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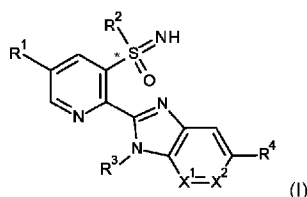
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(54) Title: SYNTHESIS OF SULFOXIMINES CONTAINING A BENZIMIDAZOLE MOIETY

(57) Abstract: A process for the preparation of enantiomerically enriched sulfoximines of formula (I) is provided, wherein R^1 , R^2 , S^* , R^3 , R^4 , X and X^2 are as defined in the description.



(I)



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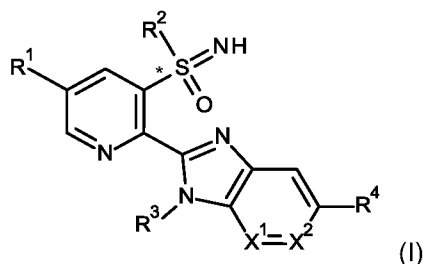
SYNTHESIS OF SULFOXIMINES CONTAINING A BENZIMIDAZOLE MOIETY

The present invention relates to the enantioselective synthesis of sulfoximines containing a benzimidazole moiety. Such compounds are useful as active ingredients, which have pesticidally activity, in particular insecticidally activity and are used for controlling animal pests, including arthropods and in particular insects.

Pesticidally active heterocyclic sulfoximine derivatives have previously been described in the literature, for example, in WO2015/071180, WO2016/039441, WO2018/206348, WO2019/219689, WO2019/229089, WO2019/234158, WO2020/084075 and WO2020/141136.

WO2022/253841 discloses the stereoselective synthesis of sulfoximines by means of a stereoselective oxidation, followed by a stereospecific imination reaction.

The present invention provides a novel enantioselective synthesis of a similar class of sulfoximines leading to a compound of formula (I):



wherein:

R¹ is halogen, C₁-C₆-haloalkyl, cyano-C₁-C₆-alkyl, cyano-C₁-C₆-alkoxy, cyano-C₃-C₆-cycloalkyl, or aryl, wherein said aryl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C₁-C₃-alkyl, or C₁-C₃-alkoxy;

R² is C₁-C₄-alkyl;

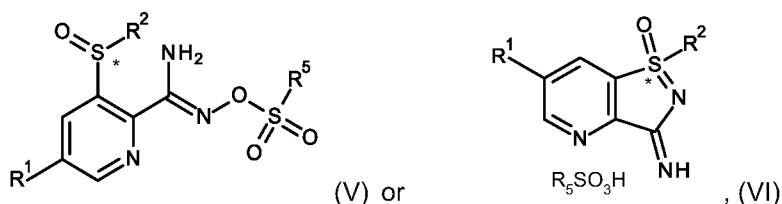
R³ is hydrogen or C₁-C₄-alkyl;

R⁴ is hydrogen, halogen, or C₁-C₄-haloalkyl;

S* is a stereogenic sulfur atom which is in *R*- or *S*-configuration; and

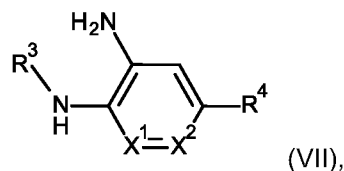
X¹ and X² are independently selected from CH or N, with the proviso that at least one of X¹ and X² is nitrogen,

wherein said process comprises reacting a compound of formula (V) or a compound of formula (VI)



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wherein R^1 , R^2 and S^* are as defined for compounds of formula (I), and R^5 selected from C_1 - C_4 -alkyl or phenyl, wherein said phenyl is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, or methyl; with a compound of formula (VII)

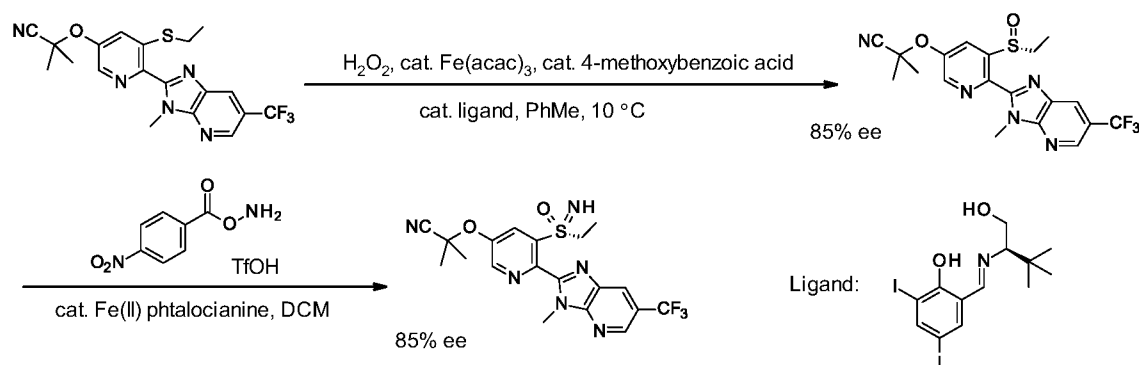


- 5 wherein R^3 , R^4 , X^1 and X^2 are as defined for a compound of formula (I), in an appropriate solvent at an appropriate temperature to produce a compound of formula (I).

In previously published patent application (WO2022/253841) compounds of this sort were prepared as shown in Scheme 1 for a specific example.

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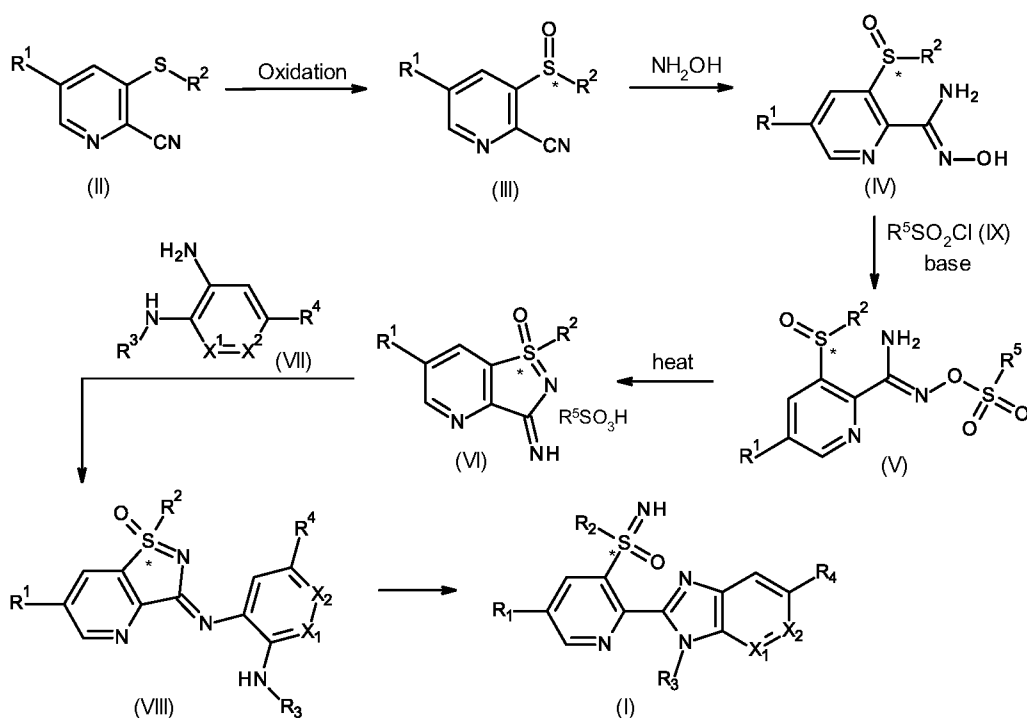
Scheme 1



- 15 The fully formed sulfide analogue was first synthesized (as described in WO2019/234158) and in the last steps the sulfide underwent enantioselective oxidation followed by a stereospecific imination at sulfur. This method is fully amenable for making a wide variety of analogues however for a large-scale synthesis this method is not ideal. First, oxidation conditions have to be adjusted for every substrate and even then enantiomeric excess obtained is not always sufficient. Even more importantly the reagent used for imination must be synthesized separately and is difficult to use on a large scale due to safety concerns.

- 20 Therefore, there is a need for an atom-efficient approach for the synthesis of enantiomerically pure or enriched chiral sulfoximine 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. Surprisingly, we have now found that sulfoximine compounds of formula (I) can be prepared from the corresponding sulfide compounds via cyclic sulfoximine intermediates as shown in Scheme 2.

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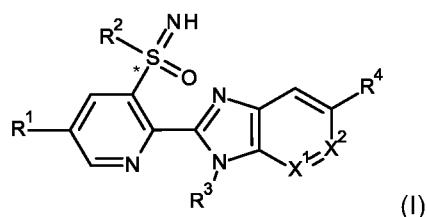
Scheme 2

A compound of formula (II), wherein R^1 and R^2 are as defined for a compound of formula (I), is first oxidized in an enantioselective manner to yield a compound of formula (III), wherein R^1 , R^2 and $^*S$ are as defined for a compound of formula (I). Nucleophilic addition of hydroxylamine (NH_2OH) to the cyano moiety then provides a compound of formula (IV). Activation of amidine oxime with a sulfonyl chloride compound of formula (IX), wherein R^5 is selected from C_1 - C_4 -alkyl or phenyl, wherein said phenyl is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, or methyl; in the presence of a base, provides an intermediate of formula (V). Heating of this intermediate provides a cyclic imino sulfoximine compound of formula (VI) as a sulfonic acid salt. Such intramolecular imination is surprising and has not been previously reported. The compound of formula (VI) is then reacted with a compound of formula (VII), wherein R^3 , R^4 , X^1 and X^2 are as defined for a compound of formula (I), to yield via an intermediate of formula (VIII), which can be converted to a compound of formula (I). A compound of formula (VI) may be isolated, but in many cases, it is advantageous to proceed immediately to a compound of formula (I) by heating a mixture of a compound of formula (V) and a compound of formula (VII).

The condensation of a compound of formula (VI) to yield an intermediate of formula (VIII) which could in certain cases be isolated followed by rearrangement to yield a compound of formula (I) has no close literature precedents and constitutes a novel approach in this class of compounds.

The present invention provides a process for the preparation of sulfoximines of formula (I) in an enantiomerically pure or enantiomerically enriched form

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wherein

R¹ is halogen, C₁-C₆-haloalkyl, cyano-C₁-C₆-alkyl, cyano-C₁-C₆-alkoxy, cyano-C₃-C₆-cycloalkyl, or aryl, wherein said aryl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen,

5 C₁-C₃-alkyl, or C₁-C₃-alkoxy;

R² is C₁-C₄-alkyl;

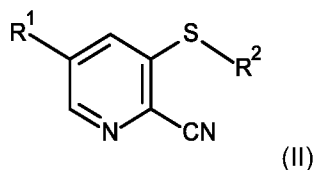
R³ is hydrogen or C₁-C₄-alkyl;

R⁴ is hydrogen, halogen, or C₁-C₄-haloalkyl;

S* is a stereogenic sulfur atom which is in *R*- or *S*-configuration; and

10 X¹ and X² are independently selected from CH or N, with the proviso that at least one of X¹ and X² is nitrogen,

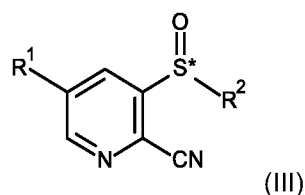
by A) stereoselective oxidation of a sulfanyl compound of formula (II)



15 wherein R¹ and R² are as defined for compounds of formula (I);

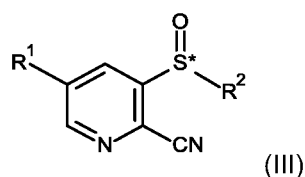
in the presence of an oxidant, in the presence of a chiral reagent or catalyst, optionally in the presence of a suitable acid additive, in an appropriate solvent (or diluent);

to produce a sulfinyl compound of formula (III)



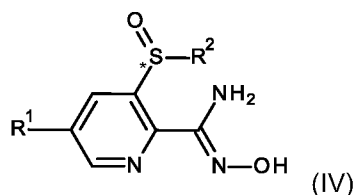
20 wherein R¹, R² and S* are as defined for compounds of formula (I);

and B) reacting the compound of formula (III)



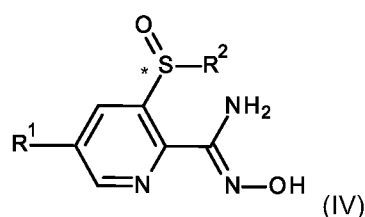
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wherein R¹, R² and S* are as defined previously with hydroxylamine in an appropriate solvent at an appropriate temperature to produce a compound of formula (IV)

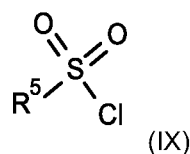


wherein R¹, R² and S* are as defined for a compound of formula (I);

5 and C) reaction of the sulfinyl compound of formula (IV)

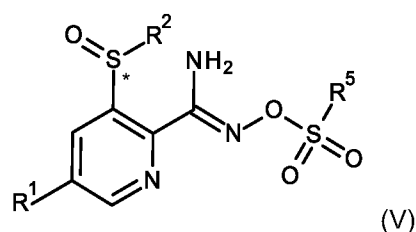


wherein R¹, R², and S* are as defined for compounds of formula (I) with a sulfonyl chloride of formula (IX)



10 wherein R⁵ is C₁-C₄-alkyl or phenyl, wherein said phenyl is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, or methyl; preferably R⁵ is selected from methyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-cyanophenyl, 4-nitrophenyl, or 2,4-dinitrophenyl;

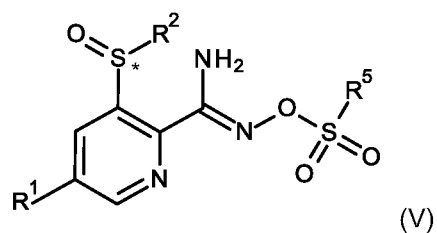
in the presence of an appropriate base and in an appropriate solvent to produce a compound of formula (V)



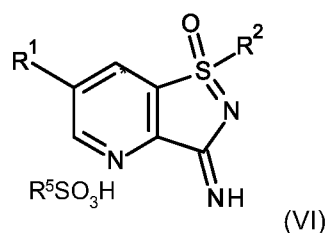
15 wherein R¹, R² and S* are as defined for compounds of formula (I) and R⁵ is as defined for a compound of formula (IX);

and D) thermally rearranging the compound of formula (V)

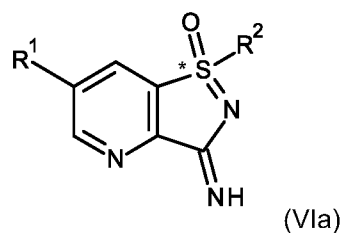
-6-



wherein R^1 , R^2 and S^* are as defined for compounds of formula (I) and R^5 is as defined for a compound of formula (IX); in a solvent to produce a compound of formula (VI)

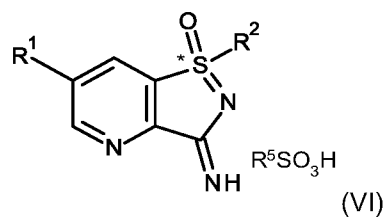


- 5 wherein R^1 , R^2 and S^* are as defined for compounds of formula (I) and R^5 is as defined for a compound of formula (IX), optionally a compound of formula (VIa) could be produced by adding an appropriate base and used in step (E)

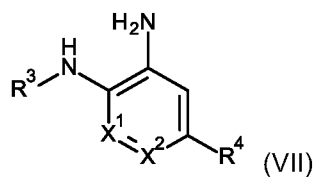


wherein R^1 , R^2 and S^* are as defined for compounds of formula (I);

- 10 and E) reacting a compound of formula (VI)

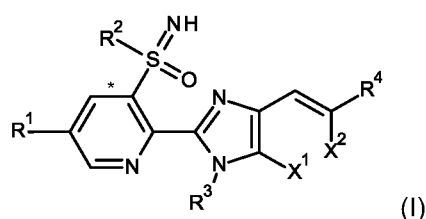


wherein R^1 , R^2 and S^* are as defined for compounds of formula (I) and R^5 is as defined for a compound of formula (IX), with a compound of formula (VII)



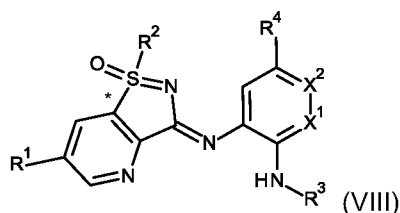
- 15 wherein R^3 , R^4 , X^1 and X^2 are as defined for a compound of formula (I); in an appropriate solvent at an appropriate temperature to produce a compound of formula (I)

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wherein R^1 , R^2 , S^* , R^3 , R^4 , X^1 and X^2 are as previously defined.

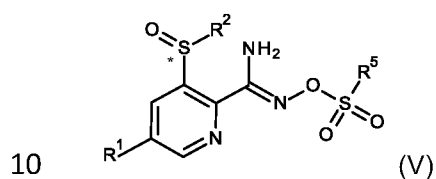
It is understood that this condensation and rearrangement proceeds via an intermediate of formula (VIII)



5 wherein R^1 , R^2 , S^* , R^3 , R^4 , X^1 and X^2 are as defined for a compound of formula (I).

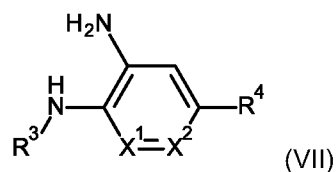
In cases where the rearrangement step is slower than the condensation step the compound of formula (VIII) could be isolated.

Optionally a compound of formula (V)



wherein R^1 , R^2 and S^* are as defined for compounds of formula (I), and R^5 is as defined for a compound of formula (IX);

is reacted in an appropriate solvent at an appropriate temperature with a compound of formula (VII)



15 wherein R^3 , R^4 , X^1 and X^2 are as defined for a compound of formula (I), to directly produce a compound of formula (I) without a need to isolate either a compound of formula (VI) or a compound of formula (VIII).

In one embodiment of the invention, this condensation of a compound of formula (VI) to yield an intermediate of formula (VIII) may be carried out in the presence of an acidic additive. In one embodiment of the invention, said condensation reaction may be carried out in the presence of citric acid.

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Further it has been surprisingly found that the compounds of formula (I) have, for practical purposes, a very advantageous level pesticidal activity, in particular insecticidal activity and are used for controlling animal pests, including arthropods and in particular insects.

As used herein, the term "hydroxyl" or "hydroxy" means an -OH group.

5 As used herein, the term "nitro" means a -NO₂-group.

As used herein, cyano means a -CN 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.

10 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-hexyl, 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,
15 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
20 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-haloalkyl" refers to a straight-chain or branched saturated alkyl radical attached
25 via any of the carbon atoms having 1 to n carbon atoms (as mentioned above), where some or all of the hydrogen atoms in these radicals may be replaced by fluorine, chlorine, bromine and/or iodine, i.e., for example, but not limited to chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-
30 2-fluoroethyl, 2,2,2-trichloroethyl, 2-fluoropropyl, 3-fluoropropyl, 2,2-difluoropropyl, 2,3-difluoropropyl, 2-chloropropyl, 3-chloropropyl, 2,3-dichloropropyl, 2-bromopropyl, 3-bromopropyl.

As used herein, the term "cyano-C₁-C_n-alkyl", refers to a straight chain or branched saturated C₁-C_n-alkyl radicals (as mentioned above) which is substituted by a cyano group, for example cyanomethylene, cyanoethylene, 1,1-dimethylcyanomethyl, cyanoisopropyl, cyanomethyl, cyanoethyl, and 1-
35 dimethylcyanomethyl. This term can be used interchangeably with "C₁-C_n-cyanoalkyl".

As used herein, the term cyano-C₁-C_n-alkoxy refers to a straight chain or branched saturated C₁-C_n-alkoxy radicals (as mentioned above) which is substituted by a cyano group. This term can be used interchangeably with "C₁-C_n-cyanoalkoxy".

The term "cyano-C₃-C_n-cycloalkyl" as used herein refers to a 3-6 membered cycloalkyl group (as mentioned above) which is substituted by a cyano group. This term can be used interchangeably with "C₃-C_n-cyanocycloalkyl".

