepared from the methods described in WO 2021/249800) + TX; 1-[2-chloro-4-(difluoromethoxy)phenyl]-2-(1,2,4-triazol-1-yl)-1-[1-(trifluoromethyl)cyclopropyl]ethanol (this compound may be prepared from the methods described in WO 2021/249800) + TX; 1-(5,6-dimethyl-3-pyridyl)-4,4-difluoro-3,3-dimethyl-isoquinoline (this compound may be prepared from the methods described in WO 2017/016915) + TX; N-methyl-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzenecarbothioamide (this compound may be prepared from the methods described in WO 2015/185485) + TX; 2,2-difluoro-N-methyl-2-[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]acetamide (this compound may be prepared from the methods described in WO 2017/178245) + TX; flufenoxadiazam + TX; N-methyl-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzamide (this compound may be prepared from the methods described in WO 2015/185485) + TX; (Z,2E)-5-[1-(2,4-dichlorophenyl)pyrazol-3-yl]oxy-2-methoxyimino-N,3-dimethyl-pent-3-enamide (this compound may be prepared from the methods described in WO 2018/153707) + TX; (Z,2E)-5-[1-(4-chlorophenyl)pyrazol-3-yl]oxy-

2-methoxyimino-N,3-dimethyl-pent-3-enamide (this compound may be prepared from the methods described in WO 2013/092224) + TX; methyl (2E)-2-methoxyimino-2-[3-methyl-2-[(E)-1-[4-(trifluoromethyl)-2-pyridyl]ethylideneamino]oxymethyl]phenyl]acetate (this compound may be prepared from the methods described in WO 2022/033906) + TX; (2E)-2-methoxyimino-N-methyl-2-[3-methyl-2-[(E)-1-[4-(trifluoromethyl)-2-pyridyl]ethylideneamino]oxymethyl]phenyl]acetamide (this compound may be prepared from the methods described in WO 2022/033906) + TX; (2E)-2-[2-[(E)-[3-(4-fluorophenyl)-1-methyl-prop-2-ynylidene]amino]oxymethyl]-3-methyl-phenyl]-2-methoxyimino-N-methyl-acetamide (this compound may be prepared from the methods described in WO 2021/249928) + TX; methyl (2E)-2-[2-[(E)-[3-(4-fluorophenyl)-1-methyl-prop-2-ynylidene]amino]oxymethyl]-3-methyl-phenyl]-2-methoxyimino-acetate (this compound may be prepared from the methods described in WO 2021/249928) + TX; 3-[2-(1-chlorocyclopropyl)-3-(3-chloro-2-fluoro-phenyl)-2-hydroxy-propyl]imidazole-4-carbonitrile (this compound may be prepared from the methods described in WO 2016/156290) + TX; 3-[2-(1-chlorocyclopropyl)-3-(2-fluorophenyl)-2-hydroxy-propyl]imidazole-4-carbonitrile (this compound may be prepared from the methods described in WO 2016/156290) + TX; 2-[6-(4-bromophenoxy)-2-(trifluoromethyl)-3-pyridyl]-1-(1,2,4-triazol-1-yl)propan-2-ol (this compound may be prepared from the methods described in WO 2017/029179) + TX; 2-[6-(4-chlorophenoxy)-2-(trifluoromethyl)-3-pyridyl]-1-(1,2,4-triazol-1-yl)propan-2-ol (this compound may be prepared from the methods described in WO 2017/029179) + TX; 5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-N-[1-(2-fluorophenyl)ethyl]pyrimidin-2-amine (this compound may be prepared from the methods described in WO 2021/255093) + TX; 5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-N-[1-(3,5-difluorophenyl)ethyl]pyrimidin-2-amine (this compound may be prepared from the methods described in WO 2021/255093) + TX; N-[1-(2-fluorophenyl)cyclopropyl]-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]pyrimidin-2-amine (this compound may be prepared from the methods described in WO 2021/255093) + TX; 5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-N-[1-(2,6-difluorophenyl)ethyl]pyrimidin-2-amine (this compound may be prepared from the methods described in WO 2021/255093) + TX; 2-(difluoromethyl)-5-[2-[1-(2,6-difluorophenyl)cyclopropoxy]pyrimidin-5-yl]-1,3,4-oxadiazole (this compound may be prepared from the methods described in WO 2021/255093) + TX; 5-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-N-[1-(2-fluorophenyl)cyclopropyl]pyrimidin-2-amine (this compound may be prepared from the methods described in WO 2021/255093) + TX; 5-[(4-bromo-2-methyl-phenyl)methyl]-3-[3-(3-chloro-2-fluoro-phenoxy)-6-methyl-pyridazin-4-yl]-5,6-dihydro-4H-1,2,4-oxadiazine (this compound may be prepared from the methods described in WO 2021/255070) + TX; 3-[3-(3-cyclopropyl-2-fluoro-phenoxy)-6-methyl-pyridazin-4-yl]-5-[(2,4-dimethylphenyl)methyl]-5,6-dihydro-4H-1,2,4-oxadiazine (this compound may be prepared from the methods described in WO 2021/255070) + TX; N-(2,2,2-trifluoroethyl)-2-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]oxazole-4-carboxamide (this compound may be prepared from the methods described in WO 2022/133114) + TX; ethyl 1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenoxy]methyl]pyrazole-4-carboxylate (this compound may be prepared from the methods described in WO 2022/133114) + TX; ethyl 1-[[4-[(Z)-2-ethoxy-3,3,3-trifluoro-prop-1-enoyl]phenyl]methyl]pyrazole-4-carboxylate (this compound may be prepared from the methods described in WO 2020/056090 and WO 2021/183707) + TX; ethyl 1-[[4-[[2-(trifluoromethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]methyl]pyrazole-4-carboxylate (this compound may be prepared from the methods described in WO 2020/056090 and WO

2021/183707) + TX; methyl N-[[5-[4-(2,4-dimethylphenyl)triazol-2-yl]-2-methyl-phenyl]methyl]carbamate (this compound may be prepared from the methods described in WO 2020/097012) + TX; methyl N-[[5-[1-(2,6-difluoro-4-isopropyl-phenyl)pyrazol-3-yl]-2-methyl-phenyl]methyl]carbamate (this compound may be prepared from the methods described in WO 2020/097012) + TX; methyl N-[[5-[1-(4-cyclopropyl-2,6-difluoro-phenyl)pyrazol-3-yl]-2-methyl-phenyl]methyl]carbamate (this compound may be prepared from the methods described in WO 2020/097012) + TX; methyl 2-[2-chloro-4-(4-chlorophenoxy)phenyl]-2-hydroxy-3-(1,2,4-triazol-1-yl)propanoate (this compound may be prepared from the methods described in WO 2019/093522) + TX; 4,4,5-trifluoro-3,3-dimethyl-1-(3-quinolyl)isoquinoline + TX; 5-fluoro-3,3,4,4-tetramethyl-1-(3-quinolyl)isoquinoline + TX; 2-methoxy-N-[methoxy-[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-thienyl]methyl]acetamide (this compound may be prepared from the methods described in WO 2020/256113) + TX; N-[methoxy-[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-thienyl]methyl]-2-methyl-propanamide (this compound may be prepared from the methods described in WO 2020/256113) + TX; N-[methoxy-[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-thienyl]methyl]butanamide (this compound may be prepared from the methods described in WO 2020/256113) + TX; 2-(difluoromethyl)-N-[(3R)-3-ethyl-1,1-dimethyl-indan-4-yl]pyridine-3-carboxamide (this compound may be prepared from the methods described in WO 2014/095675) + TX; 2-(difluoromethyl)-N-(3-ethyl-1,1-dimethyl-indan-4-yl)pyridine-3-carboxamide (this compound may be prepared from the methods described in WO 2014/095675) + TX; 2-(difluoromethyl)-N-(1,1,3-trimethylindan-4-yl)pyridine-3-carboxamide + TX; (5R)-3-[3-(3-chloro-2-fluoro-phenoxy)-6-methyl-pyridazin-4-yl]-5-[(2-chloro-4-methyl-phenyl)methyl]-5,6-dihydro-4H-1,2,4-oxadiazine (this compound may be prepared from the methods described in WO 2020/127780, WO 2021/255070) + TX; (5S)-3-[3-(3-chloro-2-fluoro-phenoxy)-6-methyl-pyridazin-4-yl]-5-[(2-chloro-4-methyl-phenyl)methyl]-5,6-dihydro-4H-1,2,4-oxadiazine (this compound may be prepared from the methods described in WO 2020/127780, WO 2021/255070) + TX; 3-[3-(3-chloro-2-fluoro-phenoxy)-6-methyl-pyridazin-4-yl]-5-[(2-chloro-4-methyl-phenyl)methyl]-5,6-dihydro-4H-1,2,4-oxadiazine (this compound may be prepared from the methods described in WO 2020/127780, WO 2021/255070) + TX; methyl (Z)-3-methoxy-2-(2-methyl-5-phenyl-phenoxy)prop-2-enoate (this compound may be prepared from methods as described in JP2023078251) +TX; 2-[(2,6-difluoro-4-pyridyl)-(2-methylpropanoyl)amino]-N-(2,2-dimethylcyclobutyl)-5-methyl-thiazole-4-carboxamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109511A1, WO2021244952A1); 2-[(2,6-difluoro-4-pyridyl)-(tetrahydropyran-4-carbonyl)amino]-N-(2,2-dimethylcyclobutyl)-5-methyl-thiazole-4-carboxamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109511A1, WO2021244952A1); 2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109509A1); 2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-(2,2-dimethylcyclobutyl)-5-methyl-thiazole-4-carboxamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109509A1); 2-[(2,6-difluoro-4-pyridyl)-(2-methoxyacetyl)amino]-N-(2,2-dimethylcyclobutyl)-5-methyl-thiazole-4-carboxamide + TX; or the (R)

or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109511A1, WO2021244952A1); 2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109511A1, WO2021244952A1); N-methoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]cyclopropanecarboxamide (this compound may be prepared from the methods described in WO 2017/055473) +TX; methyl (Z)-2-(5-cyclopentyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate (this compound may be prepared from the methods described in WO2020/193387) +TX; methyl (Z)-2-(5-cyclohexyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate (this compound may be prepared from the methods described in WO2020/193387) +TX; N-[(1R)-1-benzyl-1,3-dimethylbutyl]-8-fluoroquinoline-3-carboxamide (this compound may be prepared from the methods described in WO2017/153380) +TX; N-[(1S)-1-benzyl-1,3-dimethylbutyl]-8-fluoroquinoline-3-carboxamide (this compound may be prepared from the methods described in WO2017/153380) +TX; 2-[(2,6-difluoro-4-pyridyl)-(oxetane-3-carbonyl)amino]-N-(2,2-dimethylcyclobutyl)-5-methyl-thiazole-4-carboxamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109511A1, WO2021244952A1); 2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-(2,2-dimethylcyclobutyl)-5-methyl-thiazole-4-carboxamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO2017207362A1, WO2019105933A1, WO2020109511A1, WO2021244952A1); N,2-dimethoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide + TX; or the (R) or (S) enantiomer or mixtures thereof +TX (this compound may be prepared from the methods described in WO 2017/055473).

The references in brackets behind the active ingredients, e.g., [3878-19-1] refer to the Chemical Abstracts Registry number. The above-described mixing partners are known. Where the active ingredients are included in "The Pesticide Manual" [The Pesticide Manual - A World Compendium; Thirteenth Edition; Editor: C. D. S. Tomlin; The British Crop Protection Council], they are described therein under the entry number given in round brackets hereinabove for the particular compound; for example, the compound "abamectin" is described under entry number (1). Where "[CCN]" is added hereinabove to the particular compound, the compound in question is included in the "Compendium of Pesticide Common Names", which is accessible on the internet [A. Wood; Compendium of Pesticide Common Names, Copyright © 1995-2004]; for example, the compound "acetoprole" is described under the internet address <http://www.alanwood.net/pesticides/acetoprole.html>.

Most of the active ingredients described above are referred to hereinabove by a so-called "common name", the relevant "ISO common name" or another "common name" being used in individual cases. If the designation is not a "common name", the nature of the designation used instead is given in round brackets for the particular compound; in that case, the IUPAC name, the IUPAC/Chemical Abstracts name, a "chemical name", a "traditional name", a "compound name" or a "development code" is used or, if neither one of those designations nor a "common name" is used, an "alternative name" is employed. "CAS Reg. No" means the Chemical Abstracts Registry Number.

The active ingredient mixture of the compound selected from compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), is preferably in a mixing ratio of from 100:1 to 1:100, especially from 50:1 to 1:50, more especially in a ratio of from 20:1 to 1:20, even more especially from 10:1 to 1:10, and still more especially from 5:1 to 1:5 Those mixing ratios are by weight.

The mixtures as described above can be used in a method for controlling pests, which comprises applying a composition comprising a mixture as described above to the pests or their environment, with the exception of a method for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body.

The compositions according to the invention can also comprise further solid or liquid auxiliaries, such as stabilizers, for example unepoxidized or epoxidized vegetable oils (for example epoxidized coconut oil, rapeseed oil or soya oil), antifoams, for example silicone oil, preservatives, viscosity regulators, binders and/or tackifiers, fertilizers or other active ingredients for achieving specific effects, for example bactericides, fungicides, nematocides, plant activators, molluscicides or herbicides.

The compounds, and compositions according to the invention are prepared in a manner known per se, in the absence of auxiliaries for example by grinding, screening and/or compressing a solid active ingredient and in the presence of at least one auxiliary for example by intimately mixing and/or grinding the active ingredient with the auxiliary (auxiliaries). These processes for the preparation of the compositions and the use of the compounds (I) for the preparation of these compositions are also a subject of the invention.

Another aspect of the invention is related to the use of a compound as defined in any one of embodiments according to the invention, of a composition comprising at least one compound as defined in, or of a fungicidal or insecticidal mixture comprising at least one compound as defined in any one of embodiments according to the invention, in admixture with other fungicides or insecticides as described above, for controlling or preventing infestation of plants, e.g. plants such as crop plants, propagation material thereof, e.g. seeds, harvested crops, e.g. harvested food crops, or non-living material by insects or by phytopathogenic microorganisms, preferably fungal organisms.

A further aspect of invention is related to a method of controlling or preventing an infestation of plants, e.g. plants such as crop plants, propagation material thereof, e.g. seeds, harvested crops, e.g. harvested food crops, or of non-living materials by phytopathogenic or spoilage microorganisms or organisms potentially harmful to man, especially fungal organisms, which comprises the application of a compound as defined in any one of embodiments according to the invention as active ingredient to the plants, to parts of the plants or to the locus thereof, to the propagation material thereof, or to any part of the non-living materials.

Controlling or preventing means reducing infestation by insects or by phytopathogenic or spoilage microorganisms or organisms potentially harmful to man, especially fungal organisms, to such a level that an improvement is demonstrated.

A preferred method of controlling or preventing an infestation of crop plants by phytopathogenic microorganisms, especially fungal organisms, or insects which comprises the application of a compound as defined in any one of embodiments according to the invention, or an agrochemical composition which contains at least one of said compounds, is foliar application. The frequency of application and the rate of application will depend on the risk of infestation by the corresponding pathogen or insect.

However, the compounds of formula (I), preferably in association with a compound (B), can also penetrate the plant through the roots via the soil (systemic action) by drenching the locus of the plant with a liquid formulation, or by applying the compounds in solid form to the soil, e.g., in granular form (soil application). In crops of water rice such granulates can be applied to the flooded rice field. The compounds of formula (I) may also be applied to seeds (coating) by impregnating the seeds or tubers either with a liquid formulation of the fungicide or coating them with a solid formulation.

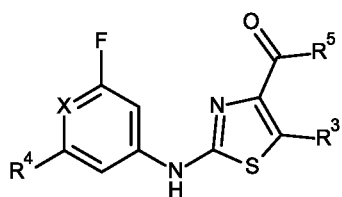
Further characteristics of preferred binary compositions comprising compounds of formula (III), (VI), or (VII), their application methods to cereals and their use rates are as described for compositions comprising compounds of formula (III), (VI), or (VII), and additionally preferably at least one component (B) as described above.

Their application can be both before and after the infection of the plants or parts thereof with the fungi. The treatment is preferably carried out prior to the infection. When a compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), is used on its own, the application rates in the method according to the invention are as described above, e.g., typical are rates of 5 to 2000 g a.i./ha, particularly 10 to 1000 g a.i./ha, e.g., 50, 75, 100 or 200 g a.i./ha. Compounds of formula (I) can be applied to the plants once or more than once during a growing season.

For use in the method according to the invention, the compounds of compound of formula (III), (VI) or (VII), or compounds selected from compounds listed in Tables A.1 to A.5, or compounds listed in Table P (below), can be converted into the customary formulations described above, e.g., solutions, emulsions, suspensions, dusts, powders, pastes and granules. The use form will depend on the particular intended purpose; in each case, it should ensure a fine and even distribution of the compound of formula (III), (VI), or (VII).

The term "plant" as used herein includes seedlings, bushes and crops of fruits and vegetables.

Table A.1: This table discloses compounds 1.01 to 1.12 according to formula (IV) of the present invention, wherein X, R⁴, R⁴ and R⁵ are defined in the following table.

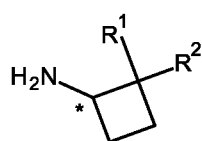


(IV)

Compound No.	X	R ⁴	R ⁴	R ⁵
1.01	CH	H	methyl	OH
1.02	CH	H	methyl	OCH ₃

1.03	CH	H	methyl	OCH ₂ CH ₃
1.04	CH	F	methyl	OH
1.05	CH	F	methyl	OCH ₃
1.06	CH	F	methyl	OCH ₂ CH ₃
1.07	N	H	methyl	OH
1.08	N	H	methyl	OCH ₃
1.09	N	H	methyl	OCH ₂ CH ₃
1.10	N	F	methyl	OH
1.11	N	F	methyl	OCH ₃
1.12	N	F	methyl	OCH ₂ CH ₃

Table A.2: This table discloses compounds 2.01 to 2.03 according to formula (I) of the present invention, wherein R¹ and R² are defined in the following table.

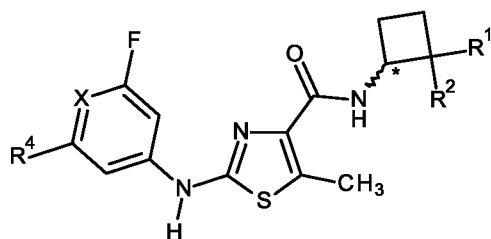


(I)

Compound No.	R ¹	R ¹
2.01	methyl	methyl
2.02	cyclobutyl	
2.03	cyclopentyl	

5

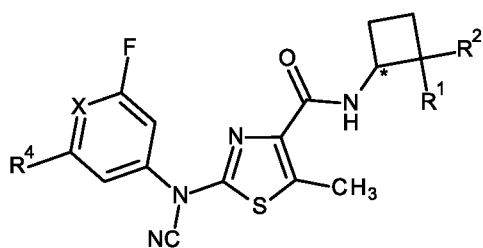
Table A.3: This table discloses compounds 3.01 to 3.12 according to formula (III) of the present invention, wherein R³ is methyl and wherein X, R¹, R², and R⁴ are defined in the following table.



(III)

Compound No.	X	R ⁴	R ¹	R ²
3.01	CH	H	methyl	methyl
3.02	CH	H	cyclobutyl	
3.03	CH	H	cyclopentyl	
3.04	CH	F	methyl	methyl
3.05	CH	F	cyclobutyl	
3.06	CH	F	cyclopentyl	
3.07	N	H	methyl	methyl
3.08	N	H	cyclobutyl	
3.09	N	H	cyclopentyl	
3.10	N	F	methyl	methyl
3.11	N	F	cyclobutyl	
3.12	N	F	cyclopentyl	

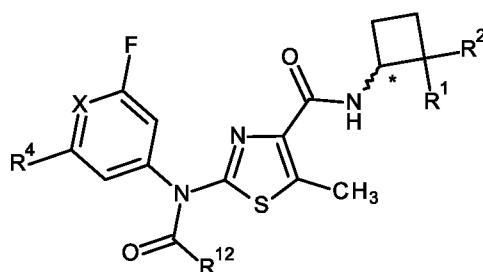
Table A.4: This table discloses compounds 4.01 to 4.12 according to formula (VI) of the present invention, wherein R³ is methyl and wherein X, R¹, R², and R⁴ are defined in the following table.



(VI)

Compound No.	X	R ⁴	R ¹	R ²
4.01	CH	H	methyl	methyl
4.02	CH	H	cyclobutyl	
4.03	CH	H	cyclopentyl	
4.04	CH	F	methyl	methyl
4.05	CH	F	cyclobutyl	
4.06	CH	F	cyclopentyl	
4.07	N	H	methyl	methyl
4.08	N	H	cyclobutyl	
4.09	N	H	cyclopentyl	
4.10	N	F	methyl	methyl
4.11	N	F	cyclobutyl	
4.12	N	F	cyclopentyl	

5 Table A.5: This table discloses compounds 5.01 to 5.140 according to formula (VII) of the present invention, wherein R³ is methyl and wherein X, R¹, R², R⁴ and R¹² are defined in the following table.



(VII)

Compound No.	X	R ⁴	R ¹	R ²	R ¹²
5.01	CH	H	methyl	methyl	methyl
5.02	CH	H	cyclobutyl		methyl
5.03	CH	H	cyclopentyl		methyl
5.04	CH	H	methyl	methyl	ethyl
5.05	CH	H	cyclobutyl		ethyl
5.06	CH	H	cyclopentyl		ethyl
5.07	CH	H	methyl	methyl	isopropyl
5.08	CH	H	cyclobutyl		isopropyl
5.09	CH	H	cyclopentyl		isopropyl
5.11	CH	H	methyl	methyl	methoxy
5.12	CH	H	cyclobutyl		methoxy
5.13	CH	H	cyclopentyl		methoxy
5.14	CH	H	methyl	methyl	ethoxy

5.15	CH	H	cyclobutyl	ethoxy
5.16	CH	H	cyclopentyl	ethoxy
5.17	CH	H	methyl methyl	methoxymethyl
5.18	CH	H	cyclobutyl	methoxymethyl
5.19	CH	H	cyclopentyl	methoxymethyl
5.20	CH	H	methyl methyl	1-methoxyethyl
5.22	CH	H	cyclobutyl	1-methoxyethyl
5.23	CH	H	cyclopentyl	1-methoxyethyl
5.24	CH	H	methyl methyl	oxetane-3-yl
5.25	CH	H	cyclobutyl	oxetane-3-yl
5.26	CH	H	cyclopentyl	oxetane-3-yl
5.27	CH	H	methyl methyl	tetrahydrofuran-2-yl
5.28	CH	H	cyclobutyl	tetrahydrofuran-2-yl
5.29	CH	H	cyclopentyl	tetrahydrofuran-2-yl
5.30	CH	H	methyl methyl	tetrahydrofuran-3-yl
5.31	CH	H	cyclobutyl	tetrahydrofuran-3-yl
5.33	CH	H	cyclopentyl	tetrahydrofuran-3-yl
5.34	CH	H	methyl methyl	tetrahydropyran-4-yl
5.35	CH	H	cyclobutyl	tetrahydropyran-4-yl
5.36	CH	H	cyclopentyl	tetrahydropyran-4-yl
5.37	CH	F	methyl methyl	methyl,
5.38	CH	F	cyclobutyl	methyl
5.39	CH	F	cyclopentyl	methyl
5.40	CH	F	methyl methyl	ethyl
5.41	CH	F	cyclobutyl	ethyl
5.42	CH	F	cyclopentyl	ethyl
5.44	CH	F	methyl methyl	isopropyl
5.45	CH	F	cyclobutyl	isopropyl
5.46	CH	F	cyclopentyl	isopropyl
5.47	CH	F	methyl methyl	methoxy
5.48	CH	F	cyclobutyl	methoxy
5.49	CH	F	cyclopentyl	methoxy
5.50	CH	F	methyl methyl	ethoxy
5.51	CH	F	cyclobutyl	ethoxy
5.52	CH	F	cyclopentyl	ethoxy
5.53	CH	F	methyl methyl	methoxymethyl
5.55	CH	F	cyclobutyl	methoxymethyl
5.56	CH	F	cyclopentyl	methoxymethyl
5.57	CH	F	methyl methyl	methyl
5.58	CH	F	cyclobutyl	1-methoxyethyl
5.59	CH	F	cyclopentyl	1-methoxyethyl
5.60	CH	F	methyl methyl	oxetane-3-yl
5.61	CH	F	cyclobutyl	oxetane-3-yl
5.62	CH	F	cyclopentyl	oxetane-3-yl
5.63	CH	F	methyl methyl	tetrahydrofuran-2-yl
5.64	CH	F	cyclobutyl	tetrahydrofuran-2-yl
5.66	CH	F	cyclopentyl	tetrahydrofuran-2-yl
5.67	CH	F	methyl methyl	tetrahydrofuran-3-yl
5.68	CH	F	cyclobutyl	tetrahydrofuran-3-yl
5.69	CH	F	cyclopentyl	tetrahydrofuran-3-yl
5.70	CH	F	methyl methyl	tetrahydropyran-4-yl
5.71	CH	F	cyclobutyl	tetrahydropyran-4-yl
5.72	CH	F	cyclopentyl	tetrahydropyran-4-yl
5.73	CH	H	methyl methyl	methyl,
5.74	CH	H	cyclobutyl	methyl

5.75	CH	H	cyclopentyl	methyl
5.75	N	H	methyl	methyl
5.77	N	H	cyclobutyl	ethyl
5.78	N	H	cyclopentyl	ethyl
5.79	N	H	methyl	methyl
5.80	N	H	cyclobutyl	isopropyl
5.81	N	H	cyclopentyl	isopropyl
5.82	N	H	methyl	methyl
5.83	N	H	cyclobutyl	methoxy
5.84	N	H	cyclopentyl	methoxy
5.85	N	H	methyl	methyl
5.86	N	H	cyclobutyl	ethoxy
5.88	N	H	cyclopentyl	ethoxy
5.89	N	H	methyl	methyl
5.90	N	H	cyclobutyl	methoxymethyl
5.91	N	H	cyclopentyl	methoxymethyl
5.92	N	H	methyl	methyl
5.93	N	H	cyclobutyl	1-methoxyethyl
5.94	N	H	cyclopentyl	1-methoxyethyl
5.95	N	H	methyl	methyl
5.96	N	H	cyclobutyl	oxetane-3-yl
5.97	N	H	cyclopentyl	oxetane-3-yl
5.99	N	H	methyl	methyl
5.100	N	H	cyclobutyl	tetrahydrofuran-2-yl
5.101	N	H	cyclopentyl	tetrahydrofuran-2-yl
5.102	N	H	methyl	methyl
5.103	N	H	cyclobutyl	tetrahydrofuran-3-yl
5.104	N	H	cyclopentyl	tetrahydrofuran-3-yl
5.105	N	H	methyl	methyl
5.106	N	H	cyclobutyl	tetrahydropyran-4-yl
5.107	N	H	cyclopentyl	tetrahydropyran-4-yl
5.108	N	F	methyl	methyl
5.109	N	F	cyclobutyl	methyl
5.110	N	F	cyclopentyl	methyl
5.111	N	F	methyl	methyl
5.112	N	F	cyclobutyl	ethyl
5.113	N	F	cyclopentyl	ethyl
5.114	N	F	methyl	methyl
5.115	N	F	cyclobutyl	isopropyl
5.116	N	F	cyclopentyl	isopropyl
5.117	N	F	methyl	methyl
5.118	N	F	cyclobutyl	methoxy
5.119	N	F	cyclopentyl	methoxy
5.120	N	F	methyl	methyl
5.121	N	F	cyclobutyl	ethoxy
5.122	N	F	cyclopentyl	ethoxy
5.123	N	F	methyl	methyl
5.124	N	F	cyclobutyl	methoxymethyl
5.125	N	F	cyclopentyl	methoxymethyl
5.126	N	F	methyl	methyl
5.127	N	F	cyclobutyl	1-methoxyethyl
5.128	N	F	cyclopentyl	1-methoxyethyl
5.129	N	F	methyl	methyl
5.130	N	F	cyclobutyl	oxetane-3-yl
5.131	N	F	cyclopentyl	oxetane-3-yl

5.132	N	F	methyl	methyl	tetrahydrofuran-2-yl
5.133	N	F	cyclobutyl		tetrahydrofuran-2-yl
5.134	N	F	cyclopentyl		tetrahydrofuran-2-yl
5.135	N	F	methyl	methyl	tetrahydrofuran-3-yl
5.136	N	F	cyclobutyl		tetrahydrofuran-3-yl
5.137	N	F	cyclopentyl		tetrahydrofuran-3-yl
5.138	N	F	methyl	methyl	tetrahydropyran-4-yl
5.139	N	F	cyclobutyl		tetrahydropyran-4-yl
5.140	N	F	cyclopentyl		tetrahydropyran-4-yl

Preferably, the compound of formula (I) is selected from (1S)-2,2-dimethylcyclobutanamine, (1R)-2,2-dimethylcyclobutanamine, (3S)-spiro[3.3]heptan-3-amine, (3R)-spiro[3.3]heptan-3-amine, (3S)-spiro[3.4]octan-3-amine, or (3R)-spiro[3.4]octan-3-amine.

- 5 Preferably the compound of formula (IV) is selected from ethyl 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-thiazole-4-carboxylate; or ethyl 2-(3,5-difluoroanilino)-5-methyl-thiazole-4-carboxylate.

In one embodiment the compound of formula (IV) is ethyl 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-thiazole-4-carboxylate.

- 10 In another embodiment the compound of formula (IV) is ethyl 2-(3,5-difluoroanilino)-5-methyl-thiazole-4-carboxylate.

- Preferably the compound of formula (III) is selected from 2-[(2,6-difluoro-4-pyridyl)amino]-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-[(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide, 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide, 2-(3,5-difluoroanilino)-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-(3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-(3,5-difluoroanilino)-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide, or 2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide.

- Preferably, the compound of formula (VI) is selected from 2-cyano-[(2,6-difluoro-4-pyridyl)amino]-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-cyano-[(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-cyano-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-cyano-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-cyano-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide, 2-cyano-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide, 2-(N-cyano-3,5-difluoroanilino)-N-[(1S)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-(N-cyano-3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-

N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide, 2-[3,5-difluoro-N-(tetrahydropyran-4-carbonyl)amino]-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-[3,5-difluoro-N-(tetrahydropyran-4-carbonyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]-thiazole-4-carboxamide, 2-[3,5-difluoro-N-(tetrahydropyran-4-carbonyl)amino]-5-methyl-N-[(3S)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide, or 2-[3,5-difluoro-N-(tetrahydropyran-4-carbonyl)amino]-5-methyl-N-[(3R)-spiro[3.3]heptan-3-yl]-thiazole-4-carboxamide.

EXAMPLES

The Examples which follow serve to illustrate the invention and are not meant in any way to limit the invention.

The compounds of the invention can be distinguished from known compounds by virtue of greater efficacy at low application rates, which can be verified by a person skilled in the art using the experimental procedures outlined in the Examples, using lower application rates, if necessary, for example 60 ppm, 20 ppm or 2 ppm.

Compounds of formula (I) may possess any number of benefits including, *inter alia*, advantageous levels of biological activity for protecting plants against diseases that are caused by fungi or superior properties for use as agrochemical active ingredients (for example, greater biological activity, an advantageous spectrum of activity, an increased safety profile (including improved crop tolerance), improved physico-chemical properties, or increased biodegradability).

FORMULATION EXAMPLES

20	<u>Wettable powders</u>	a)	b)	c)
	active ingredients	25 %	50 %	75 %
	sodium lignosulfonate	5 %	5 %	-
	sodium lauryl sulfate	3 %	-	5 %
	sodium diisobutylphenylsulfonate	-	6 %	10 %
25	phenol polyethylene glycol ether (7-8 mol of ethylene oxide)	-	2 %	-
	highly dispersed silicic acid	5 %	10 %	10 %
	Kaolin	62 %	27 %	-

The combination is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording wettable powders that can be diluted with water to give suspensions of the desired concentration.

30	<u>Powders for dry seed treatment</u>	a)	b)	c)
	active ingredients	25 %	50 %	75 %
	light mineral oil	5 %	5 %	5 %
	highly dispersed silicic acid	5 %	5 %	-
	Kaolin	65 %	40 %	-
35	Talcum	-	-	20 %

The combination is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording powders that can be used directly for seed treatment.

Emulsifiable concentrate

	active ingredients	10 %
5	octylphenol polyethylene glycol ether (4-5 mol of ethylene oxide)	3 %
	calcium dodecylbenzene sulfonate	3 %
	castor oil polyglycol ether (35 mol of ethylene oxide)	4 %
	Cyclohexanone	30 %
	xylene mixture	50 %
10	Emulsions of any required dilution, which can be used in plant protection, can be obtained from this concentrate by dilution with water.	

Dusts

	a)	b)	c)
Active ingredients	5 %	6 %	4 %
Talcum	95 %	-	-
15 Kaolin	-	94 %	-
mineral filler	-	-	96 %

Ready-for-use dusts are obtained by mixing the combination with the carrier and grinding the mixture in a suitable mill. Such powders can also be used for dry dressings for seed.

Extruder granules

20	Active ingredients	15 %
	sodium lignosulfonate	2 %
	carboxymethylcellulose	1 %
	Kaolin	82 %

The combination is mixed and ground with the adjuvants, and the mixture is moistened with water. The mixture is extruded and then dried in a stream of air.

Coated granules

	Active ingredients	8%
	polyethylene glycol (mol. wt. 200)	3 %
	Kaolin	89 %
30	The finely ground combination is uniformly applied, in a mixer, to the kaolin moistened with polyethylene glycol. Non-dusty coated granules are obtained in this manner.	