The term "aryl" represents a mono-, bi- or polycyclical aromatic system with preferably 6 to 14, more preferably 6 to 10 ring-carbon atoms, for example phenyl, naphthyl, anthryl, phenanthrenyl, preferably phenyl. "Aryl" also represents polycyclic systems, for example tetrahydronaphtyl, indenyl, indanyl, fluorenyl, biphenyl. Arylalkyls are examples of substituted aryls, which may be further substituted with the same or different substituents both at the aryl or alkyl part. benzyl and phenylethyl are examples of such arylalkyls.

Where not otherwise defined the term "optionally substituted" means that the group in question can be substituted with zero up to the maximum number of substituents with groups independently selected from: halogen, methyl, ethyl, propyl, isopropyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, trifluoromethyl, difluoromethyl, chlorodifluoromethyl, trichloromethyl, methoxy, ethoxy, trifluoromethoxy, difluoromethoxy, nitro, cyano, hydroxy, sulfhydryl, acetyl, acetoxyl, COOH, COOMe, COOEt, CONH₂, CONHMe, CONMe₂, amino, methlamino, dimethylamino, phenyl.

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 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%.

As used herein, the term "room temperature" or "RT" or "rt" or "ambient temperature" 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 "condensation" refers to a reaction in which two molecules combine to form a single molecule.

As used herein the term "appropriate solvent" refers to a solvent that is suitable or fitting for a particular reaction step. The term "appropriate solvent" can be used interchangeably with the term "suitable solvent" or "diluent"

As used herein the term "appropriate temperature" refers to a temperature that is suitable or fitting for a particular reaction step. The term "appropriate temperature" can be used interchangeably with the term "temperature suitable for".

As used herein, the R-groups as used in the Markush-structures of the present invention can be interchangeably disclosed as R_x or R^x , wherein the x is used to label the R-group.

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 R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , 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 present invention, R^1 is halogen, C_1 - C_4 -haloalkyl, cyano- C_1 - C_4 -alkyl, cyano- C_1 - C_4 -alkoxy, cyano- C_3 - C_6 -cycloalkyl, or aryl; wherein said any of said aryl is unsubstituted or substituted with 1, 2 or 3 substituents independently from each other selected from halogen, C_1 - C_3 -alkyl, or C_1 - C_3 -alkoxy. Preferably, R^1 is halogen, C_1 - C_2 -haloalkyl, cyano- C_1 - C_3 -alkyl, cyano- C_1 - C_3 -alkoxy, cyano- C_3 - C_6 -cycloalkyl, or phenyl; wherein said phenyl is unsubstituted or substituted with 1, or 2 substituents independently from each other selected from halogen.

In one embodiment of the present invention, R^2 is C_1 - C_4 -alkyl. Preferably, R^2 is C_1 - C_3 -alkyl. More preferably, R^2 is methyl, or ethyl. Even more preferably, R^2 is ethyl.

In one embodiment of the present invention, R^3 is hydrogen or C_1 - C_4 -alkyl. Preferably, R^3 is hydrogen or C_1 - C_3 -alkyl. More preferably, R^3 is hydrogen or methyl. In one embodiment, R^3 is hydrogen. In another embodiment, R^3 is methyl. Preferably, embodiment, R^3 is methyl.

In one embodiment of the present invention, R^4 is hydrogen, halogen, or C_1 - C_4 -haloalkyl. Preferably,

In one embodiment of the present invention, S^* is a stereogenic sulfur atom which is in (R)- or (S)-configuration.

In a preferred embodiment of the present invention, S^* is a stereogenic sulfur atom which is in (R)-configuration. In another preferred embodiment of the present invention, S^* is a stereogenic sulfur atom which is in (S)-configuration.

In one embodiment of the present invention, X^1 and X^2 are independently selected from CH or N, with the proviso that at least one of X^1 and X^2 is nitrogen. Preferably, X^1 is N, and X^2 is CH; or X^1 is CH, and X^2 is N; or X^1 is N, and X^2 is N. More preferably, X^1 is N, and X^2 is CH; or X^1 is CH, and X^2 is N.

In one embodiment of the invention step (A) comprises:

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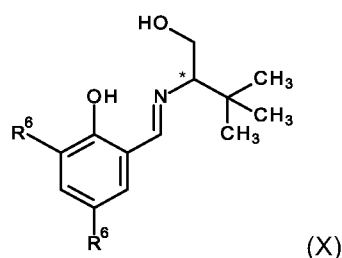
Oxidizing a sulfanyl compound of formula (II), in the presence of an oxidant, in the presence of a metal derivative, in the presence of a chiral ligand, in an appropriate solvent (or diluent) and optionally in the presence of a suitable acid additive.

Examples of suitable and preferred oxidants are inorganic peroxides, such as hydrogen peroxide or organic peroxides, such as tert-butyl hydroperoxide. Preferably the oxidant is hydrogen peroxide. The ratio of the oxidant used, based on the amount of the sulfanyl compound of formula (II), is in the range from 8:1 to 0.8:1, preferably between 5:1 and 1:1, more preferably between 3:1 and 1:1.

Example of suitable and preferred metal derivatives are salts of vanadium and iron. Preferably iron salts are used. Suitable examples include but are not limited to VOCl_2 , $\text{VO}(\text{acac})_2$, $\text{Fe}(\text{acac})_3$, $\text{Fe}(\text{acac})_2$. The amount of metal catalyst used, based on the amount of the sulfanyl compounds of formula (II) is in the range from 0.1 mol% to 50 mol%. Preferably between 0.5 mol % and 10 mol%.

Examples of suitable and preferred chiral ligands are selected from Schiff bases formed from salicylaldehyde derivatives and chiral amines.

In a preferred embodiment of the invention the metal derivative is selected from iron and the chiral ligand is a Schiff base formed from salicylaldehyde derivatives and chiral amino-alcohols represented by a compound of formula (X),



wherein R^6 is halogen and the carbon marked with a * represents an enantioenriched chiral center in either (R)- or (S)-configuration. Preferably, R^6 is chloro, iodo or bromo.

The chiral ligand is used as an enantioenriched compound. The enantiomeric ratio of the ligand is from 80:20 to 100:0 [R]:[S] or [S]:[R], preferably the enantiomeric ratio of the ligand is from 90:10 to 100:0 [R]:[S] or [S]:[R].

The amount of the ligand used, based on the amount of the sulfanyl compound of formula (II), is in the range from 0.1 to 30 mol %, preferably from 1 to 15 mol%, most preferably from 2 to 10 mol%.

Optionally, the ligand can be formed *in situ* in the reaction by adding the appropriate salicylaldehyde derivative and an appropriate amino alcohol. Alternatively, the ligand can be prepared in a separate step.

Example of suitable and preferred acid additives are carboxylic acids. Preferably the acid additive is a benzoic acid, optionally mono-, di- or tri-substituted by methyl, ethyl, isopropyl, methoxy or dimethylamino, optionally in form of a lithium, sodium or potassium salt. More preferably the additive is a methoxybenzoic acid or a dimethylaminobenzoic acid (optionally in form of a lithium, sodium or potassium salt), even more preferably 4-

methoxybenzoic acid. The amount of the acid additive used, compared to the sulfanyl compound of formula (II), is in the range from 0.1 to 10 mol %, most preferably from 0.5 to 5 mol %.

In the most preferred embodiment, the oxidizing agent is hydrogen peroxide; the metal salt is $\text{Fe}(\text{acac})_3$; the ligand is selected from (2R)-2-[(E)-(3,5-diiodophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2S)-2-[(E)-(3,5-diiodophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2R)-2-[(E)-(3,5-dibromophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2S)-2-[(E)-(3,5-dibromophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2R)-2-[(E)-(3,5-dichlorophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, or (2S)-2-[(E)-(3,5-dichlorophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol; and the additive is 4-methoxybenzoic acid.

Examples of suitable and preferred solvents (or diluents) are esters, nitriles, alcohols, ethers, and aliphatic, aromatic or halogenated hydrocarbons. Examples include but are not limited to: ethyl acetate, isopropyl acetate, acetonitrile, butyronitrile, ethanol, methanol, isopropanol, n-propanol, tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentylmethyl ether, t-butylmethyl ether, diethyl ether, 1,4-dioxane pentane, hexane, cyclohexane, heptane, dichloromethane, 1,2-dichloroethane, chloroform, benzene, toluene, xylene, chlorobenzene, fluorobenzene, dichlorobenzene, methoxybenzene, trifluoromethylbenzene, p-cymene, mesitylene, ethylbenzene, isopropylbenzene, or mixtures thereof.

Preferably the solvent is an aromatic or halogenated hydrocarbon, for example: dichloromethane, 1,2-dichloroethane, chloroform, benzene, toluene, xylene, chlorobenzene, fluorobenzene, dichlorobenzene, methoxybenzene, trifluoromethylbenzene, p-cymene, mesitylene, ethylbenzene, isopropylbenzene, or mixtures thereof.

More preferably the solvent is selected from dichloromethane, toluene, xylene, chlorobenzene, methoxybenzene, or mixtures thereof.

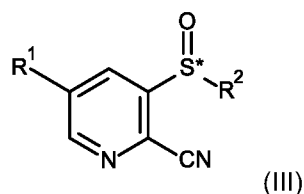
The ratio of enantiomers produced is from 50.5:49.5 to 100:0 [R]:[S] or [S]:[R]. Preferably the enantiomeric ratio of the product is from 70:30 to 100:0 [R]:[S] or [S]:[R], even more preferably 90:10 to 100:0 [R]:[S] or [S]:[R]. The enantiomeric ratio of the product can be either lower or higher than the enantiomeric ratio of the chiral ligand used in the reaction.

The ratio of enantiomers produced can be increased by crystallization if required. Such methods are known to those skilled in the art and include crystallization from an organic solvent, a mixture of organic solvents or a mixture of organic solvents with water.

It has been proven by X-ray crystallography (see Example 8) that the chiral ligand of formula (X) enriched in R enantiomer provides an enantioenriched sulfoxide of formula (I) enriched in R enantiomer. Correspondingly, the chiral ligand of formula (X) enriched in S enantiomer yields enantioenriched sulfoxide of formula (I) enriched in S enantiomer.

Step (B) comprises reacting a compound of formula (III)

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wherein R¹, R² and S* are as defined for a compound of formula (I); with an aqueous solution of hydroxylamine in an appropriate solvent at an appropriate temperature. The ratio of hydroxylamine used compared to a compound of formula (III) is in the range between 2:1 and 1:1, preferably between 1.5:1 and 1:1.

- 5 Optionally in place of hydroxylamine free base hydroxylamine hydrochloride or hydroxylamine sulfate could be used in combination with 1 eq (relative to hydroxylamine salt) of an appropriate base. Appropriate bases include but are not limited to: sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and sodium bicarbonate.

10 Examples of suitable and preferred solvents (or diluents) for step B are alcohols, ethers, and aliphatic, aromatic or halogenated hydrocarbons.

Examples include but are not limited to: tetrahydrofuran, 2-methyl tetrahydrofuran, dichloromethane, 1,2-dichloroethane, chlorobenzene, toluene, anisole, xylenes, t-butylmethyl ether, fluorobenzene, ethanol, methanol and isopropanol.

15 The reaction is advantageously carried out in a temperature range from -20°C to 80°C. The preferred temperature is between 0°C and 30°C.

Step (C) comprises

20 Reacting a compound of formula (IV) with a compound of formula (IX) in the presence of an appropriate base in an appropriate solvent (or diluent). The ratio of the compound of formula (IX) used, compared to the compound of formula (IV), is in the range from 3:1 to 1:1, preferably between 1.5:1 and 1:1, more preferably between 1.2:1 and 1:1.

25 Example of suitable and preferred bases for step C are trialkylamines such as triethylamine and tributylamine, alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal hydroxide such as potassium hydroxide and sodium hydroxide. Preferably the base is a trialkylamine, more preferably triethylamine. The ratio of a base used, compared to sulfonyl chloride of formula (IX), is from 1.5:1 to 1:1, more preferably between 1.2:1 and 1:1.

Examples of suitable and preferred solvents (or diluents) for step C are esters, nitriles, ethers, and aliphatic, aromatic or halogenated hydrocarbons.

30 Examples include but are not limited to: tetrahydrofuran, 2-methyl tetrahydrofuran, acetonitrile, butyronitrile, dichloromethane, 1,2-dichloroethane, chlorobenzene, ethyl acetate, toluene, xylenes, dioxane, cyclopentylmethyl ether, t-butylmethyl ether, diethyl ether, anisole, fluorobenzene.

Preferably the solvent is an ether, nitrile or a halogenated hydrocarbon, for example: tetrahydrofuran, 2-methyl tetrahydrofuran, acetonitrile, dichloromethane and chlorobenzene.

Step (D) comprises

- 5 A thermal rearrangement of compounds of formula (V) to compounds of formula (VI) in a suitable solvent (or diluent) at an appropriate temperature.

Suitable solvents (or diluents) are polar aprotic solvents, nitriles, esters, ketones, alcohols, aromatic hydrocarbons, carbonates and ethers or mixtures thereof.

- 10 Examples of appropriate and preferred solvents include but are not limited to: acetonitrile, butyronitrile, benzonitrile, ethylene glycol, methanol, ethanol, methyl isobutyl ketone, nitrobenzene, trifluorotoluene, polyethelene glycol, n-propanol, 2-methoxyethanol, chlorobenzene, tetrahydrofuran, 2-methyl-tetrahydrofuran, 1,4-dioxane, anisole, N,N-dimethyl formamide, N-methyl pyrrolidine, sulfolane, 2,5-dimethyl isosorbide, dimethyl acetamide, cyrene, or mixture thereof.

More preferably the solvent (or diluent) is N-methyl pyrrolidine, sulfolane, acetonitrile, ethylene glycol, ethanol, n-propanol, or mixtures thereof.

- 15 The rearrangement is advantageously carried out in a temperature range from 0°C to 150°C. The preferred temperature is dependent on the electronic nature of R⁵ substituent. If R⁵ is highly electron withdrawing (for example 2,4-dinitro phenyl) the appropriate reaction temperature is in the range from 0°C to 40°C. Whereas, if R⁵ is neutral (for example methyl) or moderately electron withdrawing (for example tosyl) the preferred temperature is between 60°C and 100°C.

- 20 In one embodiment related to the process according to the invention of making compounds of formula (VI), steps (C) and (D) could be advantageously carried out in one pot without isolating intermediate compound of formula (V). This is most preferable when R₅ in sulfonyl chloride of formula (IX) is highly electron withdrawing (for example 2,4-dinitrophenyl).

Step (E) comprises

- 25 Reacting a compound of formula (VI) with a compound of formula (VII) in an appropriate solvent (or diluent) at an appropriate temperature to produce a compound of formula (I) via an intermediate compound of formula (VIII). The ratio of the compound of formula (VII) used, compared to the compound of formula (VI), is in the range from 2:1 to 1:1, preferably between 1.5:1 and 1:1, more preferably between 1.2:1 and 1:1.

- 30 Suitable solvents (or diluents) are polar aprotic solvents, nitriles, esters, ketones, alcohols, aromatic hydrocarbons, carbonates, and ethers, or mixtures thereof.

Examples of appropriate and preferred solvents include but are not limited to: acetonitrile, butyronitrile, benzonitrile, ethylene glycol, methanol, ethanol, n-butanol, n-propanol, 2-methoxyethanol, methyl isobutyl ketone, nitrobenzene, trifluorotoluene, polyethelene glycol, chlorobenzene, tetrahydrofuran, 2-methyl-

tetrahydrofuran, 1,4-dioxane, anisole, N,N-dimethyl formamide, N-methyl pyrrolidine, sulfolane, 2,5-dimethyl isosorbide, dimethyl acetamide, cyrene, or mixture thereof.

The condensation rearrangement cascade is advantageously carried out in a temperature range from 20°C to 150°C. The preferred temperature is between 60°C and 100°C.

- 5 In one embodiment related to the process according to the invention of making compounds of formula (I) steps D and E could be advantageously carried out in one pot without isolating intermediate compounds of formula (VI) and (VIII).

In another embodiment related to the process according to the invention of making compounds of formula (I) steps D and E could be advantageously carried out in one pot in the presence of an appropriate acidic additive.

- 10 The most preferred additive is citric acid. The preferred molar percentage of acidic additive versus the product of step C is between 1 and 10 mol%.

The chiral center at sulfur is fully preserved during the entire sequence starting from chiral sulfoxide (after step A). It has been proven that no inversion takes place, that is R sulfoxide of formula (III) leads to R compound of formula (I) and vice versa, by comparing the compound made in experimental procedure 43 with the same compound prepared in WO2022/253841 where its absolute configuration has been established by X-ray crystallography.

- 15

Certain preferred embodiments according to the invention are provided as set out below.

Embodiment 1 provides a process for the preparation of enantiomerically enriched sulfoximines of formula (I) as defined above.

- 20 The compounds of formula (I) described according to the invention are preventively and/or curatively valuable active ingredients in the field of pest control, even at low rates of application, which have a very favorable biocidal spectrum and are well tolerated by warm-blooded species, fish, and plants.

EXAMPLES

- 25 The following examples further illustrate, but do not limit, the invention. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

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.

- 30

ABBREVIATIONS

CDCl₃ deuterated chloroform

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	CPME	cyclopentylmethylether
	DMF	N,N-dimethylformamide
	DMSO	dimethyl sulfoxide
	EtOAc	ethyl acetate
5	HCl	hydrochloric acid
	h/hrs	hour/hours
	LC-MS	Liquid Chromatography Mass Spectrometry (LC-MS, LCMS or LC/MS)
	MeCN	acetonitrile (MeCN or ACN)
	min	minutes
10	MeTHF	2-methyl tetrahydrofuran
	NaHCO ₃	sodium hydrogencarbonate
	Na ₂ CO ₃	sodium carbonate
	Na ₂ SO ₄	sodium sulphate
	rt	room temperature
15	Rt	retention time
	sat.	saturated
	TEA	triethylamine (TEA or Et ₃ N)
	THF	tetrahydrofuran

20 PREPARATION EXAMPLES

The compound of formula (I) according to the invention may be prepared using the synthetic techniques described both above and below.

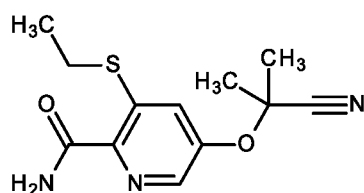
Throughout this description, temperatures are given in degrees Celsius [°C] and “m.p.” means melting point. LC/MS means Liquid Chromatography Mass Spectroscopy.

25 As used herein, the term “room temperature” or “RT” or “rt” or “ambient temperature” 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.

¹H NMR and ¹⁹F NMR measurements were recorded on a Bruker 400MHz spectrometer, chemical shifts are given in ppm relevant to a TMS (¹H) and CFC1₃ (¹⁹F) standard. Spectra were measured in deuterated solvents as indicated.

30 SYNTHESIS OF SULFIDE STARTING MATERIALS

Example 1: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carboxamide

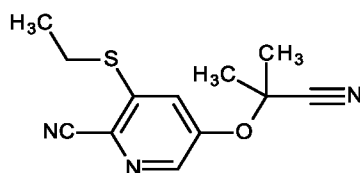


-17-

To a suspension of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carboxylic acid (1.00 g, 98% purity, 3.68 mmol) in EtOAc (9.0 mL) was added few drops of DMF. Oxalyl chloride (0.360 mL, 4.05 mmol) was added to this reaction mixture drop wise at rt over 2 hrs. Thus prepared acid chloride solution was slowly dosed to a biphasic mixture of NaHCO₃ (0.372 g, 4.42 mmol), water (2.7 mL), EtOAc (2.5 mL) and ammonium hydroxide
5 in water (4.31 g, 36.9 mmol) and cooled to 0°C. After addition the reaction mixture was stirred for further 1 h at rt. Phases were separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to yield the title compound (1.00 g, 83% purity, 85% yield) as a brown solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (d, *J*=2.3 Hz, 1H), 7.99 (s, 1H), 7.54 (m, 2H), 2.89 (q, *J*=7.3 Hz, 2H),
10 1.77 (s, 6H), 1.27 (t, *J*=7.3 Hz, 3H).