Suspension concentrates

	active ingredients	40 %
	propylene glycol	10 %
35	nonylphenol polyethylene glycol ether (15 mol of ethylene oxide)	6 %

Sodium lignosulfonate	10 %
carboxymethylcellulose	1 %
silicone oil (in the form of a 75 % emulsion in water)	1 %
Water	32 %

- 5 The finely ground combination is intimately mixed with the adjuvants, giving a suspension concentrate from which suspensions of any desired dilution can be obtained by dilution with water. Using such dilutions, living plants as well as plant propagation material can be treated and protected against infestation by microorganisms, by spraying, pouring or immersion.

Flowable concentrate for seed treatment

10 active ingredients	40 %
propylene glycol	5 %
copolymer butanol PO/EO	2 %
Tristyrenephenol with 10-20 moles EO	2 %
1,2-benzisothiazolin-3-one (in the form of a 20% solution in water)	0.5 %
15 monoazo-pigment calcium salt	5 %
Silicone oil (in the form of a 75 % emulsion in water)	0.2 %
Water	45.3 %

- The finely ground combination is intimately mixed with the adjuvants, giving a flowable concentrate from which solutions of any desired dilution can be obtained by dilution with water, which can be used directly for seed treatment. Using such dilutions, living plants as well as plant propagation material can be treated and protected against infestation by microorganisms, by spraying, pouring or immersion.

Slow-Release Capsule Suspension

- 28 parts of the combination are mixed with 2 parts of an aromatic solvent and 7 parts of toluene diisocyanate/polymethylene-polyphenylisocyanate-mixture (8:1). This mixture is emulsified in a mixture of 1.2 parts of polyvinylalcohol, 0.05 parts of a defoamer and 51.6 parts of water until the desired particle size is achieved. To this emulsion a mixture of 2.8 parts 1,6-diaminohexane in 5.3 parts of water is added. The mixture is agitated until the polymerization reaction is completed. The obtained capsule suspension is stabilized by adding 0.25 parts of a thickener and 3 parts of a dispersing agent. The capsule suspension formulation contains 28% of the active ingredients. The medium capsule diameter is 8-15 microns. The resulting formulation is applied to seeds as an aqueous suspension in an apparatus suitable for that purpose.

- Formulation types include an emulsion concentrate (EC), a suspension concentrate (SC), a suspo-emulsion (SE), a capsule suspension (CS), a water dispersible granule (WG), an emulsifiable granule (EG), an emulsion, water in oil (EO), an emulsion, oil in water (EW), a micro-emulsion (ME), an oil dispersion (OD), an oil miscible flowable (OF), an oil miscible liquid (OL), a soluble concentrate (SL), an ultra-low volume suspension (SU), an ultra-low volume liquid (UL), a technical concentrate (TK), a dispersible concentrate (DC), a wettable powder

(WP), a soluble granule (SG) or any technically feasible formulation in combination with agriculturally acceptable adjuvants.

ABBREVIATIONS

	ACN	acetonitrile
5	CDCl ₃	deuterated chloroform
	DABCO	1,4-diazabicyclo[2.2.2]octane, also known as triethylenediamine or TEDA
	DEA	diethylamine
	DMSO	dimethyl sulfoxide
	DMSO-d ₆	deuterated Dimethyl sulfoxide
10	e.e.	Enantiomeric excess (also Ee or ee)
	equiv.	equivalent
	Et ₃ N	triethylamine
	EtOAc	ethyl acetate
	HCl	hydrochloric acid
15	h/hrs	hour/hours
	IPA	2-propanol (or isopropanol)
	LC-MS	Liquid Chromatography Mass Spectrometry (LC-MS or LCMS)
	rh	relative humidity
	rt	room temperature
20	Rt	retention time
	ssp.	subspecies
	THF	tetrahydrofuran

PREPARATION EXAMPLES

25 The compounds according to the invention may be prepared using the synthetic techniques described both above and below.

“Mp” means melting point in °C. Free radicals represent methyl groups. ¹H NMR and ¹⁹F NMR measurements were recorded on a Bruker 400MHz spectrometer (or 600MHz as indicated), chemical shifts are given in ppm relevant to a TMS (¹H) and CFCI₃ (¹⁹F) standard. Spectra measured in deuterated solvents as indicated. Either
30 one of the LC-MS methods below was used to characterize the compounds. The characteristic LCMS values obtained for each compound were the retention time (“Rt”, recorded in minutes) and the measured molecular ion (M+H)⁺ or (M-H)⁻.

LC-MS Method 1: Spectra were recorded on a Mass Spectrometer from Waters (SQD2 or QDA Single quadrupole mass spectrometer) equipped with an electrospray source (Polarity: Positive and Negative Polarity
35 Switch), Capillary: 0.8-3.00 kV, Cone range: 25; Source Temperature: 120-150°C, Desolvation Temperature: 500-600°C, Cone Gas Flow: 50 L/h, Desolvation Gas Flow: 1000 L/h, Mass range: 110 to 850 Da; and an

Acquity UPLC from Waters: Quaternary solvent manager, heated column compartment, diode-array detector. Column: Waters UPLC HSS T3, 1.8 μm , 30 x 2.1 mm, Temp: 40°C, PDA Wavelength range (nm): 200 to 400, Solvent Gradient: A = Water with 0.1% formic acid: Acetonitrile: 95: 5 v/v, B= Acetonitrile with 0.05% formic acid, Gradient: 0 min-1.0 min 10% B - 90% A; 1.0 min-4.50 min 10% -100% B; 4.51 min-5.30 min 100% B, 0% A; 5.31 min-5.50 min 100% -10% B; 5.51 min-6.00 min 10% B, 90% A; Flow (ml/min) 0.6.

LC-MS Method 2: Spectra were recorded on a Mass Spectrometer from Waters (SQD2 or QDA Single quadrupole mass spectrometer) equipped with an electrospray source (Polarity: Positive and Negative Polarity Switch), Capillary: 0.8-3.00 kV, Cone range: 25, Source Temperature: 120-150°C, Desolvation Temperature: 500-600°C, Cone Gas Flow: 50 L/h, Desolvation Gas Flow: 1000 L/h, Mass range: 110 to 850 Da) and an Acquity UPLC from Waters: Quaternary solvent manager, heated column compartment, diode-array detector. Column: Acquity UPLC HSS T3 C18, 1.8 μm , 30 x 2.1 mm, Temp: 40°C, DAD Wavelength range (nm): 200 to 400, Solvent Gradient: A = water + 5% Acetonitrile + 0.1 % HCOOH, B= Acetonitrile + 0.05 % HCOOH: gradient: 0 min 10% B; 0.-0.2 min 10-50% B; 0.2-0.6 min 50-100% B; 0.6-1.3 min 100% B; 1.3-1.4 min 100-10% B; 1.4-1.6 min 10% B; Flow (mL/min) 0.6.

LC-MS Method 3: Spectra were recorded on a Mass Spectrometer from Waters (SQD2 or QDA Single quadrupole mass spectrometer) equipped with an electrospray source (Polarity: Positive and Negative Polarity Switch), Capillary: 0.8-3.00 kV, Cone range: 25 Source Temperature: 120-150°C, Desolvation Temperature: 500-600°C, Cone Gas Flow: 50 L/h, Desolvation Gas Flow: 1000 L/h, Mass range: 110 to 850 Da) and an Acquity UPLC from Waters: Quaternary solvent manager, heated column compartment, diode-array detector. Column: Acquity UPLC HSS T3 C18, 1.8 μm , 30 x 2.1 mm, Temp: 40°C, DAD Wavelength range (nm): 200 to 400, Solvent Gradient: A = water + 5% Acetonitrile + 0.1 % HCOOH, B= Acetonitrile + 0.05 % HCOOH: gradient: 0 min 10% B; 0.0-0.5 min 10% B; 0.5-2 min 100% B; 2-3 min 100% B; 3-3.5 min 10% B; 3.5-4 min 10% B; Flow (mL/min) 0.6.

GC-MS Method 4: Spectra were recorded on a Mass Spectrometer from SHIMADZU GCMS-QP2010 Ultra equipped with an Electron Impact (EI) Ion source, Ion Source Temperature: 200°C, Interface Temperature: 220°C, Scan speed: 2500, Carrier Gas: Helium, Mass range: 50 to 650 Da and GC-2010 PLUS from Shimadzu, Capillary Column: SH-Rxi- 17 Sil MS, Column Length: 30m, Internal diameter: 0.25 mm, Film Thickness: 0.25 μm , Column oven Temperature: 40°C, Combi-PAL autosampler, Injector Temperature: 250°C, Injection Mode: Split, Split Ratio: 30:1, Flow Control Mode: Pressure, Total Flow (mL/min): 33.0, Column Flow (mL/min): 1.0, Purge Flow (mL/min): 2.0, Runtime: 15min, Temperature Program: Initial temp. 40°C for 1 min, then 40-280°C with constant rate of 25°C per min, Temperature hold at 280°C for 4.4 min.

General experimental procedure for Ru-catalysed reductive amination

A pressure autoclave, at 24°C, was charged with a mixture of 2,2-dimethylcyclobutanone, ammonium salt, Ruthenium catalyst, a solution of ammonia in methanol, and solvent, and the mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure of 10 to 30 bar was applied, and the reaction mixture was heated at 80 to 100°C under constant hydrogen pressure for 8 to 20 h. Chemical yields were determined by ^1H NMR spectroscopy in the presence of an internal standard.

Chiral analysis: To a 500 mL aliquot of the reaction mixture at 24°C was added 2,4-dinitrofluorobenzene (1.5 equiv.) and diisopropylethylamine (2.5 equiv.) and the mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (2 mL) and washed with water. 30 µL of the organic phase was diluted with 1.5 mL acetonitrile and submitted for chiral analysis.

5 **Chiral method:** SFC: Waters Acquity UPC²/QDa; PDA Detector Waters Acquity UPC²

Method of Chiral Analysis: Column: Daicel SFC CHIRALPAK® IG, 3mm, 0.46cm x 10cm, 40°C, Mobile phase: A: CO₂ B: MeOH / isocratic: 20% B in 5 min, ABPR: 1800 psi, Flow rate: 2.0 mL/min, Detection: 345 nm, Sample preparation: 1 mg/mL in acetonitrile, Injection: 1 mL

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 2.28	Retention time (min) ~ 2.73

10

Example P1: Effect of solvent and concentration

A pressure autoclave, at 24°C, was charged with a 2 mmol of 2,2-dimethylcyclobutanone, NH₄Cl (2 equiv., based on 2,2-dimethylcyclobutanone), Ru(II)-(R)-3;5-XYLYL-BINAP (1 mol%), a solution of ammonia in methanol (7 M, 4 eq.), and solvent, and the mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure of 30 bar was applied, and the reaction mixture was heated at 80°C under constant hydrogen pressure for 20 h. The effect of the solvent on the enantiomeric excess of the ruthenium-catalyzed reaction are shown in Table 1.

15

Table 1: Effect of the solvent and concentration

Example	Solvent (concentration)	Yield (%)	e.e. (%)
P1-1	MeOH (0.4 M)	85	83
P1-2	EtOH (0.4 M)	25	77
P1-3	Toluene (0.4 M)	12	77
P1-4	MeOH (1 M)	87	82

20 **Example P2: Effect of the nature of the ammonium salt:**

A pressure autoclave, at 24°C, was charged with a 2 mmol of 2,2-dimethylcyclobutanone, ammonium salt (Table 2, equiv. are based on 2,2-dimethylcyclobutanone), Ru(II)-(R)-3;5-XYLYL-BINAP (1 mol%), a solution of ammonia in methanol (7 M, 2 eq.), and methanol, and the reaction mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure of 30 bar was applied, and the reaction mixture was heated at 80°C under constant hydrogen pressure for 20 h. The effect of the ammonium salt on the enantiomeric excess of the ruthenium-catalyzed reaction are shown in Table 2.

25

Table 2: Effect of the nature of the ammonium salt

Example	Ammonium source (equiv.)	Yield (%)	e.e. (%)
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P2-1	ammonium chloride (2 equiv.)	85	82
P2-2	ammonium bromide (2 equiv.)	80	80
P2-3	triethylamine (2 equiv.), HCl (36% w/w, 2 equiv.)	86	83
P2-4	triethylamine (0.1 equiv.), HCl (36% w/w, 1.1 equiv.)	64	83
P2-5	triethylamine (0.5 equiv.), HCl (36% w/w, 0.3 equiv.)	77	83
P2-6	triethylamine hydrochloride (2 equiv.)	83	84
P2-7	triethylamine (2 equiv.), HBr (48% w/w, 2 equiv.)	84	82
P2-8	triethylamine hydrobromide (2 equiv.)	65	81
P2-9	trimethylamine hydrochloride (2 equiv.)	93	83
P2-10	DABCO (2 equiv.), HCl (36% w/w, 2 equiv.)	86	83
P2-11	4-Methyl-Morpholine (2 equiv.), HCl (36% w/w, 2 equiv.)	90	85
P2-12	dimethylamine hydrochloride (Me ₂ NH.HCl) (2 equiv.)	54	78
P2-13	Pyrrolidine (2 equiv.), HCl (36% w/w, 2 equiv.)	30	73
P2-14	diisopropylamine (DIPA) (2 equiv.), HCl (36% w/w, 2 equiv.)	27	80
P2-15	Piperidine (2 equiv.), HCl (36% w/w, 2 equiv.)	87	83
P2-16	Morpholine (2 equiv.), HCl (36% w/w, 2 equiv.)	80	60
P2-17	dimethylamine hydrochloride (Me ₂ NH.HCl) (2 equiv.)	44	80
P2-18	n-butylamine (n-BuNH ₂) (2 equiv.), HCl (36% w/w, 2 equiv.)	64	79
P2-19	benzylamine (2 equiv.), HCl (36% w/w, 2 equiv.)	62	82
P2-20	tert-butylamine (2 equiv.), HCl (36% w/w, 2 equiv.)	59	77
P2-21	Aniline (2 equiv.), HCl (36% w/w, 2 equiv.)	68	85
P2-22	Quinine (2 equiv.), HCl (36% w/w, 2 equiv.)	35	83
P2-23	Quinidine (2 equiv.), HCl (36% w/w, 2 equiv.)	30	75
P2-24	Cinchonidine (2 equiv.), HCl (36% w/w, 2 equiv.)	66	84
P2-25	(R)-Phenylethylamine (2 equiv.), HCl (36% w/w, 2 equiv.)	80	-36
P2-26	(S)-Phenylethylamine (2 equiv.), HCl (36% w/w, 2 equiv.)	88	76

Example P3: Effect of the nature and equivalents of ammonia and the ammonium salt

A pressure autoclave, at 24°C, was charged with a 2 mmol of 2,2-dimethylcyclobutanone, ammonium salt (Table 3, equiv. are based on 2,2-dimethylcyclobutanone), Ru(II)-(R)-3;5-XYLYL-BINAP (1 mol%), a solution of ammonia in methanol (7 M, 1 eq.), and methanol, and the reaction mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure of 30 bar was applied, and the reaction mixture was heated at 80°C under constant hydrogen pressure for 20 h. The effect of the ammonium salt and equivalent (based on cyclobutanone) on the enantiomeric access of the ruthenium-catalyzed reaction are shown in Table 3.

Table 3: Effect of the nature and equivalents of ammonia and the ammonium salt

Example	Ammonium source (equiv.)	Yield (%)	e.e. (%)
P3-1	NH ₄ Cl (1.1 equiv)	85	83
P3-2	Et ₃ N (1.1 equiv.), HCl (36% w/w, 0.2 equiv.)	65	77
P3-3	Et ₃ N (1.1 equiv.), HCl (36% w/w, 0.5 equiv.)	83	82
P3-4	Et ₃ N (1.1 equiv.), HCl (36% w/w, 0.5 equiv.)	90	83
P3-5	Et ₃ N (0.5 equiv.), HCl (36% w/w, 0.5 equiv.)	83	82
P3-6	tripropylamine (TPA, n-Pr ₃ N) (1.1 equiv.), HCl (36% w/w, 0.5 equiv.)	89	84
P3-7	tri-n-butylamine (n-Bu ₃ N) (1.1 equiv.), HCl (36% w/w, 0.5 equiv.)	89	83
P3-8	4-MeMorpholine (1.1 equiv.), HCl (36% w/w, 1.1 equiv.)	93	84
P3-9	Piperidine (1.1 equiv.), HCl (36% w/w, 1.1 equiv.)	86	69
P3-10	Morpholine (1.1 equiv.), HCl (36% w/w, 1.1 equiv.)	90	60
P3-11	DABCO (1.1 equiv.), HCl (36% w/w, 1.1 equiv.)	93	83
P3-12	Pyridine (1.1 equiv.), HCl (36% w/w, 1.1 equiv.)	84	84
P3-13	2,2-dimethylcyclobutylamine (1 equiv.), HCl (36% w/w, 1.0 equiv.)	98	86
P3-14	2,2-dimethylcyclobutylamine (0.5 equiv.), HCl (36% w/w, 0.5 equiv.)	97	84

Example P4: Effect of the temperature and pressure

A pressure autoclave, at 24°C, was charged with a 2 mmol of 2,2-dimethylcyclobutanone, 2,2-dimethylcyclobutylamine (1 equiv. based on 2,2-dimethylcyclobutanone), HCl (36% w/w, 1.0 equiv.), Ru(II)-(R)-3;5-XYLYL-BINAP (1 mol%), a solution of ammonia in methanol (7 M, 1.1 eq.), and methanol (concentration 2,2-dimethylcyclobutanone 0.4M), and the reaction mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure was applied, and the reaction mixture was heated under constant hydrogen pressure for 20 h. The effect of the temperature and pressure on the enantiomeric excess of the ruthenium-catalyzed reaction are shown in Table 4.

Table 4: Effect of the temperature and pressure

Example	Pressure (bar)	Temperature (°C)	Yield (%)	e.e. (%)
P4-1	30	80	98	86
P4-2	10	100	97	84

Example P5: Effect of the ligand

A pressure autoclave, at 24°C, was charged with a 2 mmol of 2,2-dimethylcyclobutanone, NH₄Cl (1 equiv. based on 2,2-dimethylcyclobutanone), HCl (36% w/w, 1.0 equiv.), Ru(II)-(R)-3;5-XYLYL-BINAP (1 mol%), a solution of ammonia in methanol (7 M, 1.1 eq.), and methanol (concentration 2,2-dimethylcyclobutanone 0.45 M), and the reaction mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure of 30 bar was applied, and the reaction mixture was heated at 80°C under constant hydrogen pressure for 20 h. The effect of the ligand on the enantiomeric excess of the

ruthenium-catalyzed reaction are shown in Table 5.

Table 5: Effect of the ligand

Example	Ligand	Yield (%)	e.e. (%)
P5-1	(R)-Xyl-BINAP	98	86
P5-2	(R)-BINAP	64	80

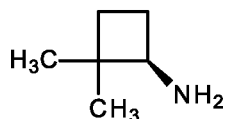
Example P6: Effect of the Ruthenium catalyst

- 5 A pressure autoclave, at 24°C, was charged with a 2 mmol of 2,2-dimethylcyclobutanone, NH₄Cl (1 equiv. based on 2,2-dimethylcyclobutanone), HCl (36% w/w, 1.0 equiv.), Ru-catalyst, a solution of ammonia in methanol (7 M, 1.1 eq.), and methanol (concentration 2,2-dimethylcyclobutanone 0.45 M), and the reaction mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure of 30 bar was applied, and the reaction mixture was heated at 80°C under constant
- 10 hydrogen pressure for 20 h. The effect of the ruthenium-catalyst on the enantiomeric access of the ruthenium-catalyzed reaction are shown in Table 6

Table 6: Effect of the Ruthenium catalyst

Example	Ru catalyst (mol%)	Yield (%)	e.e. (%)
P6-1	[NH ₂ Me ₂][{RuCl((R)-xylbinap)} ₂ (μ-Cl) ₃] (0.5 mol%)	92	83
P6-2	Ru(OAc) ₂ [(R)-xylbinap] (1 mol%)	91	82

Example P7: Large scale preparation of (1R)-2,2-dimethylcyclobutanamine (compound P.04, table P)



(compound P.04, table P)

- 15 A pressure autoclave, at 24°C, was charged with a mixture of 2,2-dimethylcyclobutanone (6.10 g, 62.3 mmol), ammonium chloride (1.0 equiv., 62.3 mmol, 3.33 g), (R)-[(RuCl(DM-BINAP))₂(μ-Cl)₃][NH₂Me₂] (0.005 equiv., 0.311 mmol, 0.589 g) and a solution of ammonia in methanol (7 M, 1.1 equiv., 68.5 mmol, 9.78 mL), methanol (0.5 M, 120 mL), and the reaction mixture was purged with nitrogen gas. The reaction flask was
- 20 flushed with hydrogen gas for three times, then a hydrogen pressure of 10 bar was applied and the reaction mixture was heated at 100°C under constant hydrogen pressure (10 bar) for 8 h. The reaction mixture was cooled to 0-5°C, acidified with concentrated aqueous hydrochloric acid (36% w/w) to ~pH to 0.5-0.7, and concentrated under reduced pressure. The residue was diluted with water (14.0 mL) and basified with an aqueous solution of sodium hydroxide (30% w/w) to pH~12-12.5. The above mixture was distilled (60-70°C,
- 25 100-300 mbar) under reduced pressure to provide (1R)-2,2-dimethylcyclobutanamine (7.24 g, 73% w/w, 53.5 mmol, 86% yield).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.93 (s, 3 H), 0.96 (s, 3 H), 1.26 – 1.38 (m, 2 H), 1.51 (tt, *J* = 10.7, 9.1 Hz, 1 H), 1.95 – 2.03 (m, 1 H), 2.85 (ddd, *J* = 9, 9, 0.9 Hz, 1 H), 0.50 – 4.00 (broad peak, 2H).

Chiral analysis: To a solution of the amine (1 equiv., 0.22 mmol) in methanol (0.45 M, 0.5 mL) at 24°C was added 2,4-dinitrofluorobenzene (1.5 equiv., 0.33 mmol, 0.062 g) and diisopropylethylamine (2.5 equiv., 0.55 mmol, 0.072 g) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (2 mL) and washed with water. 30 µL of the organic phase was diluted with 1.5 mL acetonitrile and submitted for chiral analysis.

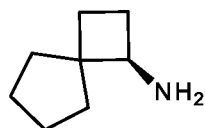
Chiral method: SFC: Waters Acquity UPC²/QDa; PDA Detector Waters Acquity UPC²

Method of Chiral Analysis: Column: Daicel SFC CHIRALPAK® IG, 3mm, 0.46cm x 10cm, 40°C; Mobile phase: A: CO₂, B: MeOH, isocratic: 20% B in 5 min; ABPR: 1800 psi; Flow rate: 2.0 ml/min; Detection: 345 nm; Sample preparation: 1 mg/mL in acetonitrile; Injection: 1 mL

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 2.28	Retention time (min) ~ 2.73
Enantiomeric ratio 92 (R) : 8 (S)	

Example P8: Large scale preparation of (1R)-2,2-dimethylcyclobutanamine (compound P.05, table P)



(compound P.05, table P)

A pressure autoclave, at 24°C, was charged with a mixture of spiro [3.4]octan-3-one (6.60 g, 53.2 mmol), ammonium chloride (1.00 equiv., 53.2 mmol, 2.84 g), (R)-[(RuCl(DM-BINAP))₂(μ-Cl)₃][NH₂Me₂] (0.005 equiv. 0.266 mmol, 0.504 g) and a solution of ammonia in methanol (7 M, 1.10 equiv., 58.5 mmol, 8.36 mL) in methanol (0.5 M, 118 mL), and the reaction mixture was purged with nitrogen gas. The reaction flask was flushed with hydrogen gas for three times, then a hydrogen pressure of 10 bar was applied and the reaction mixture was heated at 100°C under constant hydrogen pressure (10 bar) for 8 h. The reaction mixture was then cooled to 0-5°C, acidified (pH 0.5-0.7) with HCl (conc.) and concentrated under reduced pressure at 50°C to remove methanol. The residue was diluted with water (100 mL) and extracted with TBME (3X30 mL). The aqueous phase was cooled down to 0-10°C and basified with an aqueous solution of sodium hydroxide (30% w/w) to pH~12-12.5. The mixture was extracted with TBME (3X30 mL) and the combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to provide (3R)-spiro[3.4]octan-3-amine (5.14 g, 41.1 mmol, 77% yield)

GCMS (Method 4): Rt =3.14 min, m/z 125; ¹H NMR (400 MHz, DMSO-*d*₆), δ ppm 3.01 - 3.07 (m, 1 H), 1.92 - 2.03 (m, 1 H), 1.71 - 1.83 (m, 1 H), 1.38 - 1.57 (m, 11 H), 1.29 (dt, J=12.3, 6.2 Hz, 1 H).

Chiral analysis: To a solution/suspension of the diastereomeric amine salt in MeCN at room temperature (24°C) was added 2,4-dinitrofluorobenzene (1.5 equiv.) and triethylamine (5 equiv.) and the mixture was stirred for 30 min. 30 µL of the organic phase was diluted with 1.5 mL MeCN and submitted for chiral analysis.

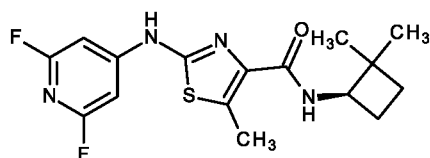
Chiral HPLC method: SFC: Waters Acquity UPC²/QDa, PDA Detector Waters Acquity UPC²

Method of Chiral Analysis: Column: Daicel SFC CHIRALPAK® AY, 3mm, 0.3cm x 10cm, 40°C, Mobile phase: A: CO₂ B: EtOH gradient: 20-60% B in 2 min, ABPR: 1800 psi, Flow rate: 2.0 ml/min; Detection: 340 nm; Sample concentration: 1 mg/mL in acetonitrile; Injection: 2 µL

5 Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 0.75	Retention time (min) ~ 0.95
Enantiomeric ratio 91 (R) : 9 (S)	

Example P9: *Preparation of 2-[(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (compound P.01, table P)*



(compound P.01, table P)

- 10 To a heated (60°C) suspension of 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-thiazole-4-carboxylic acid (89.9 mmol, 24.4 g) and dimethylformamide (0.04 equiv., 3.60 mmol 0.263 g) in isopropyl acetate (0.36 M, 250 mL) under nitrogen atmosphere, was added thionyl chloride (1.50 equiv., 134.9 mmol, 16.0 g) over a period of 1 h, and the reaction mixture was stirred at the same temperature for an additional 60 min. The reaction mixture was cooled to rt, and then transferred to a cooled mixture (0-5°C) of (1R)-2,2-dimethylcyclobutanamine hydrochloride (1.20 equiv. 107.9 mmol, 14.6 gm) and an aqueous solution of sodium hydroxide (4.5 M, 1.5 equiv., 134.9 mmol, 5.39 g) in isopropyl acetate (0.84 M, 125 mL) over 1 h, the pH of the reaction mixture was maintained between 7.5-10 by the occasional addition of an aqueous solution of sodium hydroxide (4.5 M). The reaction mixture was diluted with isopropyl acetate and aqueous layer was separated. The organic phase was concentrated under reduced pressure and the residue was re-crystallized from isopropanol/water (3:2) mixture (175 mL) to afford 2-[(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (27.2 gm, 86% yield) as an off-white solid.

LCMS (method 1): Rt= 3.12 min, m/z 353.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.08 (s, 3 H), 1.10 (s, 3 H), 1.52 (br d, J=8.93 Hz, 2 H), 2.04 - 2.14 (m, 2 H), 2.62 (s, 3 H) 4.12 (d, J=8.80 Hz, 1 H), 7.22 (s, 2 H), 7.84 (d, J=8.56 Hz, 1 H), 11.24 (s, 1 H).

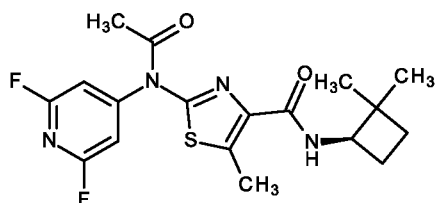
- 25 Chiral method: SFC:Waters Acquity UPC²/QDa, PDA Detector Waters Acquity UPC²

Method of Chiral Analysis: Column: Daicel SFC CHIRALPAK® IG, 3mm, 0.46cm x 10cm, 40°C, Mobile phase: A: CO₂ B: MeOH isocratic: 10% B in 4.8 min, ABPR: 1800 psi, Flow rate: 2.0 ml/min, Detection: 293 nm, Sample preparation: 1 mg/mL in acetonitrile, Injection: 1 mL

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 2.63	Retention time (min) ~ 3.57
Enantiomeric ratio 91 (R) : 9 (S)	

Example P10: *Synthesis of 2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide* (compound P.02, table P)



(compound P.02, table P)

5 A mixture of 2-[(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (1.10 mmol, 0.388 g) and an aqueous solution of sodium hydroxide (50% w/w, 1.4 equiv., 1.54 mmol, 0.124 g) in 2-methyltetrahydrofuran (0.55 M, 2.0 mL) was stirred at rt for 2 h. The reaction mixture was cooled to 0-5°C and acetyl chloride (1.5 equiv., 1.65 mmol, 0.129 g) was added over a period of 1 h. The reaction mixture was then slowly warmed to 24°C and stirred at the same temperature for 30 min. The two phases were separated and the aqueous layer was extracted with 2-Methyltetrahydrofuran (2x 5 mL). The combined organic phase was partially concentrated under reduced pressure to remove 85-90% of the solvent, and the product was precipitated by the addition of *n*-heptane (5.0 mL). The solid was filtered and dried under vacuum to afford 2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (0.373 gm, 86% yield) as a colorless solid.

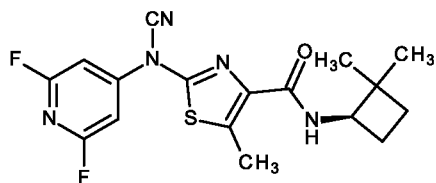
15 LCMS (method 1): Rt= 3.50 min, m/z 395.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.00 (s, 3 H), 1.04 (s, *J*=6.11 Hz, 3 H), 1.37 - 1.52 (m, 2 H), 1.73 (s, 1 H), 2.03 (br d, *J*=8.31 Hz, 1 H), 2.14 (s, 3 H), 2.63 (s, 3 H), 3.98 (d, *J*=8.80 Hz, 1 H), 7.20 (br d, *J*=9.05 Hz, 1 H), 7.58 (s, 2 H)

20 Chiral method: HPLC: Waters UPLC; DAD Wavelength range: 210 to 400 nm; Optimized Chromatographic Parameter: Column: CHIRALPAK® IG, Column length: 250mm, Internal diameter of column: 4.6mm, Particle Size: 5μ, Column oven temperature: 40°C, Detection: 257 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: hexane, Solvent B: EtOAc - ethanol (1:1), gradient: 0 to 10 min 80% A and 20% B

Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 4.94	Retention time (min) ~ 5.89
Enantiomeric ratio 91 (R) : 9 (S)	

25 **Example P11:** *Preparation of 2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide* (compound P.03, table P)

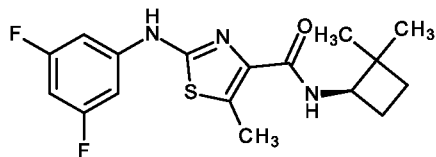


(compound P.03, table P)

A mixture of 2-[(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (1.10 mmol, 0.388 g) and finely powdered sodium hydroxide (1.4 equiv. 1.54 mmol, 0.062 g) in acetonitrile (0.55 M, 2 mL) was stirred at 24°C for 2 h. The reaction mixture was cooled to 0-5°C and a solution of cyanogen bromide in acetonitrile (50% w/w, 1.5 equiv., 1.65 mmol, 0.36 g) was added over a period of 1 h. The reaction was quenched by the addition of water (4 mL) at 0-5°C, and the precipitated solid was filtered and dried under vacuo to afford 2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (0.379 g, 91% yield) as a colorless solid.

LCMS (method 1): Rt= 3.79 min, m/z 378.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.99 (s, 3 H), 1.09 (s, 3 H), 1.38 - 1.58 (m, 2 H), 1.98 - 2.17 (m, 2 H), 2.75 (s, 3 H), 4.10 (d, *J*=8.63 Hz, 1 H), 7.27 (s, 2 H), 8.01 (br d, *J*=8.10 Hz, 1 H).

Example P12: Preparation of 2-(3,5-difluoroanilino)-N-[(1R)-(2,2-dimethylcyclobutyl)]-5-methyl-thiazole-4-carboxamide (compound P.06, table P)



(compound P.06, table P)

To a heated (60°C) suspension of 2-(3,5-difluoroanilino)-5-methyl-thiazole-4-carboxylic acid (3.48 mmol, 0.94 g) and dimethylformamide (0.04 equiv., 0.14 mmol 0.010 g) in 2-methyltetrahydrofuran (0.23 M, 15 mL) under nitrogen atmosphere, was added thionyl chloride (1.50 equiv., 5.22 mmol, 0.62 g) over a period of 20 min, and the reaction mixture was stirred at the same temperature for an additional 60 min. The reaction mixture was cooled to rt, and then transferred to a cooled mixture (0-5°C) of (1R)-2,2-dimethylcyclobutanamine hydrochloride (1.20 equiv. 4.16 mmol, 0.563 g, 82% ee) and an aqueous solution of sodium hydroxide (4.5 M, 1.5 equiv., 6.93 mmol, 1.54 g) in 2-methyltetrahydrofuran (0.84 M, 5 mL) over 1 h, the pH of the reaction mixture was maintained between 7.5-8.5 by the occasional addition of an aqueous solution of sodium hydroxide (4.5 M). The reaction mixture was diluted with 2-methyltetrahydrofuran and aqueous layer was separated. The organic phase was concentrated under reduced pressure and the residue was re-crystallized from ethanol/water (8:2) mixture (10 mL) to afford 2-(3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (0.75 gm, 62% yield) as an off-white solid.