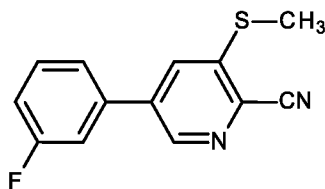
Example 2: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carbonitrile



To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carboxamide (10.0 g, 87.5% purity, 33.0 mmol) and TEA (18 mL, 132 mmol) in THF (100 mL) was added trifluoro acetic anhydride (14.1 mL, 80.42
15 mmol) dropwise over the period of 15 minutes at 0°C. After complete addition the reaction mixture was allowed to warm to rt. After 1 h of stirring water and saturated NaHCO₃ was slowly added. The aqueous layer was extracted with EtOAc, and the combined organic layers washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using cyclohexane and EtOAc as an eluent to yield the title compound (8.98 g, 82% purity, 90% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.38 (d, *J*=2.4 Hz, 1 H), 7.74 (d, *J*=2.4 Hz, 1H), 3.20 (q, *J*=7.3 Hz, 2 H), 1.81
20 (s, 6H), 1.29 (t, *J*=7.3 Hz, 3H).

Example 3: Preparation of 5-(3-fluorophenyl)-3-methylsulfanyl-pyridine-2-carbonitrile

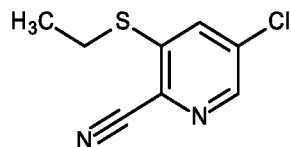


To a solution of 3-chloro-5-(3-fluorophenyl)pyridine-2-carbonitrile (3.47 g, 94.5% purity, 14.1 mmol) in tetrahydrofuran (17 mL) was added sodium methanethiolate (2.6 g, 35.2 mmol). The reaction mixture was
25 stirred at 60°C for 2 hrs followed cooling to rt and quenching with ice cold water. The resulting mixture was extracted with EtOAc, the combined organic layers washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using EtOAc and cyclohexane as an eluent to yield the title compound (2.60 g, 94% purity, 71% yield) as a brown solid.

-18-

¹H NMR (400 MHz, DMSO-d₆) δ 8.83 (d, *J*=2.0 Hz, 1H), 8.13 (d, *J*=1.83 Hz, 1H), 7.78-7.83 (m, 1H), 7.73 (d, *J*=7.5 Hz, 1H), 7.56 - 7.63 (m, 1H), 7.35 (d, *J*=2.6 Hz, 1H), 2.74 (s, 3H)

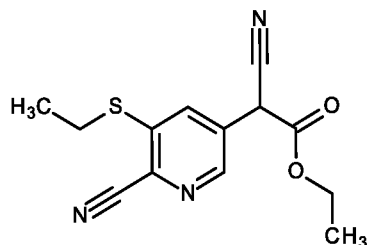
Example 4: Preparation of 5-chloro-3-ethylsulfanyl-pyridine-2-carbonitrile



- 5 To a solution of 5-chloro-3-ethylsulfanyl-pyridine-2-carboxamide (15.0 g, 97% purity, 67.0 mmol) and TEA (23.5 mL, 167.5 mmol) in dry THF (255 mL) was added trifluoro acetic anhydride (11.3 mL, 80.4 mmol) over 15 min while keeping the internal temperature under 5°C. The reaction mixture was allowed to warm to rt and stirred for further 2 h. Most of THF was evaporated under reduced pressure and water (45 mL) was slowly added. The obtained brown precipitate was filtered and washed on filter with cold water. The precipitate was dissolved in
- 10 acetone (60 mL) and the solution was slowly added to water (150 mL) under vigorous stirring. The obtained light brown colored precipitate was filtered and dried under reduced pressured to afford the title compound (13.25 g, 97% purity, 97% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, *J*=2.1 Hz, 1H), 7.66 (d, *J*=2.1 Hz, 1H), 3.07 (q, *J*=7.3 Hz, 2 H), 1.41 (t, *J*=7.4 Hz, 3 H).

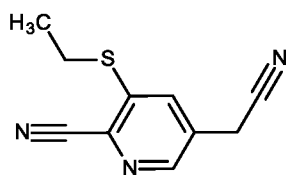
- 15 Example 5: Preparation of 2-cyano-2-(6-cyano-5-ethylsulfanyl-3-pyridyl) acetate



- To a solution of 5-chloro-3-ethylsulfanyl-pyridine-2-carbonitrile (20.0 g, 97% purity, 97.6 mmol) in dry DMF (100 mL) was added powdered potassium carbonate (34.4 g, 244 mmol). The resulting suspension was then heated at 100°C and ethyl cyanoacetate (15.9 mL, 146 mmol) was dosed over a period of 1 h. After full consumption
- 20 of starting material, the reaction mixture was cooled to rt, diluted with EtOAc and the precipitate (inorganic salts) was filtered off. The filtrate was neutralized using aqueous 2N HCl and the resulting mixture was extracted with EtOAc. The combined organic layer was washed with water, dried over Na₂SO₄ and evaporated under reduced pressure. The crude residue was purified using by silica gel chromatography using EtOAc and cyclohexane as an eluent to afford the title compound (19.12 g, 95.5% purity, 87% yield) as a gray solid.
- 25 ¹H NMR (400 MHz, CD₃CN) δ 8.50 (d, *J*=2.0 Hz, 1H), 7.90 (d, *J*=2.0 Hz, 1 H), 5.21 (s, 1 H), 4.23 (q, *J*=7.1 Hz, 2 H), 3.14 (q, *J*=7.4 Hz, 2 H), 1.34 (t, *J*=7.3 Hz, 3 H), 1.24 (t, *J*=7.1 Hz, 3 H).

Example 6: Preparation of 5-(cyanomethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile

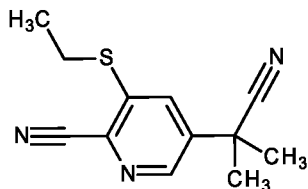
-19-



To a solution of ethyl 2-cyano-2-(6-cyano-5-ethylsulfanyl-3-pyridyl) acetate (10.00 g, 95% purity, 34.51 mmol) in a mixture of acetic acid (44 mL) and water (22.5 mL) was added sodium chloride (5.07 g, 86.3 mmol). The reaction mixture was then stirred at 100°C until the full consumption of starting material. The reaction mixture was cooled to rt and cold water (100 mL) was added. The resulting mixture was then neutralized by the portion wise addition of solid NaHCO₃ under vigorous stirring and the neutralized solution was extracted with EtOAc. The combined organic layer was washed with water, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude material was dissolved in acetone (20 mL) and slowly added into water (100 mL) at 0°C under vigorous stirring. The obtained off-white colored precipitate was filtered off, washed on filter with water (50 mL) and dried under reduced pressure to afford the title compound (7.17 g, 93% purity, 95% yield) as an off-white powder.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (d, *J*=1.8 Hz, 1H), 8.04 (d, *J*=1.7 Hz, 1 H), 4.21 (s, 2 H), 3.18 (q, *J*=7.3 Hz, 2 H), 1.30 (t, *J*=7.3 Hz, 3 H).

Example 7: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile



To a solution of 5-(cyanomethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (10.00 g, 96% purity, 47.23 mmol) in MeCN (150 mL) was added Cs₂CO₃ (47.1 g, 141.7 mmol) followed by iodomethane (6.0 mL, 94.5 mmol) and the reaction mixture was stirred at 80°C for 1 hr. After full consumption of starting material, the reaction mixture was cooled to rt and quenched by addition of water. The resulting mixture was extracted with EtOAc, and the combined organic layers washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using cyclohexane and EtOAc as an eluent to yield the title compound (11.45 g, 85% purity, 89% yield) as a white powder.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (d, *J*=2.1 Hz, 1 H), 8.03 (d, *J*=2.2 Hz, 1 H), 3.25 (q, *J*=7.3 Hz, 2 H), 1.78 (s, 6 H), 1.29 (t, *J*=7.3 Hz, 3 H).

PREPARATION OF RACEMIC SULFOXIDES FOR DEVELOPMENT OF CHIRAL ANALYTICAL METHODS:

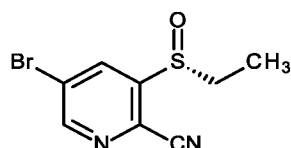
Racemic samples of sulfoxides were prepared according to the following general procedure:

-20-

Sulfide (1 eq) was dissolved in acetic acid (5 mL/mmol) and hydrogen peroxide (1.05 equiv, 30 mass%) was added at rt. The reaction mixture was stirred at 40°C for 20 h or until complete consumption of the starting material was observed by LCMS. Aqueous NaHCO₃ was added dropwise to the reaction mixture followed by EtOAc. The phases were separated, and the aqueous phase was extracted with another portion of EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated to afford the desired sulfoxide. The material was used directly for the development of a chiral HPLC method.

PREPARATION OF ENANTIOENRICHED SULFOXIDES

Example 8: Preparation of 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-bromo-3-ethylsulfanyl-pyridine-2-carbonitrile (2.157 g, 93% purity, 8.25 mmol) in anisole (8.3 ml) was added (2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol) (0.235 g, 97% purity, 0.602 mmol), 4-methoxybenzoic acid (43 mg, 0.28 mmol) and Fe(acac)₃ (0.277 g, 0.0784 mmol). The resulting dark red solution was cooled to 10 °C and 30% aq H₂O₂ (1.35 ml, 13.2 mmol) was added. The resulting biphasic mixture was stirred at 10 °C for 22 h. At this stage (full conversion of starting material) the reaction was quenched by addition of crushed ice (4 g) and 40% aq NaHSO₃ (2.6 ml). After warming to rt, the mixture was diluted with EtOAc (8 ml) and treated with 1M aqueous H₂SO₄ (0.83 ml). After stirring for 30 min, the phases were separated, organic phase washed with aqueous NaHCO₃ (8 ml) and brine (8 ml), and the organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to yield a crude product. Quantitative NMR analysis using 1,3,5-trimethoxy benzene as an internal standard indicates a chemical yield of 91% for the desired 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile. The crude product was purified by a reverse phase HPLC (MeCN/water/0.1% formic acid mobile phase) to yield the title compound (1.63 g, >99% purity, >99.5% ee, 76% isolated yield) as a white powder.

¹H NMR (400 MHz, CDCl₃) δ 1.32 (t, J=7.45 Hz, 3 H), 2.99 (dq, J=14.0, 7.2 Hz, 1 H), 3.15 - 3.36 (m, 1 H), 8.50 (d, J=2.2 Hz, 1 H), 8.85 (d, J=2.2 Hz, 1 H)

Chiral SFC method : Waters Acquity UPC²/QDa; PDA Detector Waters Acquity UPC²; Column: Daicel SFC CHIRALPAK® IC, 3μm, 0.3cm x 10cm, 40°C; Mobile phase:A: CO₂ B: IPA gradient: 20-60% B in 2 min; ABPR: 1800 psi; Flow rate: 2.0 ml/min; Detection: 240 nm; Sample concentration: 1 mg/mL in MeCN; Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 1.14	Retention time (min) ~ 1.35
Enantiomeric excess: >99.5% (R enantiomer, S enantiomer below HPLC detection limits)	

A single crystal grown from di-isopropyl ether was selected for X-ray data analysis. The crystal sample mounted had dimensions of 0.4 mm x 0.3 mm x 0.3 mm and was a colorless prism. Data collection was performed on a

Rigaku Oxford Diffraction Supernova diffractometer at 293 K. The unit cell was determined to be orthorhombic (space group $P2_12_12_1$), and the structure contained one molecule in the crystal asymmetric unit (Figure 1, a thin stick representation labelled by chirality. Figure 1 generated in Flare software package). The stereochemistry was unambiguously determined to be the R isomer, with a Flack parameter of 0.02 ± 0.03 .

- 5 Crystallographic data is summarized in Table 1 and selected geometric parameters are listed in Table 2.

Table 1. Crystal data and structure refinement for 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile

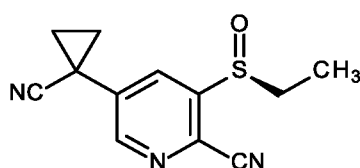
Chemical formula	$C_8H_7BrN_2OS$
M_r	259.13
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	293
a, b, c (Å)	6.7404 (2), 9.2441 (3), 15.8051 (5)
V (Å ³)	984.80 (6)
Z	4
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	7.37
Crystal size (mm)	$0.40 \times 0.30 \times 0.30$
Data collection	
Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan <i>CrysAlis PRO</i> , (Agilent, 2011)
T_{min}, T_{max}	0.11, 0.11
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	4140, 2032, 1962
R_{int}	0.037
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.632
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.041, 0.117, 0.91
No. of reflections	2024
No. of parameters	120
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}, \Delta\rho_{min}$ (e Å ⁻³)	0.40, -0.72
Absolute structure	Flack (1983), 814 Friedel-pairs
Absolute structure parameter	0.02 (3)

Computer programs: SuperNova, (Oxford Diffraction, 2010), CrysAlis PRO, (Agilent, 2011), SIR92 (Altomare et al., 1994), CRYSTALS (Betteridge et al., 2003), CAMERON (Watkin et al., 1996)

Table 2. Selected geometric parameters (Å, °)

Br1—C2	1.874 (4)	S5—C7	1.806 (4)
C2—C3	1.380 (5)	C7—C8	1.510 (6)
C2—C11	1.394 (6)	C9—N10	1.341 (4)
C3—C4	1.392 (5)	C9—C12	1.436 (5)
C4—S5	1.808 (3)	N10—C11	1.328 (5)
C4—C9	1.388 (5)	C12—N13	1.153 (6)
S5—O6	1.491 (3)		
Br1—C2—C3	121.0 (3)	O6—S5—C7	107.64 (19)
Br1—C2—C11	118.8 (2)	S5—C7—C8	114.3 (3)
C3—C2—C11	120.3 (3)	C4—C9—N10	123.7 (3)
C2—C3—C4	117.2 (3)	C4—C9—C12	121.2 (3)
C3—C4—S5	118.3 (3)	N10—C9—C12	115.1 (3)
C3—C4—C9	118.9 (3)	C9—N10—C11	117.3 (3)
S5—C4—C9	122.6 (3)	C2—C11—N10	122.6 (3)
C4—S5—O6	105.15 (17)	C9—C12—N13	179.2 (4)
C4—S5—C7	98.29 (15)		

5 Example 9a: Preparation of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfonyl-pyridine-2-carbonitrile (241.5 mg, 95% purity, 1.00 mmol), Fe(acac)₃ (17.5 mg, 0.0500 mmol), 4-methoxybenzoic acid (3.8 mg, 0.0250 mmol) and 2-[(E)-[(1S)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-diiodo-phenol (48.8 mg, 97% purity, 0.100 mmol) in PhMe (4.0 ml) was added 30% aq H₂O₂ (0.20 ml, 2.00 mmol) at rt. After stirring vigorously for 2.5 h the reaction mixture was poured into EtOAc (23 ml) and quenched by addition of 1.0M Na₂S₂O₃ (2.4 ml). Phases were separated and the organic phase was washed with 1.0M HCl (2.3 ml) and aq NaHCO₃. The organic phase was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN/0.1% formic acid mobile phase) to yield the title compound (234 mg, 97% ee, 95% yield) as a white powder.

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¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (d, *J* = 2.3 Hz, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 3.26 (dq, *J* = 13.6, 7.3 Hz, 1H), 3.04 (dq, *J* = 13.6, 7.3 Hz, 1H), 2.09 – 1.79 (m, 4H), 1.12 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, d₆-DMSO) δ = 165.7, 146.0, 144.4, 142.8, 136.0, 131.1, 121.2, 48.9, 19.2, 12.0, 6.3.

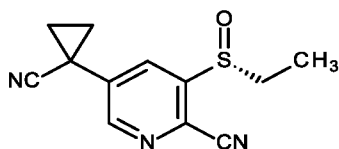
Chiral SFC method: Waters Acquity UPC²/QDa; PDA Detector Waters Acquity UPC²; Column: Daicel SFC

- 5 CHIRALPAK® IA, 3μm, 0.3cm x 10cm, 40°C; Mobile phase: A: CO₂ B: IPA gradient: 20-60% B in 1.8 min; ABPR: 1800 psi; Flow rate: 2.0 ml/min; Detection: DAD 210-500 nm; Sample preparation: dissolved in MeOH; Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.59	Retention time (min) ~ 1.04
Enantiomeric excess: 97% (S enantiomer)	

- 10 Example 9b: Preparation of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



- To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfinyl-pyridine-2-carbonitrile (237.0 mg, 97% purity, 1.00 mmol), Fe(acac)₃ (3.6 mg, 0.0101 mmol), 4-methoxybenzoic acid (3.8 mg, 0.0251 mmol) and 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dichloro-phenol (32.8 mg, 98% purity, 0.110 mmol) in PhOMe (1.0 ml) was added 30% aq H₂O₂ (0.23 ml, 2.11 mmol) at 0°C over 1 h using a syringe pump. The resulting reaction mixture was stirred for further 20 h at the same temperature. The reaction mixture was poured into EtOAc (23 ml) and quenched by addition of 1.0M NaHSO₃ (2.4 ml). Phases were separated and the organic phase was washed with 1.0M HCl (2.3 ml) and aq NaHCO₃. The organic phase was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN/0.1% formic acid mobile phase) to yield the title compound (230 mg, >99.5% ee, 93% yield) as a white powder.

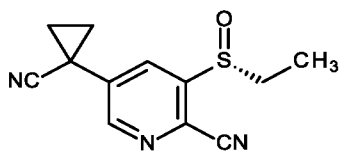
Chiral SFC method: Identical to Example 9a

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.59	Retention time (min) ~ 1.04
Enantiomeric excess: >99.5% (R enantiomer)	

- 25 Example 9c: Preparation of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile

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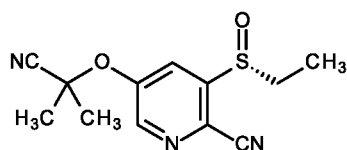
To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (10.61 g, 98% purity, 45.5 mmol), Fe(acac)₃ (0.153 g, 0.432 mmol), 4-methoxybenzoic acid (0.234 g, 1.54 mmol) and 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol (1.281 g, 97% purity, 3.30 mmol) in anisole (46 ml) was added 30% aq H₂O₂ (7.8 ml, 76.3 mmol) at 10°C over 2 h using a syringe pump. The resulting reaction mixture was stirred vigorously for further 22 h at the same temperature. The reaction was quenched by addition of 40% aq NaHSO₃ (10.6 ml) and diluted with anisole (53 ml). Phase were separated and the organic phase was washed with 1M H₂SO₄ (21 ml), aq saturated NaHCO₃ (21 ml) and brine (21 ml). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN as a mobile phase) to yield the title compound (10.44 g, >99.5% ee, 93% yield) as a white powder.

Chiral SFC method: Waters Acquity UPC²/QDa; PDA Detector Waters Acquity UPC²; Column: Daicel SFC CHIRALPAK® IA, 3μm, 0.3cm x 10cm, 40°C; Mobile phase: A:CO₂ B: IPA, gradient: 5-20% B in 9.8 min; ABPR: 1800 psi; Flow rate: 2.0 ml/min; Detection: 238 nm; Sample preparation: 1mg/mL in MeCN; Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 3.07	Retention time (min) ~ 5.73
Enantiomeric excess: >99.5% (R enantiomer)	

Example 10: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carbonitrile (2.00 g, 82% purity, 6.64 mmol), iron(III) acetylacetonate (46.9 mg, 0.133 mmol), 2,4-dichloro-6-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]phenol (0.602 g, 1.99 mmol), p-anisic acid (51 mg, 0.332 mmol) in toluene (13 mL) was added 30% aq H₂O₂ (1.36 ml, 50.1 mmol) at rt over 1h. The reaction mixture was stirred for further 5 h and then quenched by adding aqueous sat. sodium thiosulphate at 0°C. The organic layer was separated, aqueous layer extracted with EtOAc, and the combined organic layers washed with brine, dried over Na₂SO₄, concentrated under reduced pressure to get the crude compound. The crude material was purified by silica gel chromatography using cyclohexane and EtOAc as an eluent to yield the title compound (1.55 g, 89% purity, >99.5% ee, 79% yield).

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¹H NMR (400 MHz, DMSO-d₆) δ 8.71 (d, *J*=2.6 Hz, 1H) 8.02 (d, *J*=2.75 Hz, 1H) 3.28 - 3.33 (m, 1H) 2.96-3.02 (m, 1H), 1.84 (s, 6H), 1.09 (t, *J*=7.3 Hz, 3H).

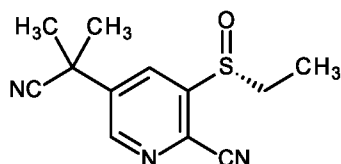
Method of chiral analysis: Chiral HPLC: WATERS ACQUITY UPLC; Column: Chiralpack-IA (4.6mm x 250mm) 5μm; Mobile phase: A: TBME B: IPA isocratic: 20% B in 13 min; Flow rate: 1.0 ml/min; Detection: 240 nm;

5 Sample preparation: 1mg/mL in EtOH; Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 5.32	Retention time (min) ~ 6.8
Enantiomeric excess: >99.5% (R enantiomer, opposite enantiomer below HPLC detection limits)	

Example 11: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



10 To a solution of 5-(1-cyano-1-methyl-ethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (6.00 g, 96.5% purity, 25.0 mmol), iron(III) acetylacetonate (0.177 g, 0.5 mmol), 2,4-dibromo-6-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]phenol (1.47 g, 3.75 mmol) in toluene (90 mL) was added 30% aqueous hydrogen peroxide (2.0 equiv., 50.1 mmol) drop wise over 1h at 0°C. The reaction mixture was stirred for 2 h at 24°C and then quenched by adding saturated Na₂S₂O₃ at 0°C. The organic layer was separated, the aqueous layer extracted

15 with EtOAc, and the combined organic layers washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to obtain the crude product. The crude material was purified by column chromatography using cyclohexane and EtOAc as an eluent to yield the title compound (5.48 g, 91% purity, 97% ee, 81% yield).

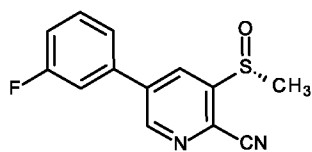
¹H NMR (400 MHz, DMSO-d₆) δ 9.10 (d, *J*=2.3 Hz, 1H), 8.35 (d, *J*=2.3 Hz, 1H), 3.28 (m, 1H), 3.04 (m, 1H), 1.82 (d, *J*=1.9 Hz, 6H), 1.12 (t, *J*=7.3 Hz, 3H)

20 Method of chiral analysis: Chiral HPLC: WATERS ACQUITY UPLC; Column: Chiralpack-IC (4.6mm x 250mm) 5μm; Mobile phase: A: n-hexane B: EtOH isocratic: 30% B in in 30 min; Flow rate: 1.0 ml/min; Detection: 225 nm; Sample preparation: 1mg/mL in EtOH ; Injection: 2 μL

Results:

R enantiomer	S enantiomer
Retention time (min) ~ 18.2	Retention time (min) ~ 21.8
Enantiomeric excess: 97% (R enantiomer)	

25 Example 12: Preparation of 5-(3-fluorophenyl)-3-[(R)-methylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(3-fluorophenyl)-3-methylsulfonylpyridine-2-carbonitrile (0.800 g, 90% purity, 2.95 mmol), iron(III) acetylacetonate (10.4 mg, 0.0295 mmol), 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethylpropyl]iminomethyl]-4,6-diiodo-phenol (0.213 g, 0.442 mmol), p-anisic acid (11.3 mg, 0.0737 mmol) in toluene (6.0 ml) was added 30% aq H₂O₂ (0.6 mL, 5.9 mmol) drop wise over 15 min, and the reaction mixture was continued to stir for further 1 hr. The reaction mixture was quenched by saturated sodium thiosulphate, the resulting mixture extracted with EtOAc, and the combined organic layers washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to get crude material. Purification by silica gel chromatography using cyclohexane and EtOAc as an eluent yielded the title compound (0.73 g, 94% purity, 97% ee, 89% yield).

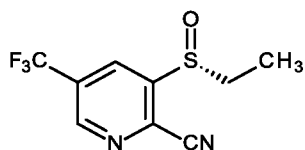
¹H NMR (400 MHz, DMSO-d₆) δ 9.29 (d, J=2.1 Hz, 1H), 8.64 (d, J=2.1 Hz, 1H), 7.89 (m, 1 H), 7.80 (d, J=7.8 Hz, 1H), 7.64 (m, 1H), 7.41 (m, 1H), 3.04 (s, 3 H)

Method of chiral analysis: Chiral HPLC: WATERS ACQUITY UPLC; Column: Chiralpack-IA (4.6mm x 250mm) 5µm; Mobile phase: A: TBME B: IPA isocratic: 30% B in 30 min; Flow rate: 1.0 ml/min; Detection: 225 nm; Sample preparation: 1mg/mL in EtOH; Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 11.0	Retention time (min) ~ 14.9
Enantiomeric excess: 97% (R enantiomer)	

Example 13: Preparation of 3-[(R)-ethylsulfinyl]-5-(trifluoromethyl)pyridine-2-carbonitrile



To a solution of 3-ethylsulfinyl-3-(trifluoromethyl)pyridine-2-carbonitrile (0.237 g, 98% purity, 1.00 mmol) in anisole (1.0 ml) was added (2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol) (28.5 mg, 97% purity, 0.073 mmol), 4-methoxybenzoic acid (5.3 mg, 0.034 mmol) and Fe(acac)₃ (3.4 mg, 0.010 mmol). The resulting dark red solution was cooled to 10°C and 30% aq H₂O₂ (0.136 ml, 1.6 mmol) was added. The resulting biphasic mixture was stirred at 10°C for 22 h. At this stage (full conversion of starting material) the reaction was quenched by addition of crushed ice (4 g) and 40% aq NaHSO₃ (0.30 ml). After warming to rt, the mixture was diluted with EtOAc (10 ml) and treated with conc. H₂SO₄ (50 µl). After stirring for 30 min phases were separated and the aqueous layer was again extracted with EtOAc (15 ml). The combined organic layer was washed with sat. aq. NaHCO₃ (8 ml) and brine (8 ml). The organic layer was dried over

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anhydrous MgSO_4 concentrated under reduced pressure. The crude material was purified by silica gel chromatography (Cyclohexane / EtOAc 100:0 to 60:40) to yield the title compound (127 mg, 98% purity, >99% ee, 50% yield) as a colourless solid.

^1H NMR (400 MHz, CDCl_3) δ 1.27 - 1.40 (m, 3 H), 2.95 - 3.09 (m, 1 H), 3.21 - 3.37 (m, 1 H) 8.65 (d, $J=1.45$ Hz, 1 H), 9.06 (d, $J=1.09$ Hz, 1 H); ^{19}F NMR (377 MHz, CDCl_3) δ -62.80 (s, 3 F)

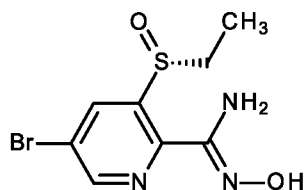
Chiral SFC method: SFC: Waters Acquity UPC²/QDa; PDA Detector Waters Acquity UPC²; Column: Daicel SFC CHIRALPAK[®] IC, 3 μm , 0.3cm x 10cm, 40°C; Mobile phase: A: CO_2 B: MeOH isocratic 3% B in 2 min; ABPR: 1800 psi; Flow rate: 2.0 ml/min; Detection: 270 nm; Sample concentration: 1 mg/mL in MeOH; Injection: 1 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.95	Retention time (min) ~ 1.26
Enantiomeric excess: >99 % (R enantiomer; S enantiomer below HPLC detection limits)	

PREPARATION OF ENANTIOENRICHED AMIDINE OXIMES

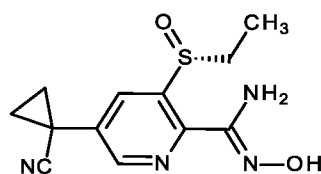
Example 14: Preparation of 5-bromo-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamide



To a solution of 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile (0.774 g, >99% purity, >99.5% ee, 2.99 mmol) in MeTHF (6.0 ml) was added 50% aqueous NH_2OH (0.37 ml, 5.98 mmol) in two portions over 10 min. After stirring for further 20 min most of the solvent was evaporated under reduced pressure (ca 1.2 ml left). CPME (2.7 ml) was added slowly leading to precipitation. The precipitate was filtered, washed on filter with CPME/MeTHF (7:3, 1.5 ml) and dried in vacuum to yield the title compound (0.713 g, 95% purity, 78% yield) as a white powder.

^1H NMR (400 MHz, CDCl_3) δ 1.27 (t, $J=7.45$ Hz, 3 H), 2.93 (dq, $J=13.1$, 7.4 Hz, 1 H), 3.32 (dq, $J=13.1$, 7.5 Hz, 1 H), 5.58 (br s, 2 H), 7.55 (s, 1 H), 8.59 (d, $J=2.2$ Hz, 1 H), 8.68 (d, $J=2.2$ Hz, 1 H).

Example 15: Preparation of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamide



A 100 ml reactor with a mechanical stirring was charged with 5-(1-cyanocyclopropyl)-3-ethylsulfinyl-pyridine-2-carbonitrile (10.60 g, 45.5 mmol, 98% assay), 4-methoxybenzoic acid (0.234 g, 1.54 mmol), $\text{Fe}(\text{acac})_3$ (0.153

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g, 0.432 mmol), 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol (1.30 g, 3.33 mmol, 97% assay) and anisole (45.5 ml). The resulting deep red solution was cooled to 10°C and 30% aq H₂O₂ (7.9 ml, 77.0 mmol) was dosed over 1 h via a syringe pump while stirring vigorously (300 rpm). After the end of dosing the reaction mixture was stirred at the same temperature for further 14 h (full conversion by LC/MS). The reaction was quenched by addition of aq 40% NaHSO₃ (10.6 ml) in two portions (exothermic). After 15 min the reaction temperature was raised to 20 °C and stirred vigorously (600 rpm) for 30 min (reaction color turns bright yellow). Phases were separated and 1M H₂SO₄ (10.6 ml) was added to the organic phase. The resulting mixture was stirred vigorously for 30 min. Phases were again separated and the organic phase was washed with brine (3 x 10 ml) until washings had a pH > 6. The organic phase was dried over Na₂SO₄. After filtration of the drying agent the obtained solution in PhOMe was telescoped to the next step. qNMR analysis using 1,3,5-trimethoxybenzene as an internal standard indicates 92% chemical yield of the chiral sulfoxide as well as ca 3% of the corresponding sulfone (overoxidation). This solution also contains most of the ligand used for oxidation.

A solution of the chiral sulfoxide prepared above (54.4 g) was charged in a 100 ml reactor with a mechanical stirring. In a separate flask a 4.7M solution of NH₂OH was prepared by treating a solution of NH₂OH.HCl with 50% aq NaOH at 0°C (exothermic). Thus, prepared solution (10.0 ml, 47.2 mmol) was dosed to the sulfoxide solution in PhOMe at rt over 1.5 h. After stirring for further 2 h (white crystals in an orange liquid) the precipitate was filtered off and washed on filter with PhOMe (23 ml) and water (2 x 23 ml). The resulting white powder was resuspended in water (51 ml) and stirred vigorously for 1.5 h to yield a stable white suspension. The precipitate was filtered, washed on filter with water (20 ml) and dried under high vacuum overnight to yield the title compound (10.42 g, 97% assay, >99.5% ee, 80% isolated yield over two steps) as a white powder.

¹H NMR (400 MHz, DMSO-d₆) δ 10.42 (s, 1H), 8.59 (d, *J* = 2.3 Hz, 1H), 8.26 (d, *J* = 2.3 Hz, 1H), 6.01 (s, 2H), 3.25 (dq, *J* = 13.0, 7.4 Hz, 1H), 2.77 (dq, *J* = 13.0, 7.4 Hz, 1H), 1.99 – 1.84 (m, 2H), 1.80 – 1.65 (m, 2H), 1.16 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, DMSO-d₆) δ 149.0, 146.1, 145.0, 140.1, 132.9, 131.1, 121.4, 48.8, 18.5, 18.5, 11.7, 6.7

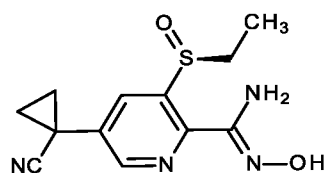
Chiral SFC method: SFC: Waters Acquity UPC²/QDa; PDA Detector Waters Acquity UPC²; Column: Daicel SFC CHIRALPAK® IA, 3μm, 0.3cm x 10cm, 40°C; Mobile phase: A: CO₂ B: MeOH gradient: 20-60% B in 1.8 min; ABPR: 1800 psi; Flow rate: 2.0 ml/min; Detection: 227 nm ; Sample preparation: 1mg/mL in MeOH; Injection: 2 μL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.85	Retention time (min) ~ 1.15
Enantiomeric excess: >99.5% (R enantiomer)	

Example 16: Preparation of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine

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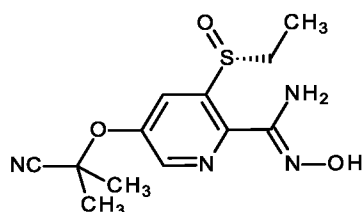
To a suspension of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]pyridine-2-carbonitrile (167.1 mg, 95% purity, 97% ee, 0.648 mmol) in ethanol (1.3 ml) was added 50% aq NH_2OH (0.062 ml, 1.01 mmol). The resulting thick suspension was stirred for 1 h. The solvent was evaporated, and the residue dried under vacuum to yield the title compound (187.4 mg, 92% purity, 97% ee, 96% yield) as a white powder.

Chiral SFC method: see Example 15

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.85	Retention time (min) ~ 1.15
Enantiomeric excess: 97% (S enantiomer)	

Example 17: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine

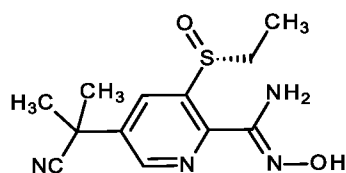


To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfinyl-pyridine-2-carbonitrile (0.500 g, 97% purity, 1.84 mmol) in ethanol (1.3 mL) was added at 0°C 50% aqueous hydroxylamine (1.00 equiv., 1.84 mmol) and the reaction was stirred for further 2 h at rt. An extra portion of 50% aq hydroxylamine (0.20 equiv., 0.368 mmol) was added and the reaction stirred for a further 1 h. EtOAc was added to the reaction mixture, the organic layer was separated, and aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure to yield the title compound (0.54 g, 93% purity, 92% yield)

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.35 (s, 1H), 8.53 (d, $J=2.7$ Hz, 1H), 8.13 (d, $J=2.7$ Hz, 1H), 6.02 (s, 2H), 3.18 - 3.29 (m, 1H), 2.85 (dd, $J=13.1$ Hz, 7.4 Hz, 1H), 1.78 (d, $J=6.0$ Hz, 6 H) 1.11 (t, $J=7.4$ Hz, 3 H)

Example 18: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine

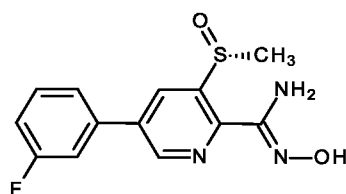
-30-



To a solution of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile (2.00 g, 91% purity, 7.38 mmol) in ethanol (5.0 ml) was added 50% aqueous hydroxylamine (0.52 ml, 8.49 mmol) at rt. After stirring for 1 h at rt an additional portion of 50% aqueous hydroxylamine (0.20 ml, 3.4 mmol) was added. Upon full conversion of the starting material the reaction mixture was concentrated under reduced pressure and product collected via filtration. The product was washed on filter with water and dried under high vacuum to yield the title compound (1.78 g, 93% purity, 81% yield).

^1H NMR (400 MHz, DMSO- d_6) δ 10.45 (s, 1H), 8.87 (d, $J=2.4$ Hz, 1H), 8.39 (d, $J=2.2$ Hz, 1H), 6.06 (s, 2H), 3.21 - 3.31 (m, 1H), 2.78 (m, 1H), 1.79 (s, 6H), 1.15 (t, $J=7.4$ Hz, 3H)

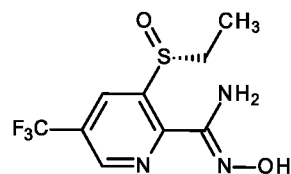
Example 19: Preparation of 5-(3-fluorophenyl) N'-hydroxy-3-[(R)-methylsulfinyl]pyridine-2-carboxamide



To a solution of 5-(3-fluorophenyl)-3-[(R)-methylsulfinyl]pyridine-2-carbonitrile (0.12 g, 94% purity, 0.434 mmol) into ethanol (0.5 mL) was added 50% aqueous hydroxylamine (0.030 mL, 0.434 mmol) at rt. The reaction mixture was stirred for 2 hrs, diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound (0.11 g, 98% purity, 85% yield) as a brown solid.

^1H NMR (400 MHz, DMSO- d_6) δ 10.48 (s, 1 H), 9.06 (d, $J=2.2$ Hz, 1 H), 8.61 (d, $J=2.1$ Hz, 1 H), 7.75 (dt, $J=10.3, 2.2$ Hz, 1 H), 7.67 - 7.71 (m, 1 H), 7.58 - 7.65 (m, 1 H), 7.34 (m, 1H), 6.07 (s, 2 H), 2.90 (s, 3 H)

Example 20: 3-[(R)-ethylsulfinyl]-N'-hydroxy-5-(trifluoromethyl)pyridine-2-carboxamide

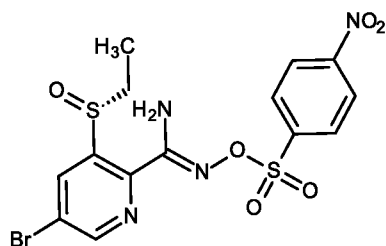


To a solution of 3-[(R)-ethylsulfinyl]-5-(trifluoromethyl)pyridine-2-carbonitrile (800 mg, 3.16 mmol) in EtOH (25 ml) was added 50% aqueous NH_2OH (300 μl , 4.9 mmol). The resulting colorless reaction mixture was stirred at rt for 14 h and was concentrated under reduced pressure to yield the title compound (892 mg, >99% yield) as a colorless solid.

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^1H NMR (400 MHz, CDCl_3) δ 1.18 (t, $J=7.45$ Hz, 3 H) 2.98 - 3.13 (m, 1 H) 3.33 - 3.49 (m, 1 H) 5.68 (s, 2 H) 8.50 - 8.70 (m, 1 H) 8.73 (d, $J=1.8$ Hz, 1 H) 8.91 (d, $J=1.1$ Hz, 1 H); ^{19}F NMR (376 MHz, CDCl_3) δ -62.27 (s, 3 F)

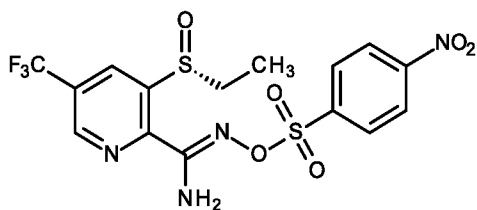
Example 21: Preparation of [(Z)-[amino-[5-bromo-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene] amino] 4-nitrobenzenesulfonate



To a solution of 5-bromo-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamide (0.611 g, 95% purity, 1.99 mmol) in THF (4.0 ml) was added TEA (0.33 ml, 2.39 mmol) followed by NsCl (0.488 g, 2.20 mmol). The reaction mixture was stirred for 3 h at rt. EtOAc (18 ml) was added, and the resulting reaction mixture was washed with water (3.5 ml), 1 M aq HCl (2.5 ml), aq NaHCO_3 (3.5 ml) and brine (5 ml). Additional EtOAc (58 ml) was added to avoid precipitation. The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield the title compound (1.024 g) in a crude form. This material was used in the next step without further purification.

^1H NMR (400 MHz, CDCl_3) δ 1.23 (t, $J=7.4$ Hz, 3H), 2.85 (dq, $J=13.35$, 7.3 Hz, 1 H), 3.27 (dq, $J=13.26$, 7.4 Hz, 1 H), 5.62 (br s, 1 H), 6.61 (br s, 1 H), 8.21 - 8.29 (m, 2 H), 8.39 - 8.48 (m, 2 H), 8.62 (d, $J=2.2$ Hz, 1 H), 8.69 (d, $J=2.2$ Hz, 1 H).