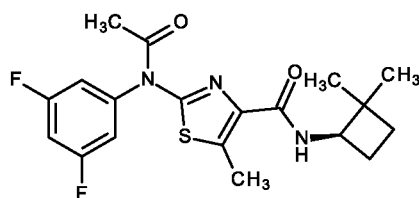
LCMS (method 3): Rt= 2.35 min, m/z 352.8 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.60 (s, 1 H), 7.70 (br d, *J*=8.80 Hz, 1 H), 7.32 (br d, *J*=8.68 Hz, 2 H), 6.75 (br t, *J*=9.17 Hz, 1 H), 4.12 (q, *J*=8.80 Hz, 1 H), 2.60 (s, 3 H), 2.07 - 2.18 (m, 1 H), 1.93 - 2.07 (m, 1 H), 1.43 - 1.61 (m, 2 H), 1.10 (s, 6 H); ¹⁹F NMR δ ppm 109.38 (2 F).

Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm; Optimized Chromatographic Parameter: Column: CHIRALPAK® IG, Column length: 250mm, Internal diameter of column: 4.6mm, Particle size: 5μ, Column oven temperature: 40°C, Detection: 298 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: hexane (95) Solvent B: IPA (5), gradient: 0.0-20 min 95% A and 5% B

5 Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 8.05	Retention time (min) ~ 9.75
Enantiomeric ratio 91 (R) : 9 (S)	

Example P13: *Synthesis of 2-(N-acetyl-3,5-difluoro-anilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (compound P.09, table P)*



(compound P.09, table P)

- 10 A mixture of 2-(3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (2.77 mmol, 0.974 g, 82% ee) and an aqueous solution of sodium hydroxide (50% w/w, 3.0 equiv., 8.32 mmol, 0.332 g) in 2-methyltetrahydrofuran (0.50 M, 5.5 mL) was stirred at rt for 2 h. The reaction mixture was cooled to 0-5°C and acetyl chloride (1.5 equiv., 4.16 mmol, 0.326 g) was added over a period of 15 min and the reaction mixture was stirred at 0°C for 1 h. The reaction mixture was then slowly warmed to 24°C and stirred at the
- 15 same temperature for 30 min. The two phases were separated, and the aqueous layer was extracted with 2-methyltetrahydrofuran (2x 5 mL). The combined organic phase was concentrated under reduced pressure. The residue was recrystallized from isopropanol:water mixture (9:1 v/v; 6 mL). The solid was filtered and dried under vacuum to afford 2-(N-acetyl-3,5-difluoro-anilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (0.785 g, 72% yield, 82% ee) as a colorless solid.
- 20 LCMS (method 3): Rt= 2.25 min, m/z 394.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 7.42 - 7.53 (m, 3 H), 7.12 (br d, J=8.93 Hz, 1 H), 3.97 (q, J=8.93 Hz, 1 H), 2.62 (s, 3 H), 2.09 (s, 3 H), 2.03 - 2.06 (m, 1 H), 1.56 - 1.67 (m, 1 H), 1.37 - 1.54 (m, 2 H), 1.00 (s, 3 H), 0.78 (s, 3 H); ¹⁹F NMR δ ppm 109.08 (2 F)

Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm, Optimized Chromatographic Parameter; Column: CHIRALPAK® IG, Column length: 250mm, Internal diameter of column: 4.6mm, Particle

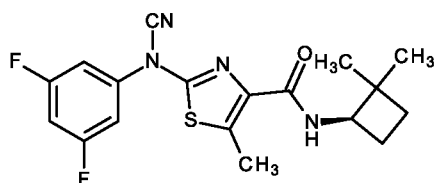
25 Size: 5μ, Column oven temperature: 40°C, Detection: 254 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: hexane (85), Solvent B: IPA+0.1%DEA (15), gradient: 0 to 18 min 85%A and 15%B

Results:

First eluting enantiomer	Second eluting enantiomer
--------------------------	---------------------------

Retention time (min) ~ 8.96	Retention time (min) ~ 10.37
Enantiomeric ratio 91 (R) : 9 (S)	

Example P14: *Preparation of 2-(N-cyano-3,5-difluoro-anilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (compound P.10, table P)*



(compound P.10, table P)

- 5 A mixture of 2-(3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (2.70 mmol, 0.950 g, 82% ee) and finely powdered sodium hydroxide (1.4 equiv. 3.78 mmol, 0.150 g) in acetonitrile (0.55 M, 5 mL) was stirred at 24°C for 1 h. The reaction mixture was cooled to 0-5°C and a solution of cyanogen bromide in acetonitrile (5 M, 1.5 equiv., 4.06 mmol, 0.89 g) was added over a period of 1 h, and the reaction mixture was stirred at 0°C for 1 h. The reaction was quenched by the addition of water (5 mL) at 0-5°C, and
- 10 the precipitated solid was filtered and dried under vacuo to afford 2-(N-cyano-3,5-difluoro-anilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide (0.768 g, 76% yield, 82% ee) as a colorless solid.

LCMS (method 3): Rt= 2.17 min, m/z 377.8 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 7.78 (br d, J=8.22 Hz, 1 H), 7.56 (br d, 2 H), 7.45 (br t, 1 H), 4.10 (q, J=8.22 Hz, 1 H), 2.67 (s, 3 H), 1.97 - 2.16 (m, 2 H), 1.39 - 1.61 (m, 2 H), 1.10 (s, 3 H), 1.00 (s, 3 H); ¹⁹F NMR δ ppm 106.36 (2 F).

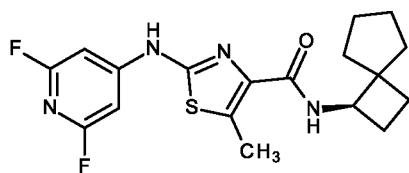
- 15 Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm; Optimized Chromatographic Parameter: Column: CHIRALPAK® IA, Column length: 250 mm, Internal diameter of column: 4.6 mm, Particle Size: 5μ, Column oven temperature: 40°C, Detection: 230 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: hexane (95), Solvent B: ethanol (5), Gradient Program:: 0 to 15 min 95%A and 5%B

Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 6.47	Retention time (min) ~ 8.04
Enantiomeric ratio 91 (R) : 9 (S)	

20

Example P15: *Preparation of 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (compound P.08, table P)*



(compound P.08, table P)

To a heated (60°C) suspension of 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-thiazole-4-carboxylic acid (8.66 mmol, 2.35 g) and dimethylformamide (0.04 equiv., 0.347 mmol, 0.025 g) in isopropyl acetate (0.35 M, 25 mL) under nitrogen atmosphere, was added thionyl chloride (1.50 equiv., 13.0 mmol, 1.55 g) over a period of 1 h, and the reaction mixture was stirred at the same temperature for an additional 60 min. The reaction mixture was cooled to rt, and then transferred to a cooled mixture (0-5°C) of (3R)-spiro[3.4]octan-3-amine (1.20 equiv. 10.4 mmol, 1.30 g, 78% ee) and an aqueous solution of sodium hydroxide (4.5 M, 1.5 equiv., 13.0 mmol, 2.89 g) in isopropyl acetate (0.84 M, 125 mL) over 1 h, while maintaining the pH of the reaction mixture was maintained between 7.5-8.5 by the occasional addition of an aqueous solution of sodium hydroxide (4.5 M). The reaction mixture was diluted with isopropyl acetate (25 mL) and aqueous layer was separated. The organic phase was concentrated under reduced pressure and the residue was triturated with methylcyclohexane (25 mL) to afford 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (2.58 g, 78.8% yield, 78% ee) as an off-white solid.

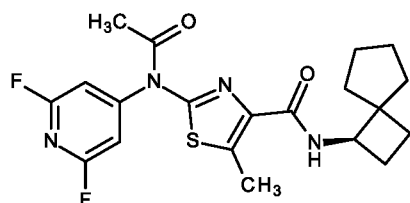
LCMS (method 3): Rt= 2.23 min, m/z 379.8[M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 11.04 - 11.31 (bs, 1 H), 7.91 (d, J=8.85 Hz, 1 H), 7.21 (s, 2 H), 4.30 (q, J=8.85 Hz, 1 H), 2.61 (s, 3 H), 1.96 - 2.13 (m, 2 H), 1.84 - 1.93 (m, 1 H), 1.44 - 1.73 (m, 9 H); ¹⁹F NMR δ ppm 70.31 (2 F)

Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm, Optimized Chromatographic Parameter: Column: CHIRALPAK® IG, Column length: 250mm, Internal diameter of column: 4.6mm, Particle Size: 5μ, Column oven temperature: 40°C, Detection: 298 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: hexane (90), Solvent B: IPA (10), Gradient Program:: 0 to 16 min 90%A and 10%B

Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 5.78	Retention time (min) ~ 7.97
Enantiomeric ratio 89 (R) : 11 (S)	

Example P15: Synthesis of 2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (compound P.13, table P)



(compound P.13, table P)

To a mixture of 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (1.30 mmol, 0.480 g, 78% ee) and triethylamine (1.9 equiv., 2.50 mmol, 0.258 g) in 2-methyltetrahydrofuran (0.48 M, 2.8 mL) at rt was added acetic anhydride (1.46 equiv., 1.90 mmol, 0.196 g) in one portion, and the reaction mixture was heated to 90°C and stirred at 90°C for 3 h. The reaction mixture was cooled to 24°C and stirred at the same temperature for 30 min. Water (5 mL) was added and the two phases were separated. The

aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic phase was concentrated under reduced pressure, and the residue was purified by flash chromatography (30% EtOAc in cyclohexane), concentrated and dried under vacuum to afford 2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (0.424 g, 80% yield, 80% ee) as a colorless solid.

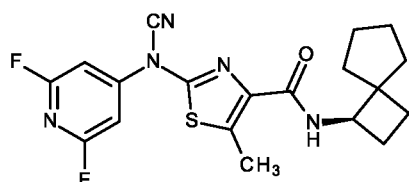
- 5 LCMS (method 3): Rt= 2.21 min, m/z 421.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 7.59 (s, 2 H), 7.27 (d, J=9.13 Hz, 1 H), 4.13 (q, J=9.13 Hz, 1 H), 2.63 (s, 3 H), 2.14 (s, 3 H), 1.97 - 2.08 (m, 1 H), 1.66 - 1.72 (m, 1 H), 1.57 - 1.61 (m, 1 H), 1.27 - 1.56 (m, 9 H); ¹⁹F NMR δ ppm 67.79 (2 F).

Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm, Optimized Chromatographic Parameter: Column: CHIRALPAK® IG, Column length: 250mm, Internal diameter of column: 4.6mm, Particle
10 Size: 5μ, Column oven temperature: 40°C, Detection: 256 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: HEXANE (90), Solvent B: IPA (10), Gradient Program:: 0 to 30 min 90%A and 10%B

Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 15.89	Retention time (min) ~ 22.79
Enantiomeric ratio 90 (R) : 10 (S)	

Example P16: *Preparation of 2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (compound P.14, table P)*
15



(compound P.14, table P)

- A mixture of 2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (1.30 mmol, 0.480 g) and finely powdered sodium hydroxide (1.4 equiv. 1.8 mmol, 0.071 gm) in acetonitrile (0.55 M, 2.5 mL) was stirred at 24°C for 2 h. The reaction mixture was cooled to 0-5°C and a solution of
20 cyanogen bromide in acetonitrile (5 M, 1.5 equiv., 1.90 mmol, 0.42 g) was added over a period of 20 min, and the reaction mixture was stirred for an additional hour at 0-5°C. The reaction was quenched by the addition of water (5 mL) at 0-5°C, and the precipitated solid was collected by filtration. The residue was recrystallised from MeCN:Water (4:3 v/v; 1.5 mL), filtered and dried under vacuo to afford 2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (0.363 g, 71% yield, 80% ee) as a colorless
25 solid.

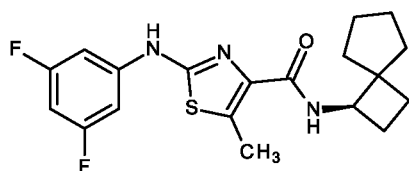
LCMS (method 3): Rt= 2.33 min, m/z 404.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 8.13 (d, J=8.51 Hz, 1 H), 7.30 (s, 2 H), 4.30 (q, J=8.51 Hz, 1 H), 2.75 (s, 3 H), 1.97 - 2.13 (m, 2 H), 1.75 (dt, J=12.19, 6.28 Hz, 2 H), 1.40 - 1.64 (m, 8 H); ¹⁹F NMR δ ppm 66.84 (2 F)

Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm, Optimized Chromatographic Parameter, Column: CHIRALPAK® IA, Column length: 250 mm, Internal diameter of column: 4.6 mm, Particle Size: 5μ, Column oven temperature: 40°C, Detection: 230 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: HEXANE (95), Solvent B: EtOH (5), Gradient Program:: 0 to 15 min 95%A and 5%B

5 Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 8.46	Retention time (min) ~ 9.94
Enantiomeric ratio 90 (R) : 10 (S)	

Example P17: *Preparation of 2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide*



(compound P.07, table P)

- 10 To a heated (60°C) suspension of 2-(3,5-difluoroanilino)-5-methyl-thiazole-4-carboxylic acid (17.4 mmol, 4.71 g) and dimethylformamide (0.04 equiv., 0.70 mmol 0.050 g) in 2-methyltetrahydrofuran (0.17 M, 100 mL) under nitrogen atmosphere, was added thionyl chloride (1.50 equiv., 26.2 mmol, 3.11 g) over a period of 20 min, and the reaction mixture was stirred at the same temperature for an additional 60 min. The reaction mixture was cooled to rt, and then transferred to a cooled mixture (0-5°C) of (3R)-spiro[3.4]octan-3-amine (1.20 equiv. 20.9
- 15 mmol, 2.62 g, 78% ee) and an aqueous solution of sodium hydroxide (4.5 M, 1.5 equiv., 26.2 mmol, 5.82 g) in 2-methyltetrahydrofuran (0.83 M, 25.2 mL) over 1 h, the pH of the reaction mixture was maintained between 7.5-8.5 by the occasional addition of an aqueous solution of sodium hydroxide (4.5 M). The reaction mixture was diluted with 2-methyltetrahydrofuran and aqueous layer was separated. The organic phase was concentrated under reduced pressure and the residue was purified by flash chromatography (1:1 v/v
- 20 EtOAc:cyclohexane) mixture to afford 2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (4.65 g, 70% yield, 80% ee) as a white solid.

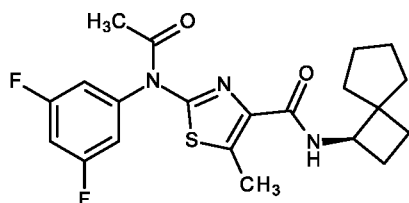
LCMS (method 2): Rt= 1.34 min, m/z 378.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 10.59 (s, 1 H), 7.77 (d, J=9.01 Hz, 1 H), 7.27 - 7.37 (m, 2 H), 6.74 (tt, J=9.27, 2.17 Hz, 1 H), 4.29 (q, J=9.01 Hz, 1 H), 2.59 (s, 3 H), 2.06 - 2.16 (m, 1 H), 1.81 - 1.99 (m, 2 H), 1.43 - 1.72 (m, 9 H); ¹⁹F NMR δ ppm 109.38 (2 F)

- 25 Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm, Optimized Chromatographic Parameter, Column: CHIRALPAK® IG, Column length: 250mm, Internal diameter of column: 4.6mm, Particle Size: 5μ, Column oven temperature: 40°C, Detection: 298 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: HEXANE (95), Solvent B: IPA (5), Gradient Program:: 0 to 20 min 95%A and 5%B

Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 9.65	Retention time (min) ~ 12.46
Enantiomeric ratio 90 (R) : 10 (S)	

Example P18: *Synthesis of 2-(N-acetyl-3,5-difluoro-anilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (compound P.11, table P)*



(compound P.11, table P)

- 5 To a mixture of 2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (2.54 mmol, 0.960 g, 80% ee) and triethylamine (2.0 equiv., 5.09 mmol, 0.514 g) in 2-methyltetrahydrofuran (0.48 M, 5.5 mL) at rt was added acetic anhydride (1.5 equiv., 3.82 mmol, 0.389 g) in one portion, and the reaction mixture was heated to 90°C and stirred at 90°C for 8 h. The reaction mixture was cooled to 24°C and stirred at the same temperature for 30 min. Water (5 mL) was added and the two phases were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic phase was concentrated under reduced pressure, and the residue was purified by flash chromatography (30% EtOAc in cyclohexane), concentrated and dried under vacuum to afford 2-(N-acetyl-3,5-difluoro-anilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (0.826 g, 77% yield, 82% ee) as a colorless solid.

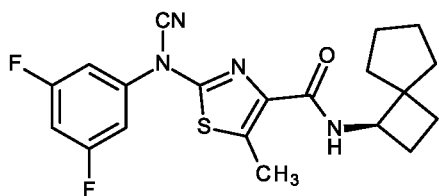
15 LCMS (method 3): Rt= 2.35 min, m/z 420.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 7.44 - 7.55 (m, 3 H), 7.18 (br d, J=9.05 Hz, 1 H), 4.10 (q, J=9.05 Hz, 1 H), 2.62 (s, 3 H), 2.08 (s, 3 H), 2.03 - 2.07 (m, 1 H), 1.40 - 1.61 (m, 7 H), 1.26 - 1.38 (m, 4 H); ¹⁹F NMR δ ppm 109.00 (2 F)

20 Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm, Optimized Chromatographic Parameter, Column: CHIRALPAK® IG, Column length: 250mm, Internal diameter of column: 4.6mm, Particle Size: 5μ, Column oven temperature: 40°C, Detection: 254 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: HEXANE (80), Solvent B: IPA+0.1%DEA (20), Gradient Program:: 0 to 16 min 80%A and 20%B

Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 7.97	Retention time (min) ~ 9.30
Enantiomeric ratio 91 (R) : 9 (S)	

Example P19: *Preparation of 2-(N-cyano-3,5-difluoro-anilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (compound P.12, table P)*



(compound P.12, table P)

A mixture of 2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (2.55 mmol, 0.964 g, 80% ee) and finely powdered sodium hydroxide (1.4 equiv. 3.58 mmol, 0.143 g) in acetonitrile (0.50 M, 5 mL) was stirred at 24°C for 1 h. The reaction mixture was cooled to 0-5°C and a solution of cyanogen bromide in acetonitrile (5 M, 1.5 equiv., 3.83 mmol, 0.84 g) was added over a period of 1 h, and the reaction mixture was stirred at 0°C for 1 h. The reaction was quenched by the addition of water (20 mL) at 0-5°C, and the precipitated solid was collected by filtration and dried under vacuo to afford 2-(N-cyano-3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide (0.817 g, 80% yield, 80% ee) as a colorless solid.

LCMS (method 3): Rt= 2.42 min, m/z 403.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆), δ ppm 7.85 (d, J=8.50 Hz, 1 H), 7.55 (d, J=7.34 Hz, 2 H), 7.45 (tt, J=9.21, 2.24 Hz, 1 H), 4.27 (q, J=8.50 Hz, 1 H), 2.67 (s, 2 H), 1.92 - 2.13 (m, 2 H), 1.67 - 1.75 (m, 2 H), 1.42 - 1.65 (m, 8 H); ¹⁹F NMR δ ppm 106.39 (2 F)

Chiral method: HPLC: Waters UPLC, DAD Wavelength range: 210 to 400 nm, Optimized Chromatographic Parameter: Column: CHIRALPAK® IA, Column length: 250 mm, Internal diameter of column: 4.6 mm, Particle Size: 5μ, Column oven temperature: 40°C, Detection: 230 nm, Flow: 1.0 mL/min, Gradient conditions: Solvent A: hexane, Solvent B: EtOH, Gradient Program: 0 to 15 min 95%A and 5%B

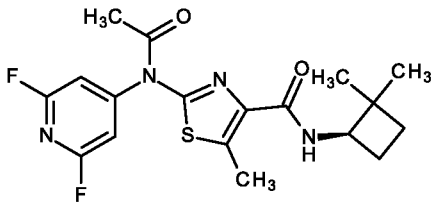
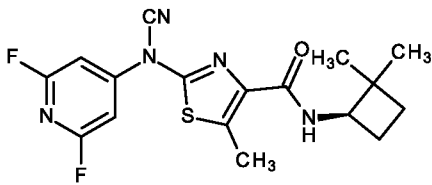
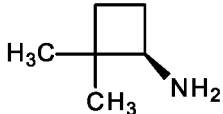
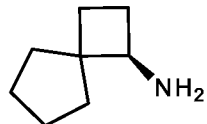
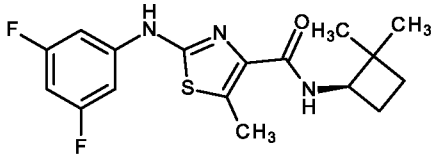
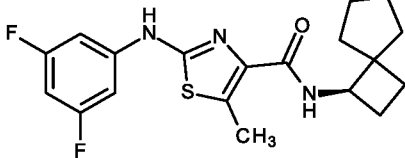
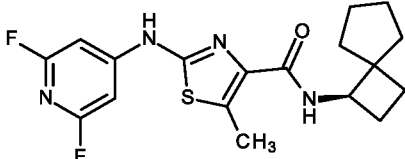
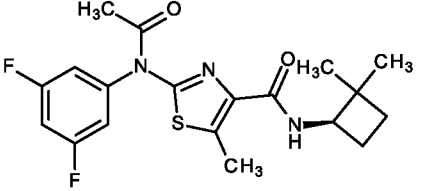
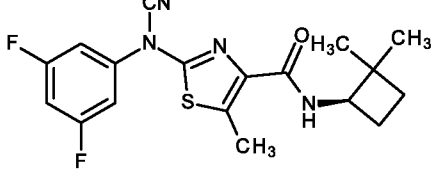
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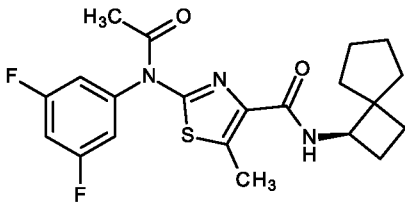
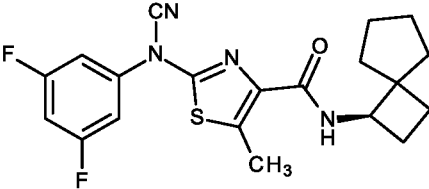
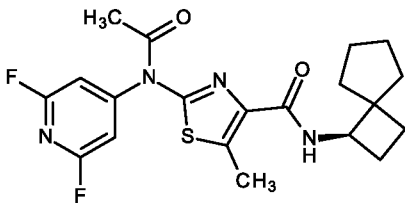
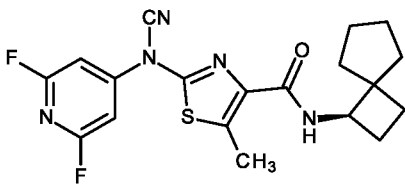
First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 5.91	Retention time (min) ~ 6.94
Enantiomeric ratio 90 (R) : 10 (S)	

Examples of synthesized compounds are shown in Table P.

Table P: Synthesized compounds and Spectral and Physical Chemical Data

Entry	IUPAC name	Structures	LCMS/GCMS		
			Rt (min)	[M+H] ⁺ (measured)	Method
P.01	2-[(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		3.12	353.3	1

P.02	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		3.50	395.4	1
P.03	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		3.79	378.3	1
P.04	(1R)-2,2-dimethylcyclobutanamine				
P.05	(1R)-2,2-dimethylcyclobutanamine		3.14	126	4
P.06	2-(3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		2.35	352.8	3
P.07	2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		1.34	378.2	2
P.08	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		2.23	379.8	3
P.09	2-(N-acetyl-3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		2.25	394.2	3
P.10	2-(N-cyano-3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		2.17	377.8	3

P.11	2-(N-acetyl-3,5-difluoro-anilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		2.35	420.3	3
P.12	2-(N-cyano-3,5-difluoro-anilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		2.42	403.2	3
P.13	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		2.21	421.9	3
P.14	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		2.33	404.3	3

BIOLOGICAL EXAMPLES

The Examples which follow serve to illustrate the invention. Certain compounds of the invention can be distinguished from known compounds by virtue of greater efficacy at low application rates, which can be verified by the person skilled in the art using the experimental procedures outlined in the Examples, using lower application rates, if necessary, e.g., 50 ppm, 12.5 ppm, 6 ppm, 3 ppm, 1.5 ppm, 0.8 ppm or 0.2 ppm.

WHOLE PLANT TESTS FOLIAR APPLICATION

Example B1: Whole plant tests with room application (general description)

Active ingredient is formulated (eg. IF) and just before spraying the formulations are mixed with water and ultrasonically agitated in order to achieve homogeneous distribution. Spray solutions are made up in water. Foliar application is at 400 L/ha in an application device providing coverage of both upper and lower leaf surfaces (placed on turntable, air assisted spraying from 2 nozzles). Preventative tests are performed as 1 or 2 day preventative applications, i.e. plants are treated with the compounds 1 or 2 days prior to artificial inoculation with fungal spores, whereas for curative tests the inoculation is carried out prior to application. A single evaluation of disease level is made 2 to 19 days after inoculation, depending on the pathosystem. Disease control relative to the untreated check plants is then calculated.

Example B2: *Alternaria solani* / tomato / preventative (Alternaria on tomato)

4-week old tomato plants cv. Roter Gnom are sprayed in a spray chamber with the formulated test compound diluted in water. The test plants are inoculated by spraying them with a spore suspension two days after application. The inoculated test plants are incubated at 22°C / 18°C (day/night) and 95% rh in a greenhouse and the percentage leaf area covered by disease is assessed when an appropriate level of disease appears on untreated check plants (5 to 7 days after application). Rates: 200-2 ppm.

Example B3: *Blumeria graminis* f. sp. *tritici* (*Erysiphe graminis* f. sp. *tritici*) / wheat / preventative (Powdery mildew on wheat)

1-week old wheat plants cv. Arina are sprayed in a spray chamber with the formulated test compound diluted in water. The test plants are inoculated by spreading powdery mildew spores over them in an inoculation chamber two days after application. The inoculated test plants are incubated at 20°C / 18°C (day/night) and 60% rh in a greenhouse and the percentage leaf area covered by disease is assessed when an appropriate level of disease appears on untreated check plants (7 to 9 days after application). Rates: 60-0.6 ppm.

Example B4: *Erysiphe necator* (*Uncinula necator*) / grape / preventative (Powdery mildew on grape)

5-week old grape seedlings cv. Gutedel are sprayed in a spray chamber with the formulated test compound diluted in water. The test plants are inoculated by shaking plants infected with grape powdery mildew above them 1 day after application. The inoculated test plants are incubated at 24°C / 22°C (day/night) and 70% rh under a light regime of 14/10 h (light/dark) and the percentage leaf area covered by disease is assessed when an appropriate level of disease appears on untreated check plants (7 to 9 days after application). Rates: 60-0.6 ppm.

Example B5: *Glomerella lagenarium* (*Colletotrichum lagenarium*) / cucumber / preventative (Anthracnose)

1-week old cucumber plants cv. Wisconsin are sprayed in a spray chamber with the formulated test compound diluted in water. The test plants are inoculated by spraying them with a spore suspension one day after application. After an incubation period of 30 h in darkness at 23°C and 100% rh, the inoculated test plants are kept at 23°C / 21°C (day/night) and 70% rh in a greenhouse. The percentage leaf area covered by disease is assessed when an appropriate level of disease appears on untreated check plants (6 to 8 days after application). Rates: 60-0.6 ppm.

Example B6: *Glomerella lagenarium* (*Colletotrichum lagenarium*) / cucumber / curative (Anthracnose)

1-week old cucumber plants cv. Wisconsin are inoculated by spraying them with a spore suspension two days before application. After an incubation period of 30 h in darkness at 23°C and 100% rh, the inoculated test plants are kept at 23°C / 21°C (day/night) and 70% rh in a greenhouse. The inoculated test plants are sprayed in a spray chamber with the formulated test compound diluted in water followed by an additional incubation at 23°C / 21°C (day/night) and 70% rh in a greenhouse. The percentage leaf area covered by disease is assessed when an appropriate level of disease appears on untreated check plants (4 to 6 days after application). Rates: 60-0.6 ppm.

Example B7: *Mycosphaerella graminicola* (*Septoria tritici*) / wheat / preventative (Septoria tritici leaf spot on wheat)

2-week old wheat plants cv. Riband are sprayed in a spray chamber with the formulated test compound diluted in water. The test plants are inoculated by spraying a spore suspension on them one day after application. After an incubation period of 1 day at 22°C / 21°C (day/night) and 95% rh, the inoculated test plants are kept at 22°C / 21°C (day/night) and 70% rh in a greenhouse. Efficacy is assessed directly when an appropriate level of disease appears on untreated check plants (16 to 19 days after application). Rates: 200-2 ppm.

Example B8: *Puccinia recondita* f. sp. *tritici* / wheat / preventative (Brown rust on wheat)

2-week old wheat plants cv. Arina are sprayed in a spray chamber with the formulated test compound diluted in water. The test plants are inoculated by spraying them with a spore suspension one day after application. After an incubation period of 1 day at 20°C and 95% rh, the inoculated test plants are kept at 20°C / 18°C (day/night) and 60% rh in a greenhouse. The percentage leaf area covered by disease is assessed when an appropriate level of disease appears on untreated check plants (12 to 14 days after application). Rates: 60-0.6 ppm.

Example B9: *Puccinia recondita* f. sp. *tritici* / wheat / curative (Brown rust on wheat)

2-week old wheat plants cv. Arina are inoculated by spraying them with a spore suspension two days before application. After an incubation period of 1 day at 20°C and 95% rh followed by 1 day at 20°C and 60% rh in a greenhouse, the inoculated test plants are sprayed in a spray chamber with the formulated test compound diluted in water. After additional incubation at 20°C / 18°C (day/night) and 60% rh in a greenhouse, the percentage leaf area covered by disease is assessed when an appropriate level of disease appears on untreated check plants (9 to 12 days after application). Rates: 200-2 ppm.

LEAF DISK ASSAYS METHODS

Example B10: General Description Leaf disk or leaf segment tests in well plates (general description)

Leaf disks or leaf segments of various plant species are cut from plants grown in the greenhouse. The cut leaf disks or segments are placed in multi well plates (24-well format) onto water agar. The leaf disks are sprayed with a test solution before (preventative) or after (curative) inoculation. Compounds to be tested are prepared as DMSO solutions (max. 10 mg/ml) which are diluted to the appropriate concentration with 0.025% Tween20 just before spraying. The inoculated leaf disks or segments are incubated under defined conditions (temperature, relative humidity, light, etc.) according to the respective test system. A single evaluation of disease level is carried out 4 to 8 days after inoculation, depending on the pathosystem. Percent disease control relative to the untreated check leaf disks or segments is then calculated.

Example B11: *Erysiphe graminis* f. sp. *tritici* (Wheat powdery mildew)

Wheat leaf segments are placed on agar in multiwell plates (24-well format) and sprayed with test solutions. After drying, the leaf disks are inoculated with spores of the fungus. After appropriate incubation the activity of a compound is assessed 7 dpi (days post inoculation) as preventive fungicidal activity. Dose range: 200-0.82 ppm.

Example B12: *Pyrenophora teres* (Net blotch)

Barley leaf segments are placed on agar in multiwell plates (24-well format) and sprayed with test solutions. After drying, the leaf disks are inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound is assessed 4 dpi (days post inoculation) as preventive fungicidal activity. Dose range: 200-0.82 ppm.

5 **Example B13: *Puccinia recondita* (Brown rust) preventive**

Wheat leaf segments are placed on agar in multiwell plates (24-well format) and sprayed with test solutions. After drying, the leaf disks are inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound is assessed 8 dpi (days post inoculation) as preventive fungicidal activity. Dose range: 200-0.82 ppm.

10 **Example B14: *Puccinia recondita* (Brown rust) curative**

Wheat leaf segments are placed on agar in multiwell plates (24-well format). The leaf disks are then inoculated with a spore suspension of the fungus. One day after inoculation the test solution is applied. After appropriate incubation the activity of a compound is assessed 8 dpi (days post inoculation) as curative fungicidal activity. Dose range: 200-0.82 ppm.

15 **Example B15: *Septoria nodorum* (Glume blotch)**

Wheat leaf segments are placed on agar in multiwell plates (24-well format) and sprayed with test solutions. After drying, the leaf disks are inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound is assessed 4 dpi (days post inoculation) as preventive fungicidal activity. Dose range: 200-0.82 ppm.

20 **Example B16: *Alternaria solani* (early blight of potato/tomato)**

Tomato leaf disks are placed on water agar in multiwell plates (24-well format) and sprayed with test solutions. After drying, the leaf disks are inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound is assessed 4 dpi (days post inoculation) as preventive fungicidal activity. Dose range: 200-0.82 ppm.

25 **LIQUID CULTURE ASSAYS**

Example B17: General description Liquid culture tests in well plates

Mycelia fragments or conidia suspensions of a fungus, prepared either freshly from liquid cultures of the fungus or from cryogenic storage, are directly mixed into nutrient broth. DMSO solutions of the test compound (max. 10 mg/ml) are diluted with 0.025% Tween20 by factor 50 and 10 µl of this solution is pipetted into a microtiter plate (96-well format). The nutrient broth containing the fungal spores/mycelia fragments is then added to give an end concentration of the tested compound. The test plates are incubated in the dark at 24°C and 96% rh. The inhibition of fungal growth is determined photometrically after 2 to 6 days, depending on the pathosystem, and percent antifungal activity relative to the untreated check is calculated.

Example B18: *Botrytis cinerea* (Gray mould)

Conidia of the fungus from cryogenic storage were directly mixed into nutrient broth (PDB potato dextrose broth). A DMSO solution of the test compounds was placed into a microtiter plate (96-well format) and the nutrient broth containing the fungal spores was added to it. The test plates were incubated at 24°C and the inhibition of growth was determined visually and/or photometrically at 620nm after 72 hrs. Dose range: 6.67-0.027 ppm.