Example 22: Preparation of [(Z)-[amino-[3-[(R)-ethylsulfinyl]-5-(trifluoromethyl)-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate

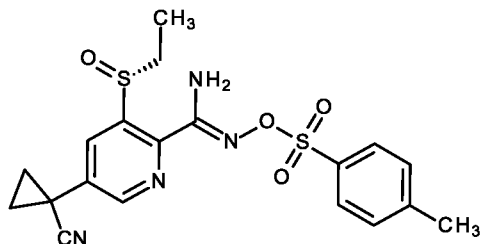


To a solution of 3-[(R)-ethylsulfinyl]-N'-hydroxy-5-(trifluoromethyl)pyridine-2-carboxamide (880 mg, 3.13 mmol) in THF (10 ml) was added TEA (523 μl , 3.75 mmol) followed by nosyl chloride (763 mg, 3.44 mmol). The reaction was stirred at rt for 7 h before being diluted with water (20 ml) and EtOAc (15 ml). Phases were separated and aqueous phase extracted with EtOAc (2 x 15 ml). The combined organic phase was washed with 1N aq. HCl (20 ml) and brine (20 ml). Drying over anhydrous MgSO_4 and concentration under reduced pressure yielded the title compound (1.32 g, 91% yield) as a colorless foam.

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^1H NMR (400 MHz, DMSO- d_6) δ 1.05 (t, J = 7.45 Hz, 3 H) 2.64 - 2.84 (m, 1 H) 2.92 - 3.13 (m, 1 H) 7.42 - 8.07 (m, 2 H) 8.27 (d, J = 8.7 Hz, 2 H) 8.42 - 8.55 (m, 3 H) 9.18 (d, J = 1.1 Hz, 1 H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.22 (s, 3 F)

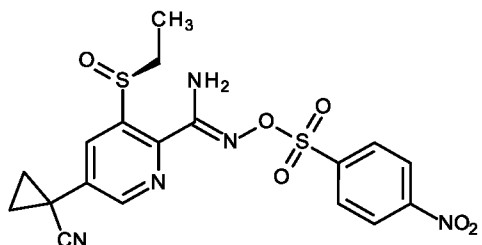
Example 23: Preparation of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]-methylene]-amino] 4-methylbenzenesulfonate



To a suspension of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (14.817 g, 94% purity, 49.9 mmol) in MeCN (50 ml) was added TEA (13.8 ml, 98.8 mmol). After stirring for 10 min p-toluenesulfonyl chloride (pTsCl) (10.13 g, 53.15 mmol) was added in five portions over 20 min. After stirring for 2 h at rt the reaction mixture was diluted with EtOAc (200 ml). The resulting solution was washed with 1M HCl (3 x 40 ml), aq saturated NaHCO_3 (40 ml) and brine (40 ml). The organic layer was dried over anhydrous Na_2SO_4 and solvents partially evaporated at 50 °C and 150 mbar to ca 20 ml. The resulting precipitate was filtered, washed on filter with EtOAc (20 ml) and dried under high vacuum to yield the title compound (14.00 g, 97% purity, 90% yield) as a grey crystalline solid.

^1H NMR (400 MHz, CDCl_3) δ 8.80 (d, J = 2.2 Hz, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 6.58 (s, 1H), 5.68 (s, 1H), 3.18 (qd, J = 7.4, 13.3 Hz, 1H), 2.76 (qd, J = 7.3, 13.3 Hz, 1H), 2.44 (s, 3H), 1.96 - 1.87 (m, 2H), 1.58 (ddd, J = 1.6, 4.2, 5.4 Hz, 2H), 1.15 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.1, 147.6, 145.4, 142.3, 141.8, 135.6, 132.4, 129.9, 129.7, 128.6, 120.4, 48.2, 21.7, 19.5, 19.5, 12.0, 6.2

Example 24: Preparation of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-2-pyridyl]-methylene]-amino] 4-nitrobenzenesulfonate



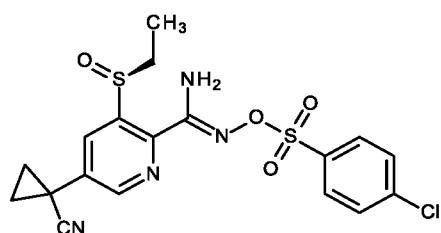
To a suspension of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (2.942 g, 94% purity, 9.92 mmol) in MeTHF (30 ml) was added TEA (2.76 ml, 19.8 mmol) followed by 4-nitrobenzenesulfonyl chloride (2.309 g, 10.42 mmol) in three portions over 10 min. After stirring at rt for 1.5 h the reaction was quenched by addition of water (11 ml). Phases were separated, organic phase washed with 1M HCl (2 x 11 ml) and sat. NaHCO_3 (11 ml), and the organic phase dried over anhydrous Na_2SO_4 and

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evaporated under reduced pressure (30°C, 50 mbar). The foamy residue was redissolved in MeTHF (9 ml) and aged for 1 h. During this time precipitate was formed which was filtered, washed on filter with MTBE and dried under high vacuum to yield the title compound (3.961 g, 93% purity, 85% yield) as an off-white crystalline solid.

¹H NMR (400 MHz, CDCl₃) δ 1.22 (t, J = 7.4 Hz, 3 H) 1.55 - 1.62 (m, 2 H) 1.90 - 1.99 (m, 2 H) 2.79 (dq, J=13.3, 7.3 Hz, 1 H) 3.18 - 3.33 (m, 1 H) 5.44 - 5.84 (m, 1 H) 6.49 - 6.90 (m, 1 H) 8.09 (d, J=2.5 Hz, 1 H) 8.21 - 8.27 (m, 2 H) 8.37 - 8.44 (m, 2 H) 8.83 (d, J=2.5 Hz, 1 H)

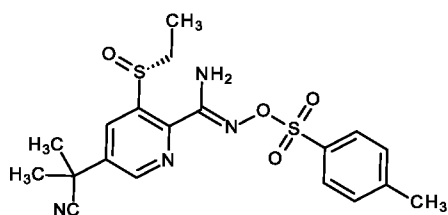
Example 25: Preparation of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-chlorobenzenesulfonate



To a solution of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (111.5 mg, 97% purity, 0.390 mmol) in MeCN (0.4 ml) was added TEA (0.121 ml, 0.872 mmol) and 4-chlorobenzenesulfonyl chloride (103.3 mg, 90% purity, 0.442 mmol). After stirring for 1 h, the reaction mixture was partitioned between EtOAc (10 ml) and sat. NaHCO₃ (10 ml). Phases were separated, the organic phase was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to yield the title compound (202 mg, 87% purity, 99% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 1.18 (t, J=7.4 Hz, 3 H) 1.56 - 1.63 (m, 2 H) 1.88 - 1.96 (m, 2 H) 2.76 (dq, J=13.3, 7.4 Hz, 1 H) 3.15 - 3.29 (m, 1 H) 5.45 - 5.96 (m, 1 H) 6.46 (s, 1 H) 6.49 - 6.82 (m, 1 H) 7.51 - 7.58 (m, 2 H) 7.93 - 8.01 (m, 2 H) 8.08 (d, J=2.2 Hz, 1 H) 8.81 (d, J=2.5 Hz, 1 H)

Example 26: Preparation of [(Z)-[amino-[5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate

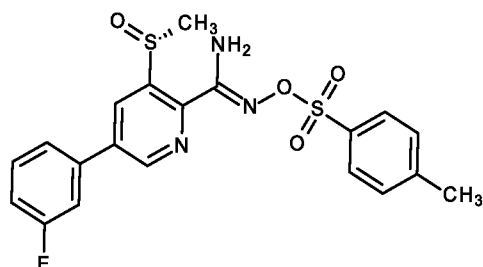


To a solution of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (1.00 g, 83% purity, 2.96 mmol) in Me-THF (10 mL) was added TEA (0.83 mL, 5.92 mmol) and p-toluenesulfonyl chloride (0.624 g, 3.11 mmol) at rt. The reaction mixture was stirred for 2 hrs and quenched by addition of water (10 mL). Layers were separated, the organic phase washed with 2 N HCl and water, and the combined organic layers dried over Na₂SO₄ and concentrated under reduced pressure to yield the title compound (1.63 g, 71.5% purity, 91% yield) as a brown solid.

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¹H NMR (400 MHz, DMSO-*d*₆) δ 8.91 (d, *J*=2.3 Hz, 1H), 8.36 (d, *J*=2.3 Hz, 1H), 7.86 (d, *J*=8.3 Hz, 2H), 7.44 (d, *J*=8.1 Hz, 2H), 6.50 (s, 2H), 2.97 (m, 1H), 2.65 (m, 1H), 2.38 (s, 3H), 1.76 (s, 6H), 1.01 - 1.04 (m, 3H)

Example 27: Preparation of [(*Z*)-[amino-[5-(3-fluorophenyl)-3-[(*R*)-methylsulfinyl]-2-pyridyl]methylene] amino] 4-methylbenzenesulfonate



5

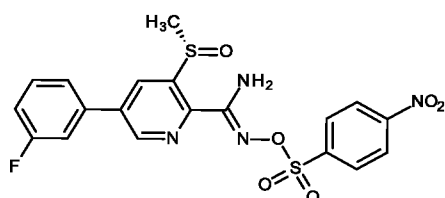
To a solution of 5-(3-fluorophenyl)-*N*'-hydroxy-3-methylsulfinyl-pyridine-2-carboxamidine (0.50 g, 89% purity, 1.51 mmol) in 2-MeTHF (3.0 mL) was added TEA (0.42 mL, 3.0 mmol) and *p*-toluenesulfonyl chloride (0.318 g, 1.58 mmol). The reaction mixture was stirred at rt for 4 hr and quenched by addition of water (10 mL). Layers were separated and the organic phase was washed with 2 N HCl and water. Combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to yield the title compound (0.685 g, 84% purity, 85% yield) as a white solid.

10

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (d, *J*=2.2 Hz, 1H), 8.56 (d, *J*=2.2 Hz, 1H), 7.89 (d, *J*=8.4 Hz, 2H), 7.76 (d, *J*=9.9 Hz, 1H), 7.65 - 7.71 (m, 1H), 7.62 (dd, *J*=8.0, 6.0 Hz, 1H), 7.50 (d, *J*=8.0 Hz, 2H), 7.35 (br d, *J*=2.4 Hz, 1H), 2.65 (s, 3H), 2.42 (s, 3H)

15

Example 28: Preparation of [(*Z*)-[amino-[5-(3-fluorophenyl)-3-[(*S*)-methylsulfinyl]-2-pyridyl]methylene] amino] 4-nitrobenzenesulfonate



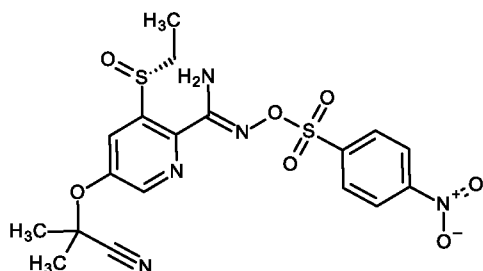
20

To a stirred solution of 5-(3-fluorophenyl)-*N*'-hydroxy-3-[(*S*)-methylsulfinyl]pyridine-2-carboxamidine (1.6 g, 86% purity, 4.69 mmol) and TEA (1.31 mL, 9.38 mmol) in 2-Me-THF (9.4 mL) was added at rt 4-nitrobenzenesulfonyl chloride (1.21 g, 4.93 mmol). After stirring for 4h the reaction mixture was quenched by adding water (10 mL), the organic layer was separated, washed with 2N aq. HCl (5mL) followed by saturated NaHCO₃ solution (10mL), and the combined organic layer dried over Na₂SO₄, and concentrated under reduced pressure to yield the title compound (2.01 g, 92% purity, 82% yield) as pale-yellow solid.

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¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.11 (d, *J*=2.3 Hz, 1 H), 8.57 (d, *J*=2.3 Hz, 1 H), 8.47 - 8.52 (m, 2 H), 8.26 - 8.32 (m, 2 H), 7.80 - 7.85 (m, 1 H), 7.73 - 7.80 (m, 1 H), 7.66 - 7.71 (m, 1 H), 7.60 (td, *J*=7.9, 6.0 Hz, 2 H), 7.31 - 7.38 (m, 1 H), 2.68 (s, 3 H)

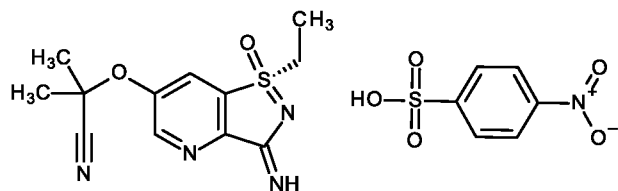
Example 29: Preparation of [(Z)-[amino-[5-(1-cyano-1-methyl-ethoxy)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate



To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamidine (0.500 g, 95% purity, 1.60 mmol) in 2-MeTHF (5.0 mL) was added TEA (0.45 mL, 3.21 mmol) and 4-nitrobenzenesulfonyl chloride (0.393 g, 1.68 mmol) at rt. The reaction mixture was stirred for 2 hrs and quenched by addition of water (5 mL) and 2-MeTHF (5 mL). The phases were separated, the organic phase was washed with 2N HCl and water, and the combined organic phase was further washed with sat. aqueous NaHCO₃ solution (10 mL) and aqueous layer extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and evaporated under reduced pressure to yield the title compound (0.82 g, 81% purity, 81% yield) as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (d, J=2.6 Hz, 1H), 8.46-8.50 (m, 2H), 8.24-8.28 (m, 2H), 8.07 (d, J=2.6 Hz, 1H), 7.83 (br s, 2H), 2.97-3.02 (m, 1H), 2.63 - 2.73 (m, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 0.98 - 1.02 (m, 3H).

Example 30: Preparation of (1R)-6-(1-cyano-1-methyl-ethoxy)-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-ylidene]ammonium 4-nitrobenzenesulfonate

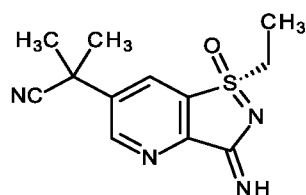


A solution of [(Z)-[amino-[5-(1-cyano-1-methyl-ethoxy)-3-[(R)-ethylsulfinyl]-2-pyridyl] methylene]amino] 4-nitrobenzenesulfonate (0.500 g, 86.5% purity, 0.900 mmol) in MeCN (5 mL) was stirred at 60°C for 2h. After full consumption of starting material, the reaction mixture was evaporated under reduced pressure. The crude material was washed with tert-butyl methyl ether and residue dried under high vacuum to afford the title compound (0.470 g, 86% purity, 99% yield) as an off-white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 10.95 (d, J=5.0 Hz, 2H), 9.04-9.05 (m, 2H), 8.18 - 8.22 (m, 2H), 7.82 - 7.86 (m, 2H), 4.46-4.53 (m, 1H), 4.27-4.32 (m, 1H), 1.90 (s, 6H), 1.41 (t, J=7.4 Hz, 3H).

Example 31: Preparation of 2-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]-2-methyl-propanenitrile

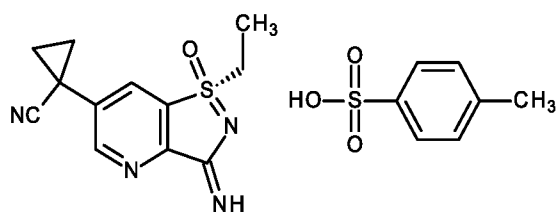
-36-



A solution of [(Z)-[amino-[5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-2-pyridyl] methylene]amino] 4-methylbenzenesulfonate (1.00 g, 70% purity, 1.60 mmol) in MeCN (10 mL) was stirred at 80°C for 18 h and then cooled down to rt and concentrated under reduced pressure. To the resulting residue was added aqueous saturated NaHCO₃ solution and the resulting mixture was extracted with EtOAc. The combined organic layers were concentrated under reduced pressure and purified by silica gel column chromatography using tert-butyl methyl ether and methanol as an eluent to yield the title compound (0.25 g, 85% purity, 50% yield) as a brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 9.26 (d, *J*=2.1 Hz, 1H), 8.95 (d, *J*=2.1 Hz, 1H), 3.91 - 4.15 (m, 2H), 3.13 - 3.19 (s, 1H), 1.84 (s, 3H), 1.83 (s, 3H), 1.09 - 1.25 (t, *J* = 7.4 Hz, 3H)

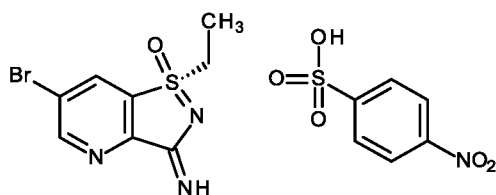
Example 32: Preparation of 1-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]cyclopropane-carbonitrile 4-methylbenzenesulfonic acid salt



A solution of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene] amino] 4-methylbenzenesulfonate (1.99 g, 97% purity, 4.47 mmol) in dry MeCN (8.9 ml) was heated in a sealed tube at 80°C for 18 h. The reaction mixture was evaporated under reduced pressure and the residue purified by a reverse phase silica gel chromatography (0.25-20% MeCN in water) to yield after lyophilization the title compound as a white solid (1.15 g, 85% purity, 51% yield)

¹H NMR (400 MHz, CD₃CN) δ 10.19 (br s, 1H), 9.45 (br s, 1H), 9.07 (d, *J* = 1.8 Hz, 1H), 8.67 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.19 - 3.91 (m, 2H), 2.34 (s, 3H), 2.05 - 1.96 (m, 2H), 1.87 - 1.76 (m, 2H), 1.39 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CD₃CN) δ 168.2, 156.6, 149.5, 145.8, 140.7, 140.2, 133.2, 132.6, 129.5, 126.8, 121.4, 49.9, 21.4, 21.4, 13.6, 7.2

Example 33: Preparation of (1R)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-b]pyridin-3-imine 4-nitrobenzenesulfonic acid salt

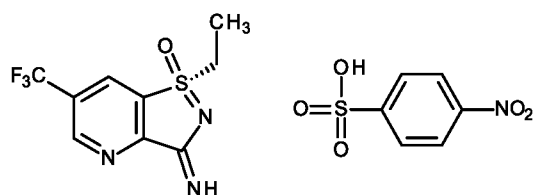


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A solution of [5-bromo-3-[(S)-ethylsulfinyl]pyridine-2-carboximidoyl]amino] 4-nitrobenzene sulfonate (0.50g, 1.04 mmol, 99% purity) in MeCN (4.2 mL) was heated to 80°C. After stirring for 16 h the reaction mixture was concentrated under reduced pressure to yield the title compound (0.40 g, 99% purity, 81% yield) as pale-yellow solid.

- 5 ¹H NMR (400 MHz, DMSO-d₆) δ: 11.05 (br s, 2 H), 9.45 (d, *J*=4.3 Hz, 2 H), 8.17 - 8.22 (m, 2 H), 7.83 (d, *J*=7.8 Hz, 2 H), 4.24 - 4.42 (m, 2 H), 1.44 (t, *J*=7.27 Hz, 3 H)

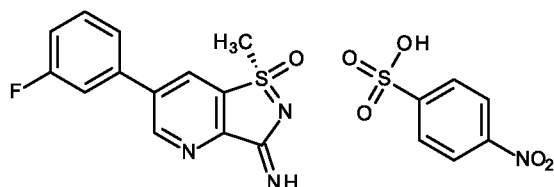
Example 34: Preparation of (1*R*)-1-ethyl-1-oxo-6-(trifluoromethyl)isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt



- 10 A solution of [3-[(S)-ethylsulfinyl]-5-(trifluoromethyl)pyridine-2-carboximidoyl]amino] 4-nitrobenzenesulfonate (1.0 g, 83% purity, 1.78 mmol) in MeCN (1.78 mL) was heated to 80°C. After stirring for 16h the reaction mixture was concentrated under reduced pressure to yield the title compound (1.01 g, 55% purity, 67% yield) as pale-yellow solid.