Example B19: *Septoria tritici* (leaf blotch)

Conidia of the fungus from cryogenic storage were directly mixed into nutrient broth (PDB potato dextrose broth). A DMSO solution of the test compounds was placed into a microtiter plate (96-well format) and the nutrient broth containing the fungal spores was added to it. The test plates were incubated at 24°C and the inhibition of growth was determined visually and/or photometrically at 620nm after 72 hrs. Dose range: 6.67-0.027 ppm.

Example B20: *Pyricularia oryzae* (rice blast)

Conidia of the fungus from cryogenic storage were directly mixed into nutrient broth (PDB potato dextrose broth). A DMSO solution of the test compounds was placed into a microtiter plate (96-well format) and the nutrient broth containing the fungal spores was added to it. The test plates were incubated at 24°C and the inhibition of growth was determined visually and/or photometrically at 620nm after 72 hrs. Dose range: 6.67-0.027 ppm.

Example B21: *Glomerella lagenarium* syn. *Colletotrichum lagenarium* (anthracnose of cucurbits)

Conidia of the fungus from cryogenic storage were directly mixed into nutrient broth (PDB potato dextrose broth). A DMSO solution of the test compounds was placed into a microtiter plate (96-well format) and the nutrient broth containing the fungal spores was added to it. The test plates were incubated at 24°C and the inhibition of growth was determined visually and/or photometrically at 620nm after 72 hrs. Dose range: 6.67-0.027 ppm.

Example B21: *Mycosphaerella arachidis* syn. *Cercospora arachidicola* (Brown leaf spot of peanut)

Conidia of the fungus from cryogenic storage were directly mixed into nutrient broth (PDB potato dextrose broth). A DMSO solution of the test compounds was placed into a microtiter plate (96-well format) and the nutrient broth containing the fungal spores was added to it. The test plates were incubated at 24°C and the inhibition of growth was determined visually and/or photometrically at 620nm after approx. 5-6 days. Dose range: 6.67-0.027 ppm.

Example B22: *Monographella nivalis* syn. *Microdochium nivale*, *Fusarium nivale* (snow mould, foot rot of cereals)

Conidia of the fungus from cryogenic storage were directly mixed into nutrient broth (PDB potato dextrose broth). A DMSO solution of the test compounds was placed into a microtiter plate (96-well format) and the nutrient broth containing the fungal spores was added to it. The test plates were incubated at 24°C and the inhibition of growth was determined visually and/or photometrically at 620nm after 72 hrs. Dose range: 6.67-0.027 ppm.

Example B23: *Sclerotinia sclerotiorum* (Cottony rot, white mold, etc.)

Mycelial fragments of the fungus prepared from a fresh liquid culture were directly mixed into nutrient broth (PDB potato dextrose broth). A DMSO solution of the test compounds was placed into a microtiter plate (96-well format) and the nutrient broth containing the fungal spores was added to it. The test plates were incubated at 24°C and the inhibition of growth was determined visually and/or photometrically at 620nm after 72 hrs. Dose range: 6.67-0.027 ppm.

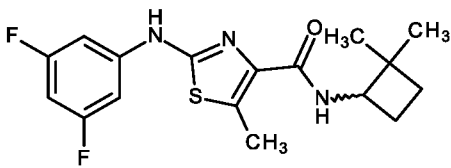
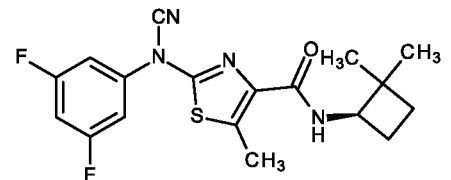
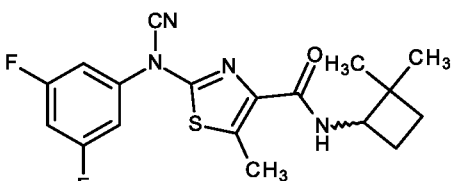
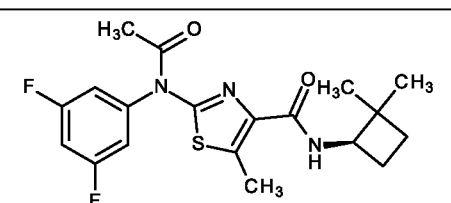
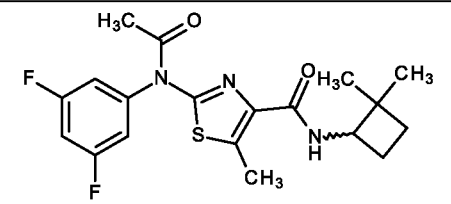
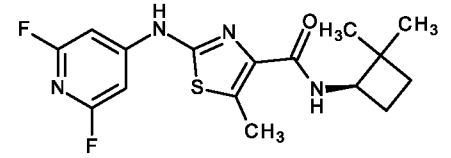
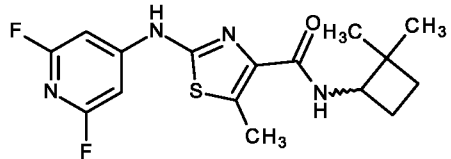
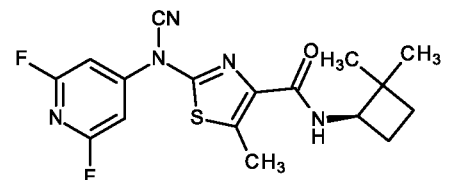
BIOLOGICAL RESULTS

Examples of tested compounds are shown in Table B.

Table B: Compounds of formula (III), (VI), and (VII) according to the present invention shown as single enantiomer compounds or enantiopure/enantiomerically enriched compounds according to the invention and the corresponding racemic compounds

Entry	IUPAC-name	Structure	Enantiomer
B-1	2-(3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R-Enantiomer ee > 99%
B-2	2-(3,5-difluoroanilino)-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide		racemic
B-3	2-(N-cyano-3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R/S 90:10
B-4	2-(N-cyano-3,5-difluoroanilino)-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide		racemic
B-5	2-(N-acetyl-3,5-difluoroanilino)-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R/S 91:9

B-6	2-(N-acetyl-3,5-difluoro-anilino)-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide		racemic
B-7	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3S)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R/S 89:11
B-8	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide		racemic
B-9	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R/S 90:10
B-10	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide		racemic
B-11	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(3R)-spiro[3.4]octan-3-yl]thiazole-4-carboxamide		R/S 90:10
B-12	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-spiro[3.4]octan-3-yl-thiazole-4-carboxamide		racemic
B-13	2-(3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer ee = 98%

B-14	2-(3,5-difluoroanilino)-N-2,2-dimethylcyclobutyl-5-methyl-thiazole-4-carboxamide		racemic
B-15	2-(N-cyano-3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer ee = 98%
B-16	2-(N-cyano-3,5-difluoroanilino)-N-2,2-dimethylcyclobutyl-5-methyl-thiazole-4-carboxamide		racemic
B-17	2-(N-acetyl-3,5-difluoroanilino)-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R-Enantiomer ee = 98%
B-18	2-(N-acetyl-3,5-difluoroanilino)-N-2,2-dimethylcyclobutyl-5-methyl-thiazole-4-carboxamide		racemic
B-19	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-[(1R)-2,2-dimethylcyclobutyl]thiazole-4-carboxamide		R/S 90:10
B-20	2-[(2,6-difluoro-4-pyridyl)amino]-5-methyl-N-2,2-dimethylcyclobutylthiazole-4-carboxamide		racemic
B-21	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R/S 90:10

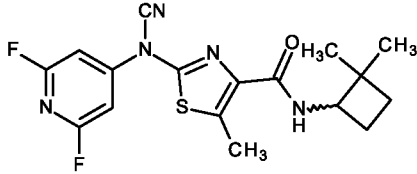
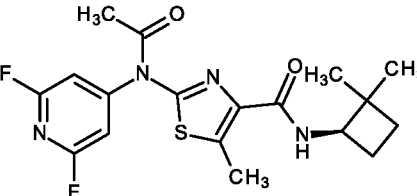
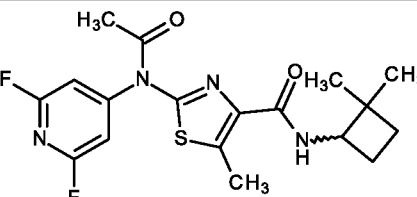
B-22	2-[cyano-(2,6-difluoro-4-pyridyl)amino]-N-2,2-dimethylcyclobutyl-5-methyl-thiazole-4-carboxamide		racemic
B-23	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-[(1R)-2,2-dimethylcyclobutyl]-5-methyl-thiazole-4-carboxamide		R/S 90:10
B-24	2-[acetyl-(2,6-difluoro-4-pyridyl)amino]-N-2,2-dimethylcyclobutyl-5-methyl-thiazole-4-carboxamide		racemic

Table C1 to Table C12 show results of the single enantiomer compounds or enantiopure/enantiomerically enriched compounds according to the invention and results of the corresponding racemic compounds, which are state of the art and can be prepared from the methods as described in WO2010/012793, WO2017/207362, WO2019/105933, WO2020/109511, WO2020/109509, WO2021/244952.

The single enantiomer compounds or enantiopure/enantiomerically enriched compounds according to the invention can be prepared according to the present invention or may be obtained either after separation of a racemic mixture using known resolution methods or obtained by means of a stereoselective synthesis. For example, first and second eluting enantiomers may be obtained by chromatographic separation using a chiral stationary phase (such as amylose- or cellulose-based CHIRALPAK® columns).

As used herein the term “Rate mg ai/L” refer to application rate of mg. a.i. (active ingredient) per L of solvent.

As used herein the term “R-enantiomer” refers to the corresponding enantiomeric compound with an enantiomeric access of at least 99%.

Efficacy was calculated as indicated in the method descriptions above.

Table C1: Biological data for compound B-2 (R-enantiomer) and compound B-1 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Tomato preventive	<i>Alternaria solani</i> (Example B1)	B-2	Racemate	6	30
		B-1	R-Enantiomer	6	56
Whole plant – Cucumber preventive	<i>Colletotrichum lagenarium</i>	B-2	Racemate	0.6	42
		B-1	R-Enantiomer	0.6	68
Leaf disc	<i>Puccinia recondita</i> (pre)	B-2	Racemate	7.4	0

	<i>Puccinia recondita (cur)</i>	B-1	R-Enantiomer	7.4	70
		B-2	Racemate	200	0
		B-1	R-Enantiomer	200	70

Table C1 shows that the single enantiomer compound B-1 according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-2 under the same conditions.

5 **Table C2:** Biological data for compound B-3 (R-enantiomer) and compound B-4 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Wheat preventive	<i>Erysiphe graminis</i>	B-4	Racemate	2	46
		B-3	R-Enantiomer	2	88
Whole plant – Wheat preventive	<i>Puccinia recondita</i>	B-4	Racemate	6	37
		B-3	R-Enantiomer	6	60
Whole plant – Wheat curative	<i>Puccinia recondita</i>	B-4	Racemate	200	10
		B-3	R-Enantiomer	200	55
Whole plant – Wheat preventive	<i>Septoria tritici</i>	B-4	Racemate	200	51
		B-3	R-Enantiomer	200	97
liquid culture	<i>Monographella nivalis</i>	B-4	Racemate	0.027	0
		B-3	90:10 (R:S)	0.027	100
leaf disc	<i>Pyrenophora teres</i>	B-4	Racemate	67	0
		B-3	90:10 (R:S)	67	90

Table C2 shows that the single enantiomer compound or the enantiomerically enriched compound B-3 according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-4 under the same conditions.

Table C3: Biological data for compound B-5 (R-enantiomer) and compound B-6 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Cucumber curative	<i>Colletotrichum lagenarium</i>	B-6	Racemate	20	27
		B-5	R-Enantiomer	20	70
liquid culture	<i>Colletotrichum lagenarium</i>	B-6	Racemate	2.2	50
		B-5	90:10 (R:S)	2.2	70
	<i>Monographella nivalis</i>	B-6	Racemate	2.2	70
		B-5	90:10 (R:S)	2.2	100

Table C3 shows that the single enantiomer compound or the enantiomerically enriched compound B-5 according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-6 under the same conditions.

Table C4: Biological data for compound B-7 (R-enantiomer) and compound B-8 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Wheat preventive	<i>Erysiphe graminis</i>	B-8	Racemate	6	64
		B-7	R-Enantiomer	6	88
Whole plant – Wheat preventive	<i>Septoria tritici</i>	B-8	Racemate	20	30
		B-7	R-Enantiomer	20	58
liquid culture	<i>Botrytis cinerea</i>	B-8	Racemate	0.082	20
		B-7	R-Enantiomer	0.082	70
	<i>Colletotrichum lagenarium</i>	B-8	Racemate	0.027	20
		B-7	R-Enantiomer	0.027	70
	<i>Mycosapherella arachidicola</i>	B-8	Racemate	0.74	20
		B-7	R-Enantiomer	0.74	70
	<i>Septoria tritici</i>	B-8	Racemate	0.082	0
		B-7	R-Enantiomer	0.082	100
	<i>Sclerotinia sclerotiorum</i>	B-8	Racemate	0.027	0
		B-7	R-Enantiomer	0.027	100
leaf disc	<i>Puccinia recondita (pre)</i>	B-8	Racemate	2.5	50
		B-7	R-Enantiomer	2.5	90
	<i>Alternaria solani</i>	B-8	Racemate	67	0
		B-7	R-Enantiomer	67	70

- 5 Table C4 shows that the single enantiomer compound B-7 according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-8 under the same conditions.

Table C5: Biological data for compound B-9 (R-enantiomer) and compound B-10 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Grape preventive	<i>Uncinula necator</i>	B-10	Racemate	0.6	25
		B-9	R-Enantiomer	0.6	50
Whole plant – Wheat curative	<i>Puccinia recondita</i>	B-10	Racemate	6	42
		B-9	R-Enantiomer	6	74
Whole plant – Wheat preventive	<i>Septoria tritici</i>	B-10	Racemate	20	9
		B-9	R-Enantiomer	20	51
Whole plant – Cucumber curative	<i>Colletotrichum lagenarium</i>	B-10	Racemate	0.6	51
		B-9	R-Enantiomer	0.6	76

leaf disc	<i>Puccinia recondita (pre)</i>	B-10	Racemate	2.5	20
		B-9	90:10 (R:S)	2.5	70
	<i>Puccinia recondita (cur)</i>	B-10	Racemate	67	0
		B-9	90:10 (R:S)	67	100
	<i>Pyrenophora teres</i>	B-10	Racemate	67	20
		B-9	90:10 (R:S)	67	70

Table C5 shows that the single enantiomer compound or the enantiomerically enriched compound B-9, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-10 under the same conditions.

Table C6: Biological data for compound B-11 (R-enantiomer) and compound B-12 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Wheat curative	<i>Puccinia recondita</i>	B-12	Racemate	60	30
		B-11	R-Enantiomer	60	81
Whole plant – Wheat preventive	<i>Septoria tritici</i>	B-12	Racemate	200	65
		B-11	R-Enantiomer	200	89
Whole plant – Cucumber preventive	<i>Colletotrichum lagenarium</i>	B-12	Racemate	20	4
		B-11	R-Enantiomer	20	86
Whole plant – Cucumber curative	<i>Colletotrichum lagenarium</i>	B-12	Racemate	60	21
		B-11	R-Enantiomer	60	70
leaf disc	<i>Erysiphe graminis</i>	B-12	Racemate	7.4	20
		B-11	90:10 (R:S)	7.4	90
	<i>Puccinia recondita (pre)</i>	B-12	Racemate	200	20
		B-11	90:10 (R:S)	200	70

- 5 Table C6 shows that the single enantiomer compound or the enantiomerically enriched compound B-11, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-12 under the same conditions.

Table C7: Biological data for compound B-13 (R-enantiomer) and compound B-14 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Grape preventive	<i>Uncinula necator</i>	B-14	Racemate	6	63
		B-13	R-Enantiomer	6	100
Whole plant – Wheat preventive	<i>Puccinia recondita</i>	B-14	Racemate	0.6	13
		B-13	R-Enantiomer	0.6	60
Whole plant – Wheat preventive	<i>Septoria tritici</i>	B-14	Racemate	60	1
		B-13	R-Enantiomer	60	58
Whole plant –	<i>Colletotrichum lagenarium</i>	B-14	Racemate	6	10

Cucumber preventive		B-13	R-Enantiomer	6	74
liquid culture	<i>Mycosaptherella arachidicola</i>	B-14	Racemate	0.25	20
		B-13	90:10 (R:S)	0.25	90
	<i>Septoria tritici</i>	B-14	Racemate	0.082	20
		B-13	90:10 (R:S)	0.082	100
	<i>Monographella nivalis</i>	B-14	Racemate	0.027	20
		B-13	90:10 (R:S)	0.027	100
	<i>Sclerotinia sclerotiorum</i>	B-14	Racemate	0.082	0
		B-13	90:10 (R:S)	0.082	70
leaf disc	<i>Puccinia recondita (cur)</i>	B-14	Racemate	67	0
		B-13	90:10 (R:S)	67	70
	<i>Septoria nodorum</i>	B-14	Racemate	200	20
		B-13	90:10 (R:S)	200	90

Table C7 shows that the single enantiomer compound or the enantiomerically enriched compound B-13, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-14 under the same conditions.