- 15 ¹H NMR (400 MHz, DMSO-d₆) δ: 11.21 (br s, 1 H), 11.18 (br s, 1 H), 9.76 (s, 1 H), 9.67 (d, *J*=1.4 Hz, 1 H), 8.17 - 8.22 (m, 2 H), 7.80 - 7.86 (m, 2 H), 4.39 - 4.48 (m, 1 H), 4.26 - 4.35 (m, 1 H), 1.47 (t, *J*=7.3 Hz, 2 H)

Example 35: Preparation of (1*R*)-6-(3-fluorophenyl)-1-methyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt

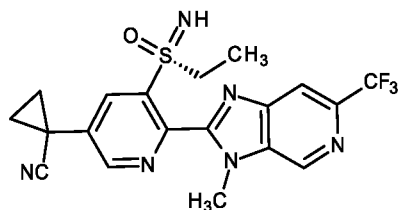


- 20 A solution of [(*Z*)-[amino-[5-(3-fluorophenyl)-3-[(S)-methylsulfinyl]-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate (1.0 g, 92% purity, 1.92 mmol) in MeCN (1.92mL) was heated to 80°C. After stirring for 16 h the reaction mixture was concentrated under reduced pressure to yield the title compound (0.48 g, 82% purity, 43% yield) as brown solid.

- 25 ¹H NMR (400 MHz, DMSO-d₆) δ: 11.00 (s, 1 H), 10.93 (s, 1 H), 9.64 (d, *J*=2.0 Hz, 1 H), 9.45 (d, *J*=2.0 Hz, 1 H), 8.18 - 8.22 (m, 2 H), 7.93 - 7.95 (m, 1 H), 7.91 - 7.92 (m, 1 H), 7.81 - 7.86 (m, 3 H), 7.70 (td, *J*=8.1, 6.1 Hz, 1 H), 7.43 - 7.51 (m, 1 H), 4.21 (s, 3 H)

Example 36a: Preparation of (1*R*)-1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-*c*]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile

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To a stirred solution of 1-[(1*R*)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-*b*]pyridin-6-yl]cyclopropane carbonitrile 4-methylbenzenesulfonic acid salt (0.100 g, 97% purity, 0.23 mmol) in MeCN (0.45 mL) was added at rt *N*3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (0.050 g, 0.25 mmol), and the reaction mixture was heated to 80°C. After stirring for 16 h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.060 g, 98% purity, >99.5% ee, 61% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.26 (s, 1 H), 8.93 (d, *J*=2.4 Hz, 1 H), 8.40 (d, *J*=2.3 Hz, 1 H), 8.28 (s, 1 H), 4.56 (s, 1 H), 3.80 (s, 3 H), 3.58 (dt, *J*=15.04, 7.30 Hz, 2 H), 2.00 - 2.05 (m, 2 H), 1.85 - 1.94 (m, 2 H), 1.15 (t, *J*=7.4 Hz, 3 H)

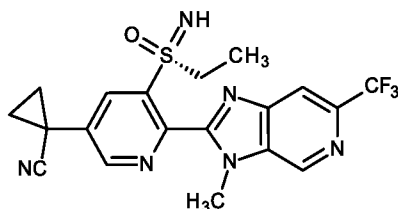
Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5μm; Flow: 1 ml/min; λ_{Max}: 272 nm; Run Time: 15 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.: 5 μL

Mobile Phase	% A (n-Hexane)	% B (EtOH)
Composition	65	35

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 6.98	Retention time (min) ~ 5.70
Enantiomeric excess: >99.5% (1st eluting enantiomer)	

Example 36b: Preparation of (1*R*)-1-[5-(ethylsulfonyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-*c*]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile

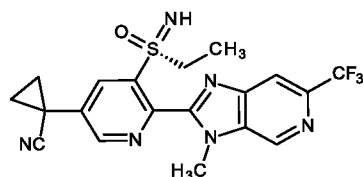


A solution of [(*Z*)-[amino-[5-(1-cyanocyclopropyl)-3-[(*R*)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate (500 mg, 99% purity, 1.14 mmol) in dry MeCN (2.3 ml) was heated at 80°C for 8 h. A solution of *N*3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (240 mg, 1.25 mmol) in dry MeCN (1.1 ml) was then added and the resulting reaction mixture was heated at the same temperature for further 20 h. The solution

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was evaporated under reduced pressure to yield the crude title compound (0.791 g, 41% purity, 65% yield). The crude product was purified via silica gel chromatography using EtOAc and cyclohexane as eluents to yield the title compound (355 mg, 84% purity, >99% ee, 60% yield) as an off-white foam.

Example 36c: Preparation of (1R)-1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile



Step 1: To a suspension of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamide (7.89 g, 96.8% purity, 27.4 mmol) in dry THF (27.4 mL) was added TEA (4.2 mL, 30.2 mmol) at rt under Argon. A solution of p-toluenesulfonyl chloride (5.50 g, 28.0 mmol) in THF (27.4 mL) was slowly added over 5 min while keeping the temperature below 20°C. The resulting suspension was stirred at rt for 16 h. The precipitate (Et₃N.HCl) was filtered over celite and washed with a small amount of dry THF. The filtrate (58.17 g) containing [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate (19% w/w%, 93% chemical yield) was used for the next step without any purification.

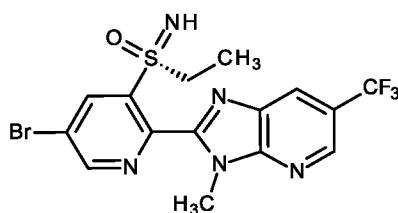
Step 2: A solution prepared in Step 1 was concentrated to about 1/3 volume under reduced pressure. Dry MeCN (20 ml) was added and about half of the volume was evaporated under reduced pressure. This procedure was repeated one more time. N3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine

(6.03 g, 30.6 mmol) and citric acid (0.25 g, 1.28 mmol) were then added. The solvent swap with MeCN was carried out one more time and finally MeCN amount was adjusted to have ca 1M concentration for Step 1 product. The resulting light suspension was stirred at 67°C for 17 h and at 74°C for further 8 h. The resulting thick suspension was diluted with MeCN (12.5 ml) and allowed to cool to 50°C. At this temperature the precipitate (NH₄OTs) was filtered off and the filtrate evaporated under reduced pressure to yield a crude title compound (65% purity, 80% chemical yield from step 1 product).

The crude material was suspended in n-PrOH (152 ml) and the mixture heated to reflux (97°C) resulting in dissolution of all material. After 10 min the solution was slowly cooled to 50°C over 40 min, seed crystals were added, and the mixture was stirred for further 30 min before cooling to rt over 1 h. The precipitate was filtered and washed on filter with n-PrOH (2 x 20 mL). The precipitate was then dried under high vacuum to yield the title compound (7.93 g, 97% purity, >99.5% ee, 69% isolated yield from step 1 product) as a beige solid.

Example 37: Preparation of R-[5-bromo-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]-ethyl-imino-oxo-λ⁶-sulfane

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To a stirred solution of (1*R*)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt (0.100 g, 99% purity, 0.22 mmol) in MeCN (0.45 mL) was added at rt *N*2-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (0.047 g, 0.24 mmol), and the reaction mixture was heated to 80°C. After stirring for 16 h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.045 g, 94% purity, 99% ee, 43% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.22 (d, *J*=2.1 Hz, 1 H), 8.87 (d, *J*=1.5 Hz, 1 H), 8.65 (dd, *J* = 8.6, 1.9 Hz, 2 H), 3.73 (s, 3 H), 3.54 - 3.71 (m, 2 H), 1.18 (t, *J*=7.4 Hz, 3 H)

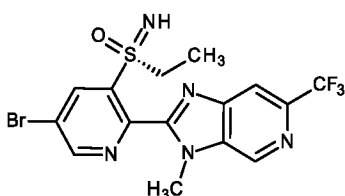
Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5μm; Flow: 1 mL/min; λ_{Max}: 290 nm; Run Time: 20 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.: 5 μL

Mobile Phase	% A (n-Hexane)	% B (EtOAc +EtOH 1:1)
Composition	70	30

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 8.22	Retention time (min) ~ 11.54
Enantiomeric excess: 98.5 % (1 st eluting enantiomer)	

Example 38: Preparation of R-[5-bromo-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-*c*]pyridin-2-yl]-3-pyridyl]-ethyl-imino-oxo-λ⁶-sulfane



To a stirred solution of (1*R*)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt (0.100 g, 99% purity, 0.22 mmol) in MeCN (0.45 mL) was added at rt *N*3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (0.049 g, 0.25 mmol), and the reaction mixture was heated to 80°C. After stirring for 16h the reaction mixture was concentrated under reduced pressure. The crude material was purified

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by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.060 g, 98% purity, 95% ee, 60% yield) as a brown solid.

^1H NMR (400 MHz, DMSO- d_6) δ : 9.27 (s, 1 H), 9.22 (d, $J=2.1$ Hz, 1 H), 8.63 (d, $J=2.1$ Hz, 1 H), 8.28 (s, 1 H), 4.60 (s, 1 H), 3.82 (s, 3 H), 3.51 - 3.68 (m, 2 H), 1.15 (t, $J=7.4$ Hz, 3 H)

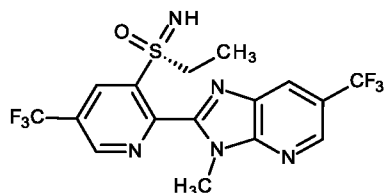
- 5 Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5 μ m; Flow: 1 ml/min; λ_{Max} : 274 nm; Run Time: 20 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.:4 μ L

Mobile Phase	% A (n-Hexane)	% B (EtOAc +EtOH 1:1)
Composition	70	30

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 10.4	Retention time (min) ~ 17.14
Enantiomeric excess: 95% (first eluting enantiomer)	

- 10 Example 39: Preparation of R-ethyl-imino-[2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-5-(trifluoromethyl)-3-pyridyl]-oxo- λ^6 -sulfane



- 15 To a stirred solution of (1*R*)-1-ethyl-1-oxo-6-(trifluoromethyl)isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt (0.500 g, 70% purity, 0.75 mmol) in MeCN (3 mL) was added at rt *N*-2-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (0.14 g, 0.75 mmol), and the reaction mixture was heated to 80°C. After stirring for 16h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.070 g, 94% purity, 99% ee, 20% yield) as a yellow solid.

- 20 ^1H NMR (400 MHz, DMSO- d_6) δ : 9.51 (dd, $J=2.06, 0.81$ Hz, 1 H), 8.91 (dd, $J=2.0, 0.63$ Hz, 1 H), 8.75 (d, $J=1.6$ Hz, 1 H), 8.69 - 8.72 (m, 1 H), 4.70 (s, 1 H), 3.76 (s, 3 H), 3.67 - 3.75 (m, 2 H), 1.10 - 1.22 (m, 3 H)

Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5 μ m, Flow: 1 ml/min, λ_{Max} :294 nm, Run Time: 10 min, Sample Preparation: 1mg/mL in EtOH, Inj. Vol.: 5 μ L

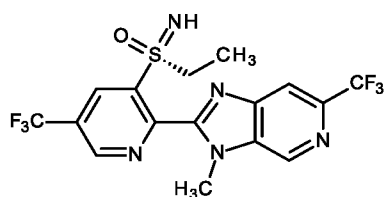
Mobile Phase	% A (n-Hexane)	% B (EtOAc +EtOH 1:1)
Composition	80	20

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Results:

First eluting enantiomer	Second eluting enantiomer
Retention time (min) ~ 6.34	Retention time (min) ~7.29
Enantiomeric excess: 99% (first eluting enantiomer)	

Example 40: Preparation of R-ethyl-imino-[2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-5-(trifluoromethyl)-3-pyridyl]-oxo- λ^6 -sulfane



5

To a stirred solution of [3-[(S)-ethylsulfinyl]-5-(trifluoromethyl)pyridine-2-carboximidoyl]amino] 4-nitrobenzenesulfonate salt (0.100 g, 70% purity, 0.15 mmol) in MeCN (0.6 mL) was added at rt N3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (0.029 g, 0.15 mmol), and the reaction mixture was heated to 80°C. After stirring for 20h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.042 g, >99% ee, 60% yield) as off-white solid.

10

¹H NMR (400 MHz, DMSO-d₆) δ : 9.51 (d, J =1.2 Hz, 1 H), 9.31 (s, 1 H), 8.74 (d, J =1.8 Hz, 1 H), 8.32 (s, 1 H), 4.70 (s, 1 H), 3.86 (s, 3 H), 3.59 - 3.74 (m, 2 H), 1.18 (t, J =7.4 Hz, 3 H)

15

Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5 μ m; Flow: 1 ml/min; λ Max.: 270 nm; Run Time: 15 min; Sample Preparation: 1mg/mL in ETOH; Inj. Vol.: 5 μ L

Mobile Phase	% A (n-Hexane)	% B (Ethanol+0.1%DEA)
Composition	60	40

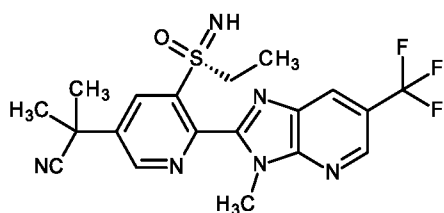
Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 6.7	Retention time (min) ~10.3
Enantiomeric excess: >99% (1st eluting enantiomer)	

20

Example 41: Preparation of R-2-[5-(ethylsulfonylimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]-2-methyl-propanenitrile

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To a stirred solution of 2-[(1*R*)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-*b*]pyridin-6-yl]-2-methyl-propanenitrile 4-methylbenzenesulfonic acid salt (0.200 g, 68% purity, 0.31 mmol) in MeCN (0.63 mL) was added at rt *N*-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (0.070 g, 0.35 mmol), and reaction mixture was heated to 80°C. After stirring for 16 h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.11 g, 98% purity, >99.5 ee, 78 % yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.23 (d, *J*=2.3 Hz, 1 H), 8.87 (d, *J*=1.3 Hz, 1 H), 8.65 (d, *J*=1.5 Hz, 1 H), 8.56 (d, *J*=2.3 Hz, 1 H), 4.56 (s, 1 H), 3.73 (s, 3 H), 3.55 - 3.71 (m, 2 H), 1.89 (d, *J*=5.3 Hz, 6 H), 1.14 - 1.17 (m, 3 H)

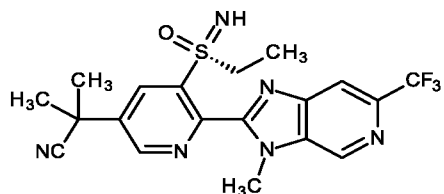
Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5μm; Flow: 1 ml/min; λ_{Max}.: 290 nm; Run Time: 40 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.:5 uL

Mobile Phase	% A (n-Hexane)	% B (EtOH)
Composition	70	30

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 20.80	Retention time (min) ~27.45
Enantiomeric excess: >99.5% (1st eluting enantiomer, opposite enantiomer below HPLC detection limits)	

Example 42: Preparation of R-2-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-*c*]pyridin-2-yl]-3-pyridyl]-2-methyl-propanenitrile



To a stirred solution of 2-[(1*R*)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-*b*]pyridin-6-yl]-2-methyl-propanenitrile 4-methylbenzenesulfonic acid salt (0.200 g, 68% purity, 0.31 mmol) in MeCN (0.63 mL) was added at rt *N*-3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (0.070 g, 0.35 mmol), and reaction mixture was heated to 80°C. After stirring for 16 h the reaction mixture was concentrated under reduced pressure. The crude material was

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purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.070 g, 98% purity, >99.5% ee, 50% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.28 (s, 1 H), 9.24 (d, *J*=2.3 Hz, 1 H), 8.56 (d, *J*=2.3 Hz, 1 H), 8.29 (s, 1 H), 4.56 (s, 1 H), 3.83 (s, 3 H), 3.52 - 3.70 (m, 2 H), 1.89 (d, *J*=5.1 Hz, 5 H), 1.17 (t, *J*=7.4 Hz, 3 H)

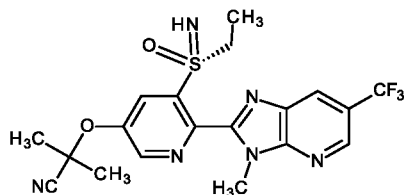
- 5 Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5μm; Flow: 1 ml/min; λMax.: 290 nm, Run Time: 40 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.:5 uL

Mobile Phase	% A (n-Hexane)	% B (EtOH)
Composition	70	30

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 23.7	Retention time (min) ~29.60
Enantiomeric excess: >99.5% (1st eluting enantiomer, opposite enantiomer below HPLC detection limits)	

- 10 Example 43: Preparation of R-2-[[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]oxy]-2-methyl-propanenitrile



- To a stirred solution of 2-[(1*R*)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-*b*]pyridin-6-yl]oxy-2-methyl-propanenitrile 4-nitrobenzenesulfonic acid salt (0.200 g, 79% purity, 0.33 mmol) in MeCN (2 mL) was added at rt *N*2-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (0.080 g, 0.36 mmol), and reaction mixture was heated to 80°C. After stirring for 24h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.060 g, 95% purity, >99.5% ee, 38% yield) as off-white solid.

- 20 ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.86 - 8.90 (m, 2 H), 8.64 (d, *J*=1.6 Hz, 1 H), 8.29 (d, *J*=2.7 Hz, 1 H), 4.58 (s, 1 H), 3.73 (s, 3 H), 3.58 - 3.71 (m, 2 H), 1.88 (d, *J*=2.7 Hz, 6 H), 1.14 - 1.18 (m, 3 H)

Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5μm; Flow: 1 ml/min; λMax.: 290 nm; Run Time: 10 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.:5 uL

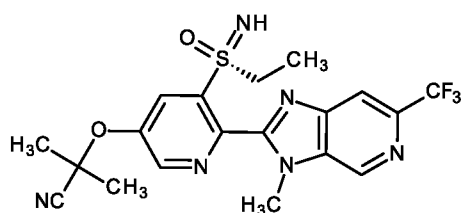
Mobile Phase	% A (TBME)	% B (EtOH)
Composition	95	5

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Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 5.27	Retention time (min) ~4.64
Enantiomeric excess: >99.5% (1st eluting enantiomer, opposite enantiomer below HPLC detection limits)	

Example 44: Preparation of R-2-[[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]oxy]-2-methyl-propanenitrile



To a stirred solution of 2-[(1*R*)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-*b*]pyridin-6-yl]oxy-2-methyl-propanenitrile 4-nitrobenzenesulfonic acid salt (0.200 g, 79% purity, 0.33 mmol) in MeCN (2 mL) was added at rt *N*3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (0.080 g, 0.36 mmol), and the reaction mixture was heated to 80°C, and stirred for 24h, and the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.070 g, 99% purity, 99% ee, 47% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.26 (s, 1 H), 8.89 (d, *J*=2.6 Hz, 1 H), 8.26 - 8.30 (m, 2 H), 4.56 (s, 1 H), 3.82 (s, 3 H), 3.52 - 3.69 (m, 2 H), 1.88 (d, *J*=2.9 Hz, 6 H), 1.12 - 1.19 (m, 3 H)

Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5μm; Flow: ; λMax.: 274 nm; Run Time: 12 min; Sample Preparation: Inj. Vol.: 2 uL

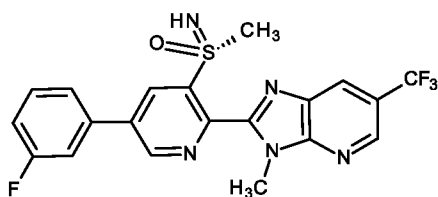
Mobile Phase	% A (TBME)	% B (Ethanol+0.1%DEA)
Composition	90	10

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 5.73	Retention time (min) ~6.83
Enantiomeric excess: 99 %	

Example 45: Preparation of R-[5-(3-fluorophenyl)-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-*b*]pyridin-2-yl]-3-pyridyl]-imino-methyl-oxo-λ⁶-sulfane

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To a stirred solution of (1*R*)-6-(3-fluorophenyl)-1-methyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt (0.200 g, 99% purity, 0.42 mmol) in MeCN (1.7 mL) was added at rt *N*2-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (0.080 g, 0.42 mmol), and reaction mixture was heated to 80°C. After stirring for 7 h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.080 g, 99% purity, 97% ee, 40% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.39 (d, *J*=2.1 Hz, 1 H), 8.88 (d, *J*=1.4 Hz, 1 H), 8.75 (d, *J*=2.3 Hz, 1 H), 8.66 (d, *J*=1.5 Hz, 1 H), 7.85 - 7.91 (m, 1 H), 7.81 (d, *J*=8.5 Hz, 1 H), 7.67 (td, *J*=8.0, 6.2 Hz, 1 H), 7.41 (br d, *J*=2.5 Hz, 1 H), 4.53 - 4.56 (m, 1 H), 3.78 (s, 3 H), 3.47 - 3.52 (m, 3 H)

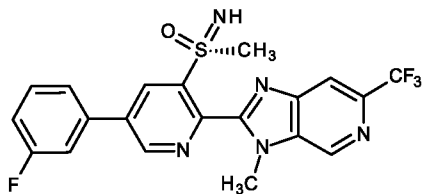
Method of Chiral Analysis: Column: Cellulose LUX (4.6mm x 250mm) 3μm; Flow: 0.7 ml/min; λ Max.: 294 nm; Run Time: 25 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.: 10 uL

Mobile Phase	% A (n-Hexane)	% B (EtOAc +EtOH)
Composition	75	25

Results:

First eluting enantiomer (S)	Second eluting enantiomer (R)
Retention time (min) ~ 9.0	Retention time (min) ~10.71
Enantiomeric excess: 97 % (2 nd eluting enantiomer)	

Example 46: Preparation of R-[5-(3-fluorophenyl)-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-*c*]pyridin-2-yl]-3-pyridyl]-imino-methyl-oxo-λ⁶-sulfane



To a stirred solution of (1*R*)-6-(3-fluorophenyl)-1-methyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt (0.200 g, 99% purity, 0.42 mmol) in MeCN (1.7 mL) was added at rt *N*3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (0.080 g, 0.42 mmol), and the reaction mixture was heated to 80°C. After stirring for 16 h the reaction mixture was concentrated under reduced pressure. The crude material was

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purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.075 g, 99% purity, 99% ee, 40% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-d₆) δ: 9.39 (d, *J*=2.08 Hz, 1 H), 9.29 (s, 1 H), 8.75 (d, *J*=2.20 Hz, 1 H), 8.29 (s, 1 H), 7.88 (br d, *J*=9.9 Hz, 1 H), 7.81 (d, *J*=7.8 Hz, 1 H), 7.67 (d, *J*=6.1 Hz, 1 H), 7.41 (br d, *J*=2.6 Hz, 1 H), 4.03 (d, *J*=7.0 Hz, 1 H), 3.87 (s, 3 H), 3.47 (s, 3 H)

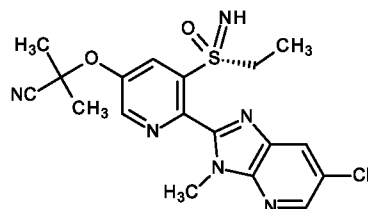
Method of Chiral Analysis: Column: Cellulose LUX (4.6mm x 250mm) 3μm; Flow: 0.7 ml/min; λ Max.: 275 nm; Run Time: 22 min; Sample Preparation: 1mg/mL in ETOH; Inj. Vol.:10 uL

Mobile Phase	% A (n-Hexane)	% B (EtOAc +EtOH)
Composition	75	25

Results:

First eluting enantiomer (S)	Second eluting enantiomer (R)
Retention time (min) ~ 11.65	Retention time (min) ~13.54
Enantiomeric excess: 99% (2 nd eluting enantiomer)	

Example 47: Preparation of R-2-[[6-(6-chloro-3-methyl-imidazo[4,5-b]pyridin-2-yl)-5-(ethylsulfonimidoyl)-3-pyridyl]oxy]-2-methyl-propanenitrile



To a stirred solution of 2-[(1*R*)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]oxy-2-methyl-propanenitrile 4-nitrobenzenesulfonic acid salt (0.200 g, 85% purity, 0.35 mmol) in MeCN (1.4 mL) was added at rt 5-chloro-*N*2-methyl-pyridine-2,3-diamine (0.062 g, 0.38 mmol), and the reaction mixture was heated to 80°C. After stirring for 7 h the reaction mixture was concentrated under reduced pressure, and the crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.900 g, 99% purity, 99.2% ee, 60% yield) as pale-yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ: 8.88 (d, *J*=2.7 Hz, 1 H), 8.52 (d, *J*=2.2 Hz, 1 H), 8.37 (d, *J*=2.2 Hz, 1 H), 8.28 (d, *J*=2.7 Hz, 1 H), 4.56 (s, 1 H), 3.58 - 3.71 (m, 5 H), 1.88 (d, *J*=3.0 Hz, 6 H), 1.16 (t, *J*=7.4 Hz, 3 H)

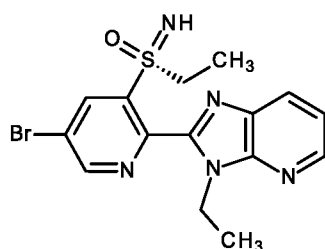
Method of Chiral Analysis: Column: Chiralpack-Lux-Cellulose (4.6mm x 250mm) 3-5μm; Flow: 1 ml/min; λMax.: 306 nm; Run Time: 30 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.: 10 uL

Mobile Phase	% A (TBME)	% B (EtOH +0.1% DEA)
Composition	95	5

Results:

First eluting enantiomer (S)	Second eluting enantiomer (R)
Retention time (min) ~ 8.45	Retention time (min) ~11.59
Enantiomeric excess: 99.2 % (2 nd eluting enantiomer)	

Example 48: Preparation of R-[5-bromo-2-(3-ethylimidazo[4,5-b]pyridin-2-yl)-3-pyridyl]-ethyl-imino-oxo- λ^6 -sulfane



To a stirred solution of (1*R*)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-imine;4-nitrobenzenesulfonic acid (0.100 g, 99% purity, 0.44 mmol) in MeCN (0.90 mL) was added at rt *N*2-ethylpyridine-2,3-diamine (0.070 g, 0.49 mmol), and the reaction mixture was stirred at 80°C for 24 h. The reaction mixture was concentrated under reduced pressure, and the crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.065 g, 96% purity, >99% ee, 40% yield) as pale-yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.20 (d, *J*=2.3 Hz, 1 H), 8.64 (d, *J*=2.3 Hz, 1 H), 8.47 (dd, *J*=4.8, 1.50 Hz, 1 H), 8.16 (dd, *J*=8.0, 1.44 Hz, 1 H), 7.38 (dd, *J*=8.0, 4.7 Hz, 1 H), 4.59 (s, 1 H), 4.13 - 4.24 (m, 2 H), 3.72 (q, *J*=7.1 Hz, 2 H), 1.31 (t, *J*=7.2 Hz, 3 H), 1.18 (t, *J*=7.4 Hz, 3 H)

Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5 μ m; Flow: 1 ml/min; λ Max.: 294 nm; Run Time: 25 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.: 7 μ L

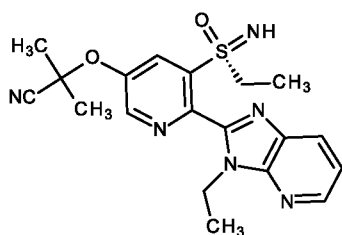
Mobile Phase	% A (n-Hexane)	% B (EtOAc +EtOH 1:1)
Composition	70	30

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 12.37	Retention time (min) ~16.57
Enantiomeric excess: 99.5% (1 st eluting enantiomer)	

Example 49: Preparation of R-2-[[6-(3-ethylimidazo[4,5-b]pyridin-2-yl)-5-(ethylsulfonimidoyl)-3-pyridyl]oxy]-2-methyl-propanenitrile

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To a stirred solution of 2-[(1*R*)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-*b*]pyridin-6-yl]oxy-2-methylpropanenitrile;4-nitrobenzenesulfonic acid (0.100 g, 80% purity, 0.17 mmol) in MeCN (1.0 mL) was added at rt *N*2-ethylpyridine-2,3-diamine (0.025 g, 0.18 mmol), and the reaction mixture was heated to 80°C. After stirring for 7 h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.045 g, 99% purity, 99.3% ee, 68% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.86 (d, *J*=2.7 Hz, 1 H), 8.46 (dd, *J*=4.7, 1.41 Hz, 1 H), 8.29 (d, *J*=2.7 Hz, 1 H), 8.14 (dd, *J*=8.0, 1.3 Hz, 1 H), 7.36 (dd, *J*=7.9, 4.8 Hz, 1 H), 4.54 (s, 1 H), 4.13-4.23 (m, 2 H), 3.63 - 3.76 (m, 2 H), 1.87 (d, *J*= 6.0 Hz, 6 H), 1.30 - 1.35 (m, 3 H), 1.14 - 1.18 (m, 3 H)

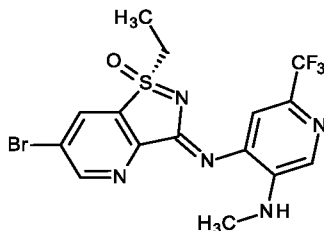
Method of Chiral Analysis: Column: Chiralpack-Lux-Cellulose (4.6mm x 250mm) 3-5μm; Flow: 1 ml/min; AMax.:295 nm; Run Time: 30 min; Sample Preparation: 1mg/mL in EtOH; Inj. Vol.: 4 uL

Mobile Phase	% A (TBME)	% B (EtOH + 0.1% DEA)
Composition	95	5

Results:

First eluting enantiomer (S)	Second eluting enantiomer (R)
Retention time (min) ~ 11.81	Retention time (min) ~13.14
Enantiomeric excess: 99.3 % (2 nd eluting enantiomer)	

Example 50: Preparation of 4-[(*Z*)-[(1*R*)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-ylidene]amino]-*N*-methyl-6-(trifluoromethyl)pyridin-3-amine



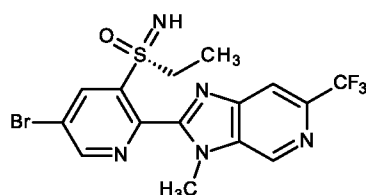
To a stirred solution of (1*R*)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-imine 4-nitrobenzenesulfonic acid salt (0.100 g, 99% purity, 0.22 mmol) in MeCN (0.45 mL) was added at rt *N*3-methyl-6-(trifluoromethyl)pyridine-3,4-diamine (0.047 g, 0.24 mmol), and the reaction mixture was heated to 50°C. After

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stirring for 8 h, the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.020 g, 99% purity, 43% yield) as off-white solid.

¹H NMR (400 MHz, CDCl₃) δ: 8.93 (d, *J*=2.1 Hz, 1 H), 8.90 (s, 1 H), 8.65 (d, *J*=2.3 Hz, 1H), 8.03 (s, 1 H), 3.80 (s, 3 H), 3.57 - 3.78 (m, 2 H), 2.64 (br s, 1 H), 1.30 (t, *J*=7.4 Hz, 3 H)

Example 51: Preparation of R-[5-bromo-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]-ethyl-imino-oxo-λ⁶-sulfane



A solution of 4-[(*Z*)-[(1*R*)-6-bromo-1-ethyl-1-oxo-isothiazolo[4,5-*b*]pyridin-3-ylidene]amino]-*N*-methyl-6-(trifluoromethyl)pyridin-3-amine (0.040 g, 99% purity) in MeCN (1.0 mL) was heated to 80°C. After stirring for 8 h the reaction mixture was concentrated under reduced pressure. The crude material was purified by neutral silica gel chromatography using cyclohexane and EtOAc as eluent to yield the title compound (0.025 g, 99% purity, 99.5% ee, 63% yield) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1 H), 9.22 (d, *J*=2.1 Hz, 1 H), 8.63 (d, *J*=2.1 Hz, 1 H), 8.28 (s, 1 H), 4.61 (s, 1 H), 3.81 (s, 3 H), 3.54 - 3.67 (m, 2 H), 1.15 (t, *J*=7.4 Hz, 3 H)

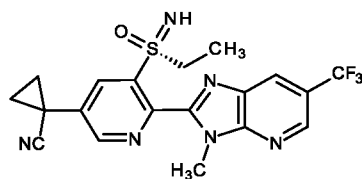
Method of Chiral Analysis: Column: Chiralpack-IG (4.6mm x 250mm) 5μm; Flow: 1 ml/min; λMax.: 274 nm; Run Time: 25 min, Sample Preparation: 1mg/mL in EtOH; Inj. Vol.: 5 uL

Mobile Phase	% A (n-Hexane)	% B (EtOAc +EtOH 1:1)
Composition	70	30

Results:

First eluting enantiomer (S)	Second eluting enantiomer (R)
Retention time (min) ~ 10.4	Retention time (min) ~ 17.14
Enantiomeric excess: 99.5% (2 nd eluting enantiomer)	

Example 52a: Preparation of R-1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo [4,5-*b*]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile



Step 1: To a suspension of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-N'-hydroxy-pyridine-2-carboxamide (2.995 g, 97% purity, >99.5% ee, 10.4 mmol) in dry THF (13.2 ml) was added TEA (1.53 ml, 10.95 mmol). To this suspension was slowly added a 2.0 M solution of *p*TsCl in dry THF (5.2 ml, 10.5 mmol) at rt. After stirring for 24 h the formed precipitate (Et₃N.HCl) was filtered off and washed on filter with a minimum amount of THF. The intermediate [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate was obtained as a 19.4% solution in THF (ca 95% yield) which could be stored and used in the next step without isolation (see Example 23 for isolation as a solid)

Step 2: To a solution of intermediate prepared in Step 1 (11.16 g, 19.4% concentration, 5.00 mmol) was added dry sulfolane (5.0 ml). THF was then removed at reduced pressure (40°C, 20 mbar) and methanol (5.0 ml) was added followed by N2-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (1.06 g, 99% purity, 5.50 mmol). The resulting brown solution was stirred at 70°C for 22 h. Methanol was then removed at reduced pressure (50°C, 20 mbar), the remaining mixture cooled to rt, and water (11 ml) added while stirring vigorously. After stirring for 2 h and aging for a further hr, the precipitate was filtered, washed on filter with sulfolane/water 3:7 (5 ml) and water (2 x 5 ml). The precipitate was then dried under high vacuum to yield the title compound (1.605 g, 95% purity, >99.5% ee, 70% yield) as a gray powder. Another 0.48 g of title compound (22% yield) remained in the mother and wash liquors.

¹H NMR (400 MHz, Solvent) δ 1.36 (t, J=7.3 Hz, 3 H), 1.61 - 1.70 (m, 2 H), 1.97 - 2.08 (m, 2 H), 3.82 - 3.98 (m, 4 H), 8.31 (d, J=1.45 Hz, 1 H), 8.34 (d, J=2.2 Hz, 1 H), 8.76 (d, J=1.1 Hz, 1 H), 8.98 (d, J=2.2 Hz, 1 H)

Method of Chiral Analysis: Column: Chiralpack-IG (0.46cm x 10cm) 3μm; Flow: 2 ml/min; λ_{Max}: 290 nm; Sample Preparation: 1mg/mL in MeOH; Inj. Vol.: 2 uL

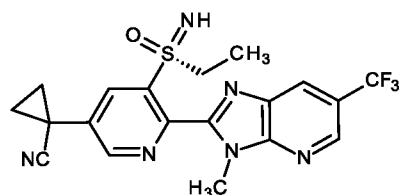
Mobile Phase	% A (CO ₂)	% B (MeOH)
Composition	75	25

Results:

First eluting enantiomer (R)	Second eluting enantiomer (S)
Retention time (min) ~ 2.35	Retention time (min) ~ 3.43
Enantiomeric excess: >99.5% (1 st eluting enantiomer, the other enantiomer below detection limits)	

Example 52b: Preparation of R-1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo [4,5-b]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile

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Using an analogous procedure to Example 52a Step 2 could be run under the following alternative conditions:

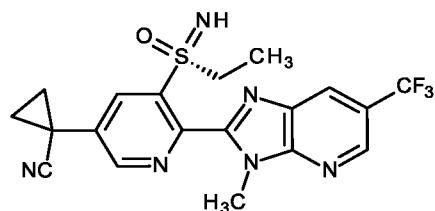
Anisole/MeOH (1:1), 80°C, 16 h: 92% yield

Benzonitrile/MeOH (1:1), 80°C, 12 h: 91% yield

5 Sulfolane/nPrOH (1:1), 80°C, 10 h: 85% yield

Anisole/ethylene glycol (1:1), 80°C, 22 h: 91% yield

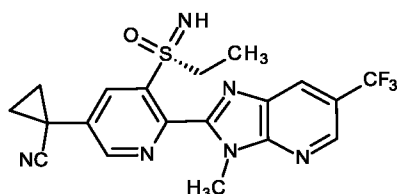
Example 52c: Preparation of R-1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo [4,5-b]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile



10 A solution of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate (1.108 g, 97% purity, >99.5% ee, 2.49 mmol) and N2-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (0.523 g, 98% purity, 2.68 mmol) in MeCN (5.0 ml) was heated at 80°C for 6 h. The reaction mixture was cooled to rt and the formed precipitate (TsOH.NH₃) was filtered off and washed on filter with MeCN. The filtrate was evaporated under reduced pressure to yield the title compound (1.21 g, 75% purity,

15 >99.5% ee, 84% yield).

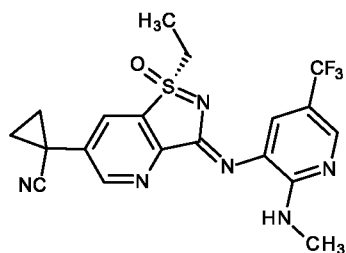
Example 52d: Preparation of R-1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo [4,5-b]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile



A solution of 1-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]cyclopropanecarbonitrile 4-methylbenzenesulfonic acid salt (88.8 mg, 97% purity, 0.200 mmol) and N2-methyl-5-(trifluoromethyl)pyridine-2,3-diamine (41.6 mg, 99% purity, 0.216 mmol) in dry MeCN (0.40 ml) was heated at 80°C for 16 h. The reaction mixture was then cooled to rt and solvent removed under reduced pressure. Analysis of crude residue with quantitative NMR using trimethoxybenzene as an internal standard indicated formation of the title compound (78.9 mg, 91% yield).

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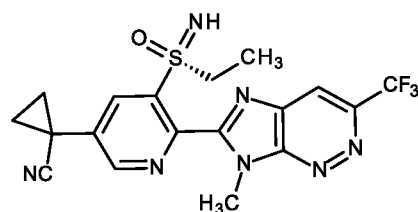
Example 53: Preparation of 1-[(1R,3Z)-1-ethyl-3-[[2-(methylamino)-5-(trifluoromethyl)-3-pyridyl]imino]-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]cyclopropanecarbonitrile



To a solution of 1-[(1R)-1-ethyl-3-imino-1-oxo-isothiazolo[4,5-b]pyridin-6-yl]cyclopropanecarbonitrile 4-methylbenzenesulfonic acid salt (0.220 g, 0.509 mmol) and N2-methyl-5-(trifluoromethyl) pyridine-2,3-diamine (0.115 g, 0.598 mmol) in dry sulfolane (1.1 ml) was added TEA (13 ml, 0.097 mmol). The resulting solution was heated at 60°C for 3 h. The reaction mixture was cooled to rt and quenched by addition of aqueous saturated NaHCO₃ and iPrOAc. The organic phase was separated, washed with water and dried over anhydrous Na₂SO₄. The solution was evaporated under reduced pressure and the crude product purified by reverse phase HPLC (water/MeCN as a mobile phase) to obtain the title compound (0.182 g, 95% purity, 78% yield) as a white fluffy solid.

¹H NMR (400 MHz, d₆-DMSO) δ 9.11 (d, *J* = 2.2 Hz, 1H), 8.80 (d, *J* = 2.2 Hz, 1H), 8.14 (dd, *J* = 1.1, 2.2 Hz, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 6.60 (q, *J* = 4.7 Hz, 1H), 4.26 - 4.02 (m, 2H), 2.95 (d, *J* = 4.7 Hz, 3H), 2.05 - 1.96 (m, 2H), 1.92 - 1.85 (m, 1H), 1.85 - 1.79 (m, 1H), 1.15 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (101 MHz, d₆-DMSO) δ 156.50, 155.87, 154.50, 154.21, 140.94 - 140.39 (m, 1C), 135.27, 130.72, 130.16, 128.44, 125.16 (d, *J* = 271.3 Hz, 1C), 123.05 (br d, *J* = 3.0 Hz, 1C), 121.16, 112.04 (q, *J* = 31.2 Hz, 1C), 47.92, 27.86, 19.48, 18.95, 11.93, 7.00

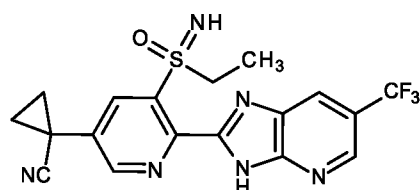
Example 54: Preparation of R-1-[5-(ethylsulfonimidoyl)-6-[7-methyl-3-(trifluoromethyl)imidazo [4,5-c]pyridazin-6-yl]-3-pyridyl]cyclopropanecarbonitrile



A solution of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate (201 mg, 95% purity, 0.441 mmol) and N3-methyl-6-(trifluoromethyl)pyridazine-3,4-diamine (102 mg, 0.529 mmol) in MeCN (0.9 ml) was heated at 80°C for 23 h. The reaction mixture was cooled to rt and solvent evaporated under reduced pressure. The crude residue was purified by silica gel chromatography using EtOAc and cyclohexane as eluents to yield the title compound (52.7 mg, 27% yield) as a gray powder.