Table C8: Biological data for compound B-15 (R-enantiomer) and compound B-16 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Wheat curative	<i>Puccinia recondita</i>	B-16	Racemate	200	4
		B-15	R-Enantiomer	200	87
Whole plant – Cucumber preventive	<i>Colletotrichum lagenarium</i>	B-16	Racemate	2	4
		B-15	R-Enantiomer	2	74
liquid culture	<i>Septoria tritici</i>	B-16	Racemate	0.082	0
		B-15	R-Enantiomer	0.082	70
	<i>Monographella nivalis</i>	B-16	Racemate	0.027	0
		B-15	R-Enantiomer	0.027	100
	<i>Sclerotinia sclerotiorum</i>	B-16	Racemate	0.74	0
		B-15	R-Enantiomer	0.74	100
leaf disc	<i>Puccinia recondita (pre)</i>	B-16	Racemate	2.5	0
		B-15	R-Enantiomer	2.5	70
	<i>Puccinia recondita (cur)</i>	B-16	Racemate	200	0
		B-15	R-Enantiomer	200	100
	<i>Septoria nodorum</i>	B-16	Racemate	200	0
		B-15	R-Enantiomer	200	90

- 5 Table C8 shows that the single enantiomer compound B-15, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-16 under the same conditions.

Table C9: Biological data for compound B-17 (R-enantiomer) and compound B-18 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Wheat preventive	<i>Erysiphe graminis</i>	B-18	Racemate	6	52
		B-17	R-Enantiomer	6	82
Whole plant – Cucumber preventive	<i>Colletotrichum lagenarium</i>	B-18	Racemate	6	10
		B-17	R-Enantiomer	6	62
liquid culture	<i>Monographella nivalis</i>	B-18	Racemate	6.7	70
		B-17	90:10 (R:S)	6.7	100
leaf disc	<i>Alternaria solani</i>	B-18	Racemate	200	0
		B-17	90:10 (R:S)	200	90

Table C9 shows that the single enantiomer compound or the enantiomerically enriched compound B-17, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-18 under the same conditions.

Table C10: Biological data for compound B-19 (R-enantiomer) and compound B-20 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Grape preventive	<i>Uncinula necator</i>	B-20	Racemate	2	13
		B-19	90:10 (R:S)	2	99
Whole plant – Cucumber curative	<i>Colletotrichum lagenarium</i>	B-20	Racemate	6	51
		B-19	90:10 (R:S)	6	82
liquid culture	<i>Septoria tritici</i>	B-20	Racemate	0.082	70
		B-19	90:10 (R:S)	0.082	100
leaf disc	<i>Erysiphe graminis</i>	B-20	Racemate	0.82	0
		B-19	90:10 (R:S)	0.82	50
	<i>Septoria nodorum</i>	B-20	Racemate	200	50
		B-19	90:10 (R:S)	200	90
	<i>Alternaria solani</i>	B-20	Racemate	7.4	20
		B-19	90:10 (R:S)	7.4	70

- 5 Table C10 shows that the enantiomerically enriched compound B-19, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-20 under the same conditions.

Table C11: Biological data for compound B-21 (R-enantiomer) and compound B-22 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Grape preventive	<i>Uncinula necator</i>	B-22	Racemate	2	38
		B-21	90:10 (R:S)	2	81

Whole plant – Cucumber preventive	<i>Colletotrichum lagenarium</i>	B-22	Racemate	6	42
		B-21	90:10 (R:S)	6	74
Whole plant – Cucumber curative	<i>Colletotrichum lagenarium</i>	B-22	Racemate	2	21
		B-21	90:10 (R:S)	2	57
leaf disc	<i>Puccinia recondita (pre)</i>	B-22	Racemate	2.5	50
		B-21	90:10 (R:S)	2.5	90
	<i>Alternaria solani</i>	B-22	Racemate	2.5	20
		B-21	90:10 (R:S)	2.5	70

Table C11 shows that enantiomerically enriched compound B-21, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-22 under the same conditions.

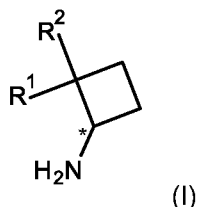
Table C12: Biological data for compound B-23 (R-enantiomer) and compound B-24 (racemic)

Test method	Species	Compound		Rate [mg ai/L]	Efficacy [%]
Whole plant – Wheat preventive	<i>Erysiphe graminis</i>	B-24	Racemate	0.6	28
		B-23	90:10 (R:S)	0.6	64
Whole plant – Wheat curative	<i>Puccinia recondita</i>	B-24	Racemate	6	62
		B-23	90:10 (R:S)	6	92
Whole plant – Cucumber preventive	<i>Colletotrichum lagenarium</i>	B-24	Racemate	20	68
		B-23	90:10 (R:S)	20	94
liquid culture	<i>Colletotrichum lagenarium</i>	B-24	Racemate	6.7	0
		B-23	90:10 (R:S)	6.7	90
	<i>Septoria tritici</i>	B-24	Racemate	6.7	0
		B-23	90:10 (R:S)	6.7	90
	<i>Pyricularia oryzae</i>	B-24	Racemate	0.25	0
		B-23	90:10 (R:S)	0.25	70
	<i>Monographella nivalis</i>	B-24	Racemate	0.74	0
		B-23	90:10 (R:S)	0.74	70
leaf disc	<i>Puccinia recondita (cur)</i>	B-24	Racemate	200	50
		B-23	90:10 (R:S)	200	100
	<i>Alternaria solani</i>	B-24	Racemate	200	0
		B-23	90:10 (R:S)	200	100

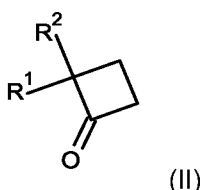
- 5 Table C12 shows that the enantiomerically enriched compound B-23, according to the present invention shows advantageous levels of biological activity for protecting plants against diseases that are caused by fungi, when compared to the racemic compound B-24 under the same conditions.

CLAIMS

1. A process for the preparation of an enantiomerically enriched compound of formula (I)



wherein R^1 and R^2 are independently selected from C_1 - C_4 -alkyl, or C_3 - C_6 -cycloalkyl; or
 R^1 and R^2 form with the carbon to which they are attached a C_3 - C_6 -cycloalkyl ring;
 said process comprising reaction of an α -tertiary cyclobutanone of formula (II)



wherein R^1 and R^2 are defined as for compounds of formula (I),

in the presence of ammonia, an ammonium salt and hydrogen in the presence of a chiral transition metal catalyst to produce a compound of formula (I), wherein said compound of formula (I) is the (*S*) or (*R*) enantiomer, wherein the asterisk marks the stereogenic center.

2. The process according to claim 1, wherein R^1 and R^2 are independently selected from methyl, or R^1 and R^2 form with the carbon to which they are attached a cyclobutyl- or cyclopentylring.

3. The process according to claim 1 or claim 2, wherein said compound of formula (I) is the (*R*) enantiomer.

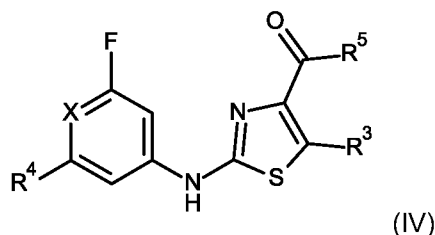
4. The process according to any one of claims 1 to 3, wherein said compound of formula (I) is the (*S*) enantiomer.

5. The process according to any one of claims 1 to 4, wherein said chiral transition metal catalyst is selected from $[NH_2Me_2][(RuCl((S)\text{-xylbinap}))_2(u\text{-Cl})_3]$, $[NH_2Me_2][(RuCl((R)\text{-xylbinap}))_2(u\text{-Cl})_3]$, $Ru(OAc)_2[(S)\text{-xylbinap}]$, or $Ru(OAc)_2[(R)\text{-xylbinap}]$.

6. The process according to any one of claims 1 to 5, wherein said ammonium salt is selected from ammonium chloride or ammonium bromide.

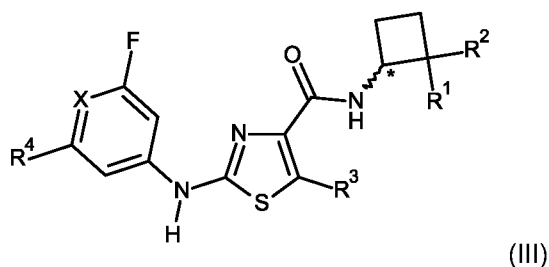
7. The process according to any one of claims 1 to 6, further comprising reacting the compound of formula (I), wherein said compound of formula (I) is the (*R*) or (*S*) enantiomer, with a compound of formula (IV)

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wherein X is CH or N; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or fluoro; and R⁵ is selected from hydroxy, halogen, or OR⁶; wherein R⁶ is selected from C₁-C₆-alkyl, C₃-C₆-alkylcarbonyl, C₃-C₆-alkoxycarbonyl, C₁-C₆-alkylsulfonyl, benzoyl, heteroarylcarbonyl, phenylsulfonyl, heteroarylsulfonyl, or heteroaryl, wherein said heteroaryl is a 5 to 6 membered aromatic heterocycle which comprises 1, 2, 3, or 4 heteroatoms individually selected from N, O or S, and wherein said phenyl, benzoyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 substituents individually selected from halogen, C₁-C₃ alkyl, or C₁-C₃-alkoxy;

to form a compound of formula (III)



wherein R¹, and R² are defined as in claim 1, and wherein R³ and R⁴ defined as for compound of formula (IV); and

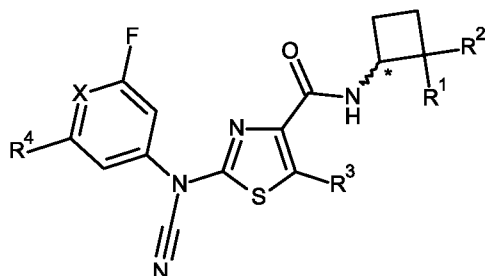
wherein said compound of formula (III) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center.

8. The process according to claim 7, wherein R¹ and R² are independently selected from methyl, or R¹ and R² form with the carbon to which they are attached a cyclobutyl- or cyclopentylring; X is N; R³ is methyl, R⁴ is fluoro; R⁵ is selected from hydroxy, halogen, or OR⁶; and R⁶ is selected from C₁-C₃-alkyl, C₃-C₆-alkylcarbonyl, or C₃-C₆-alkoxycarbonyl.

9. The process according to claim 7 or claim 8, further comprising reacting the compound of formula (III), wherein said compound of formula (III) is the (S) or (R) enantiomer, wherein the asterisk marks the stereogenic center;

with

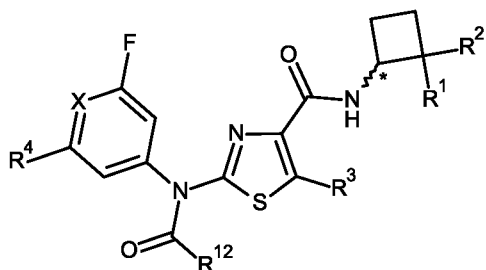
a) a compound of formula R^{11} -CN (VIII), wherein R^{11} is a leaving group, preferably halogen, optionally in the presence of a base, to form an enantiomerically enriched compound of formula (VI),



(VI)

wherein R^1 and R^2 are defined as for claim 1; and R^3 and R^4 are defined as according to claim 7; and wherein said compound of formula (VI) is the (*S*) or (*R*) enantiomer, wherein the asterisk marks the stereogenic center; or

b) a compound of formula R^{12} -C(=O) X^a (IX), wherein R^{12} is hydrogen, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, C_1 - C_3 -haloalkyl, C_1 - C_3 -hydroxyalkyl, C_1 - C_3 -alkoxy- C_1 - C_2 -alkyl, C_3 - C_4 -cycloalkyl, C_1 - C_2 -alkoxy- C_1 - C_2 -alkoxy, C_1 - C_3 -alkoxycarbonyl- C_1 - C_3 -alkyl, C_1 - C_2 -alkoxycarbonyloxy- C_1 - C_2 -alkyl, C_1 - C_2 -alkylcarbonyloxy- C_1 - C_2 -alkyl, C_3 - C_4 -alkynyloxy, C_1 - C_3 -alkylsulfanyl, or heterocyclyl, wherein said heterocyclyl moiety is a 4-, 5- or 6-membered non-aromatic monocyclic ring comprising 1 heteroatom selected from oxygen; and wherein X^a is a leaving group, optionally in the presence of a base, to form an enantiomerically enriched compound of formula (VII),

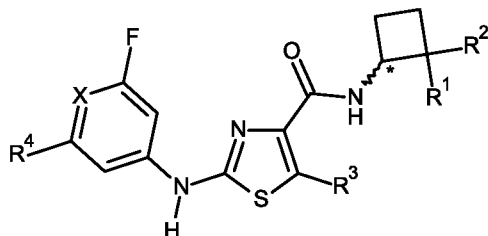


(VII)

wherein R^1 and R^2 are defined as for claim 1; R^3 and R^4 are defined according to claim 7; and wherein R^{12} is defined as for compound of formula (IX); and wherein said compound of formula (VII) is the (*S*) or (*R*) enantiomer, wherein the asterisk marks the stereogenic center.

10. The process according to claim 9, wherein R^1 and R^2 are independently selected from methyl, or R^1 and R^2 form with the carbon to which they are attached a cyclobutyl- or cyclopentylring; X is N; R^3 is methyl, R^4 is fluoro; R^5 is selected from hydroxy, halogen, or OR^6 ; and R^6 is selected from C_1 - C_3 -alkyl, C_3 - C_6 -alkylcarbonyl, or C_3 - C_6 -alkoxycarbonyl; R^{11} is bromo; R^{12} is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; and X^a is halogen.

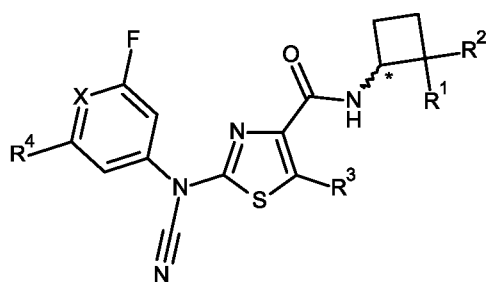
11. A compound of formula (III)



(III)

wherein X is CH or N; R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl; or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or fluoro; and wherein said compound is the (*R*) enantiomer, wherein the asterisk marks the stereogenic center.

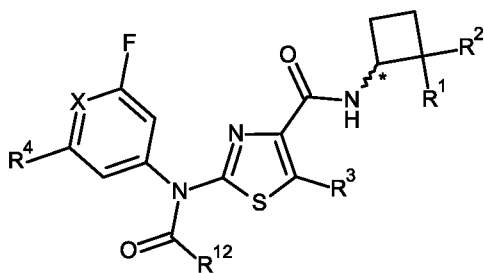
12. A compound of formula (VI)



(VI)

wherein X is CH or N; R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl; or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl; R⁴ is hydrogen or fluoro; and wherein said compound is the (*R*) enantiomer, wherein the asterisk marks the stereogenic center.

13. A compound of formula (VII)



(VII)

wherein X is CH or N; R¹ and R² are independently selected from C₁-C₄-alkyl, or C₃-C₆-cycloalkyl; or R¹ and R² form with the carbon to which they are attached a C₃-C₆-cycloalkyl ring; R³ is C₁-C₃-alkyl;

R⁴ is hydrogen or fluoro; R¹² is methyl, ethyl, isopropyl, methoxy, ethoxy, methoxymethyl, 1-methoxyethyl, oxetane-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, or tetrahydropyran-4-yl; and wherein said compound is the (*R*) enantiomer, wherein the asterisk marks the stereogenic center.

- 5 14. An agrochemical composition comprising a fungicidally effective amount of a compound as defined in any one of claims 11 to 13.
15. The agrochemical composition according to claim 14, further comprising at least one additional active ingredient and/or an agrochemically-acceptable diluent or carrier.
- 10 16. A method of controlling or preventing infestation of useful plants by phytopathogenic microorganisms, wherein a fungicidally effective amount of a compound as defined in any one of claims 11 to 13, or a composition comprising said compound, is applied to the plants, to parts thereof or the locus thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/075661

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D277/56 C07D401/12 C07C209/26 C07C211/16 A01N43/78 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 C07C A01N 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, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	WO 2019/096860 A1 (SYNGENTA PARTICIPATIONS AG) 23 May 2019 (2019-05-23) claims; examples 10-98 -----	1 - 16
Y	WO 2023/099460 A1 (SYNGENTA CROP PROTECTION AG) 8 June 2023 (2023-06-08) page 62 - page 64; claims; example P1 -----	1 - 16
A	WO 2021/244950 A1 (SYNGENTA CROP PROTECTION AG) 9 December 2021 (2021-12-09) claims; examples X03-X05, X07, X09 ----- - / - -	1 - 16
☒ Further documents are listed in the continuation of Box C. ☒ 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 4 December 2024		Date of mailing of the international search report 12/12/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Helps, Ian

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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