¹H NMR (400 MHz, CDCl₃) δ 1.38 (td, *J*=7.27, 1.82 Hz, 3 H), 1.71 (br s, 2 H), 2.07 (br s, 2 H), 3.61 - 3.93 (m, 2 H), 4.04 (s, 3 H), 8.18 (d, *J*=1.82 Hz, 1 H), 8.37 (br d, *J*=1.82 Hz, 1 H), 9.02 (br d, *J*=1.82 Hz, 1 H)

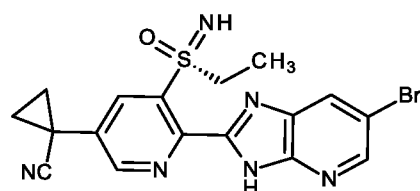
Example 55: Preparation of 1-[5-(ethylsulfonimidoyl)-6-[6-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile



A solution of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-ethylsulfinyl-2-pyridyl]methylene]amino] 4-nitrobenzenesulfonate (259.5 mg, 89% purity, 0.499 mmol) and N2-methyl-5-(trifluoromethyl) pyridine-2,3-diamine (102.6 mg, 95% purity, 0.550 mmol) in dry MeOH (1.0 ml) was heated in a closed vial at 90°C for 4 h. The reaction mixture was cooled to rt and the resulting precipitated was filtered off and dried under high vacuum to yield the title compound (204 mg, 77% purity, 75% yield) as a gray powder. For analytical purposes a small portion was purified (to >95% purity) via reverse phase HPLC (water/MeCN as eluents).

¹H NMR (600 MHz, METHANOL-d₄) δ 1.35 (t, J=7.4 Hz, 3 H) 1.71 - 1.79 (m, 2 H) 1.96 - 2.04 (m, 2 H) 3.80 - 4.17 (m, 2 H) 8.35 (br s, 1 H) 8.39 (d, J=2.4 Hz, 1 H) 8.73 (s, 1 H) 8.98 (d, J=2.2 Hz, 1 H); ¹³C NMR (151 MHz, DMSO-d₆) δ 7.5 (s, 1 C) 11.7 (s, 1 C) 19.1 (d, J=15 Hz, 1 C) 51.2 (s, 1 C) 120.1 (q, J=32 Hz, 1 C) 121.2 (s, 1 C) 124.5 (q, J=272 Hz, 1 C) 134.5 (s, 1 C) 136.7 (s, 1 C) 139.5 (s, 1 C) 141.5 (s, 1 C) 146.3 (s, 1 C) 148.7 (s, 1 C) 152.7 - 155.2 (m, 1 C)

Example 56: Preparation of R-1-[6-(6-bromo-3H-imidazo[4,5-b]pyridin-2-yl)-5-(ethylsulfonimidoyl)-3-pyridyl]cyclopropanecarbonitrile



A solution of [(Z)-[amino-[5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]-2-pyridyl]methylene]amino] 4-methylbenzenesulfonate (203 mg, 95% purity, 0.445 mmol) and 2,3-diamino-5-bromopyridine (104 mg, 97% purity, 0.534 mmol) in MeCN (0.9 ml) was heated in a closed vial at 80°C for 36 h. The reaction mixture was cooled to rt and solvent evaporated under reduced pressure. The crude residue was purified by silica gel chromatography using EtOAc and cyclohexane as eluents to yield the title compound (99 mg, 83% purity, 43% yield) as a gray powder.

¹H NMR (400 MHz, methanol-d₄) δ 1.30 (t, J=7.3 Hz, 3 H), 1.77 - 1.89 (m, 2 H), 1.97 - 2.08 (m, 2 H), 3.87 - 4.16 (m, 2 H), 7.77 (d, J=2.2 Hz, 1 H), 8.47 (d, J=2.2 Hz, 1 H), 8.68 (d, J=2.2 Hz, 1 H), 9.13 (d, J=2.2 Hz, 1 H)

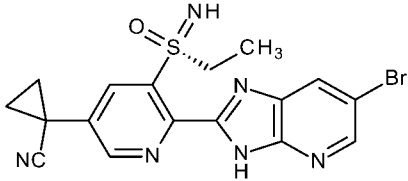
Table P: Compounds of formula (I) prepared according to the present invention

Entry	IUPAC-name	Structure
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P-1	1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile	
P-2	[5-bromo-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]-ethyl-imino-oxo-λ ⁶ -sulfane	
P-3	[5-bromo-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]-ethyl-imino-oxo-λ ⁶ -sulfane	
P-4	ethyl-imino-[2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-5-(trifluoromethyl)-3-pyridyl]-oxo-λ ⁶ -sulfane	
P-5	ethyl-imino-[2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-5-(trifluoromethyl)-3-pyridyl]-oxo-λ ⁶ -sulfane	
P-6	2-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]-2-methyl-propanenitrile	
P-7	2-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]-2-methyl-propanenitrile	
P-8	2-[[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]oxy]-2-methyl-propanenitrile	

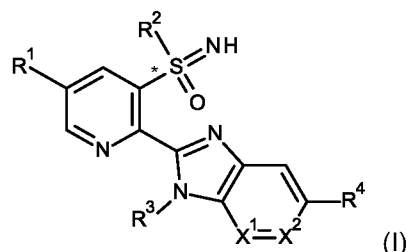
P-9	2-[[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]oxy]-2-methyl-propanenitrile	
P-10	[5-(3-fluorophenyl)-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]-imino-methyl-oxo-λ ⁶ -sulfane	
P-11	[5-(3-fluorophenyl)-2-[3-methyl-6-(trifluoromethyl)imidazo[4,5-c]pyridin-2-yl]-3-pyridyl]-imino-methyl-oxo-λ ⁶ -sulfane	
P-12	2-[[6-(6-chloro-3-methyl-imidazo[4,5-b]pyridin-2-yl)-5-(ethylsulfonimidoyl)-3-pyridyl]oxy]-2-methyl-propanenitrile	
P-13	[5-bromo-2-(3-ethylimidazo[4,5-b]pyridin-2-yl)-3-pyridyl]-ethyl-imino-oxo-λ ⁶ -sulfane	
P-14	2-[[6-(3-ethylimidazo[4,5-b]pyridin-2-yl)-5-(ethylsulfonimidoyl)-3-pyridyl]oxy]-2-methyl-propanenitrile	
P-15	1-[5-(ethylsulfonimidoyl)-6-[3-methyl-6-(trifluoromethyl)imidazo[4,5-b]pyridin-2-yl]-3-pyridyl]cyclopropanecarbonitrile	
P-16	1-[5-(ethylsulfonimidoyl)-6-[7-methyl-3-(trifluoromethyl)imidazo[4,5-c]pyridazin-6-yl]-3-pyridyl]cyclopropanecarbonitrile	

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P-17	1-[6-(6-bromo-3H-imidazo[4,5-b]pyridin-2-yl)-5-(ethylsulfonimidoyl)-3-pyridyl]cyclopropanecarbonitrile	
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CLAIMS

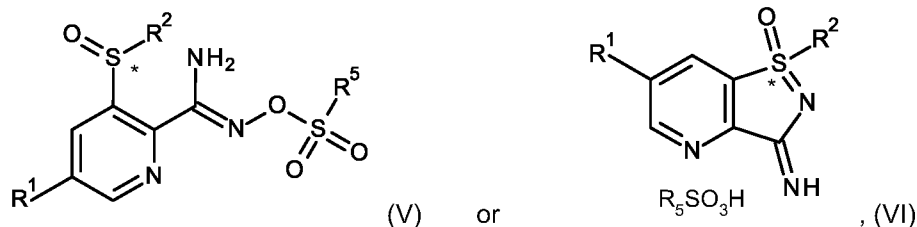
1. A process for the preparation of enantiomerically enriched sulfoximines of formula (I)



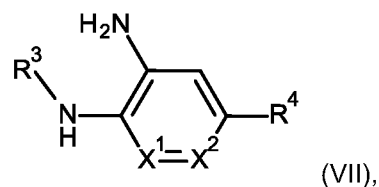
wherein

- 5 R^1 is halogen, C_1 - C_6 -haloalkyl, cyano- C_1 - C_6 -alkyl, cyano- C_1 - C_6 -alkoxy, cyano- C_3 - C_6 -cycloalkyl, or aryl, wherein said aryl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C_1 - C_3 -alkyl, or C_1 - C_3 -alkoxy;
- R^2 is C_1 - C_4 -alkyl;
- R^3 is hydrogen or C_1 - C_4 -alkyl;
- 10 R^4 is hydrogen, halogen, or C_1 - C_4 -haloalkyl;
- S^* is a stereogenic sulfur atom which is in R- or S-configuration;
- X^1 and X^2 are independently selected from CH or N, with the proviso that at least one of X^1 and X^2 is nitrogen,

- 15 wherein said process comprises reacting a compound of formula (V) or a compound of formula (VI)



wherein R^1 , R^2 and S^* are as defined for compounds of formula (I), and R^5 selected from C_1 - C_4 -alkyl or phenyl, wherein said phenyl is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, or methyl; with a compound of formula (VII)

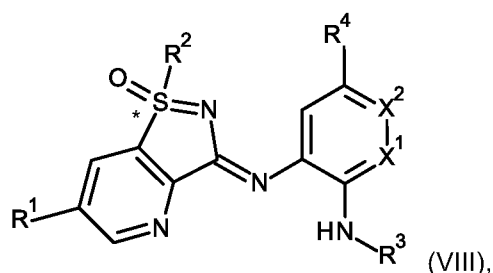


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wherein R^3 , R^4 , X^1 and X^2 are as defined for a compound of formula (I), in an appropriate solvent at an appropriate temperature to produce a compound of formula (I).

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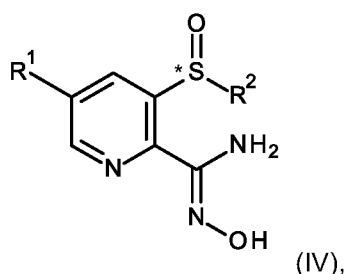
2. The process according to claim 1, wherein the compound of formula (VI) is reacted with a compound of formula (VII) to yield a compound of formula (I) via an intermediate of formula (VIII)



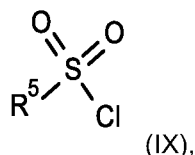
wherein R¹, R², S*, R³, R⁴, X¹ and X² are as defined for a compound of formula (I).

5

3. The process according to claim 1, wherein a compound of formula (IV)

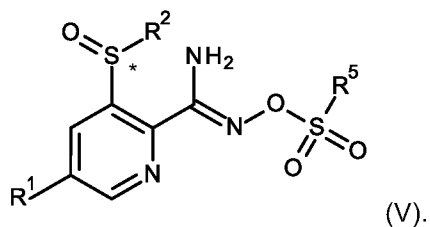


wherein R¹, R² and S* are as defined for a compound of formula (I), is reacted with a sulfonyl chloride of formula (IX)



10

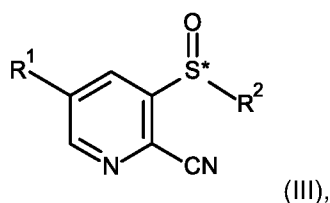
wherein R⁵ is selected from C₁-C₄-alkyl or phenyl, wherein said phenyl is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, or methyl; in the presence of a base and in a solvent to produce a compound of formula (V)



15

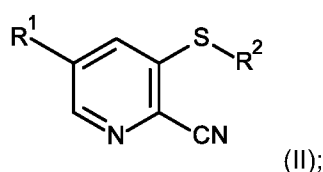
4. The process according to claim 1, wherein a sulfinyl compound of formula (III)

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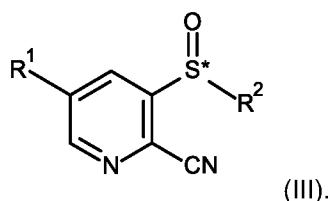


wherein R¹, R² and S* are as defined for a compound of formula (I), is reacted with hydroxylamine in a solvent at an appropriate temperature to produce a compound of formula (IV).

- 5 5. The process according to claim 1, wherein a sulfanyl compound of formula (II)



wherein R¹ and R² are as defined for compounds of formula (I); is stereoselectively oxidized in the presence of an oxidant, in the presence of a chiral reagent or catalyst, optionally in the presence of a suitable acid additive, in a solvent (or diluent); to produce a sulfinyl compound of formula (III)



10

6. The process according to claim 1, wherein the ratio of the compound of formula (VII) used, compared to the compound of formula (VI), is in the range from 2:1 to 1:1

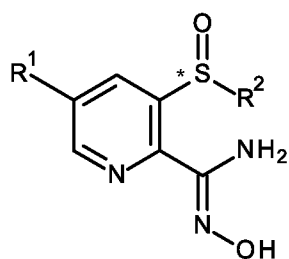
- 15 7. The process according to claim 5, wherein the solvents (or diluent) is selected from polar aprotic solvents, nitriles, esters, ketones, alcohols, aromatic hydrocarbons, carbonates and ethers and mixtures thereof.

- 20 8. The process according to claim 1, wherein the reaction of the compound of formula (V) or the compound of formula (VI) with a compound of formula (VII) is carried out in a temperature range from 20°C to 150°C.

9. The process according to claim 3, wherein the ratio of the compound of formula (IX) used, compared to the compound of formula (IV), is in the range from 3:1 to 1:1.

10. The process according to claim 3 or claim 9, wherein the base is selected from trialkylamines such as triethylamine and tributylamine, alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal hydroxide such as potassium hydroxide and sodium hydroxide.
- 5
11. The process according to any one of claims 3, 9 or 10, wherein the ratio of a base used, compared to the sulfonyl chloride of formula (IX), is from 1.5:1 to 1:1.
- 10
12. The process according to any one of claims 3, 9, 10 or 11, wherein the solvents (or diluents) are selected from esters, nitriles, ethers, and aliphatic, aromatic or halogenated hydrocarbons.
13. The process according to claims 4, wherein the reaction is carried out with an aqueous solution of hydroxylamine in an appropriate solvent at an appropriate temperature.
- 15
14. The process according to claim 4 or claim 13, wherein the ratio of hydroxylamine used compared to a compound of formula (III) is in the range between 2:1 and 1:1.
- 20
15. The process according to claims 4, wherein a free base hydroxylamine hydrochloride or hydroxylamine sulfate in combination with 1 eq (relative to hydroxylamine salt) of an appropriate base is used in place of hydroxylamine.
16. The process according to claims 15, wherein the bases is selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and sodium bicarbonate.
- 25
17. The process according to any one of claims 4, 13, 14, 15, or 16, wherein the solvents (or diluent) is selected from alcohols, ethers, and aliphatic, aromatic or halogenated hydrocarbons.
18. The process according to any one of claims 4, 13, 14, 15, 16 or 17, wherein the reaction is carried out in a temperature range from -20°C to 80°C.
- 30
19. A process for the preparation of a compound of formula (IV)

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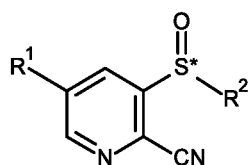
(IV); wherein

R¹ is halogen, C₁-C₆-haloalkyl, cyano-C₁-C₆-alkyl, cyano-C₁-C₆-alkoxy, cyano-C₃-C₆-cycloalkyl, or aryl, wherein said aryl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C₁-C₃-alkyl, or C₁-C₃-alkoxy;

5 R² is C₁-C₄ alkyl; and

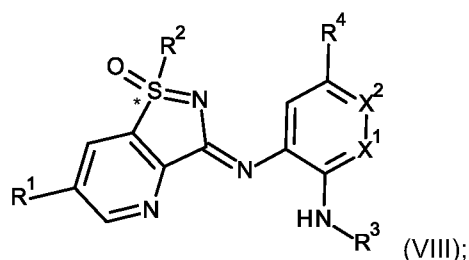
S* is a stereogenic sulfur atom which is in R- or S-configuration;

which process comprises reacting the compound of formula (III)

(III), wherein R¹, R² and S* are as defined for compounds of formula (IV), with

hydroxylamine in an appropriate solvent at an appropriate temperature to produce a compound of formula (IV).

20. A compound of formula (VIII)



(VIII);

15 wherein

R¹ is halogen, C₁-C₆-haloalkyl, cyano-C₁-C₆-alkyl, cyano-C₁-C₆-alkoxy, cyano-C₃-C₆-cycloalkyl, or aryl, wherein said aryl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C₁-C₃-alkyl, or C₁-C₃-alkoxy;

R² is C₁-C₄ alkyl;

20 R³ is hydrogen or C₁-C₄ alkyl;

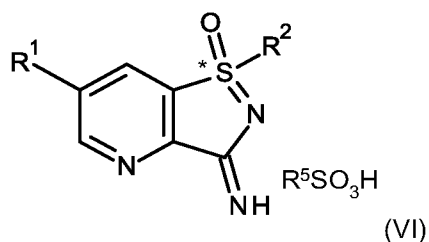
R⁴ is hydrogen, halogen, or C₁-C₄-haloalkyl;

S* is a stereogenic sulfur atom which is in R- or S-configuration; and

X¹ and X² are independently CH or N, with the proviso that at least one of X¹ and X² is nitrogen.

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21. A compound of formula (VI)



wherein

- 5 R¹ is halogen, C₁-C₆-haloalkyl, cyano-C₁-C₆-alkyl, cyano-C₁-C₆-alkoxy, cyano-C₃-C₆-cycloalkyl, or aryl, wherein said aryl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C₁-C₃-alkyl, or C₁-C₃-alkoxy;
- R² is C₁-C₄ alkyl;
- R⁵ is C₁-C₄-alkyl or phenyl, wherein said phenyl is unsubstituted or substituted by 1 or 2 substituents
10 selected from halogen, cyano, nitro, or methyl; and
- S* is a stereogenic sulfur atom which is in R- or S-configuration.

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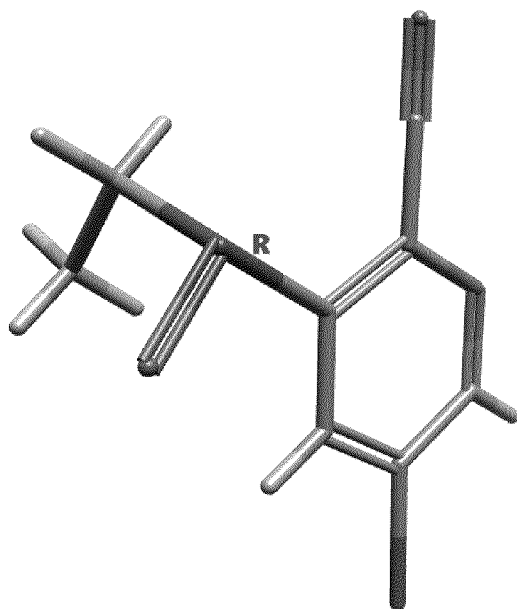


Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/075982

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D213/81 C07D471/04 C07D513/04 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 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		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2022/253841 A1 (SYNGENTA CROP PROTECTION AG [CH]) 8 December 2022 (2022-12-08) cited in the application the whole document -----	1 - 21
A	WO 2020/084075 A1 (SYNGENTA CROP PROTECTION AG [CH]) 30 April 2020 (2020-04-30) cited in the application the whole document -----	1 - 21
A	WO 2019/229089 A1 (SYNGENTA PARTICIPATIONS AG [CH]) 5 December 2019 (2019-12-05) cited in the application the whole document ----- - / - -	1 - 21
☒ 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 30 September 2024		Date of mailing of the international search report 15/10/2024
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 Sarakinis, Georgios

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/075982

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No

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