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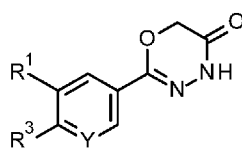
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(54) Title: OXADIAZINONE COMPOUNDS FOR THE TREATMENT OF HYPERPROLIFERATIVE DISEASES



(I)

(57) Abstract: The present invention includes name compounds of general formula (I) in which R¹, Y, and R³ are as defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds and the use of said compounds for manufacturing pharmaceutical compositions for the treatment or prophylaxis of hyperproliferative diseases, in particular of generic name diseases, as a sole agent or in combination with other active ingredients.



OXADIAZINONE COMPOUNDS FOR THE TREATMENT OF HYPERPROLIFERATIVE DISEASES

The present invention includes oxadiazinone compounds of general formula (I) as described and defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds, and the use of said compounds for manufacturing pharmaceutical compositions for the treatment or prophylaxis of diseases, in particular of hyperproliferative diseases, as a sole agent or in combination with other active ingredients.

BACKGROUND

Cancer kills over 550,000 people in the United States and over 8 million people world-wide each year. New agents, including small molecules, molecules that impact tissue-specific growth requirements, and immunomodulatory agents, have been shown to benefit a subset of patients whose cancers have unique genomic mutations or other characteristics. Unfortunately, many cancer patients are still left without effective therapeutic options.

One approach to identify new anti-cancer agents is phenotypic screening to discover novel small molecules displaying strong selectivity between cancer cell lines, followed by predictive chemogenomics to identify the cell features associated with drug response. In the 1990s, Weinstein and colleagues demonstrated that the cytotoxic profile of a compound can be used to identify cellular characteristics, such as gene-expression profiles and DNA copy number, which correlate with drug sensitivity. The ability to identify the features of cancer cell lines that mediate their response to small molecules has strongly increased in recent years with automated high-throughput chemosensitivity testing of large panels of cell lines coupled with comprehensive genomic and phenotypic characterization of the cell lines. Phenotypic observations of small molecule sensitivity can be linked to expression patterns or somatic alterations, as in the case of trastuzumab-sensitive HER2-amplified breast cancer or erlotinib-sensitive EGFR-mutant lung cancer.

Phenotypic screening identified some of the compounds known in the literature to be PDE3 inhibitors to be useful for the treatment of certain cancers. Co-expression of PDE3A and/or PDE3B and Schlafen 12 (SLFN12) polynucleotides or polypeptides are typically required for cells to be sensitive. PDE3A/B inhibitors which cause drug sensitivity have been found to stabilize the formation of a complex between PDE3A and/or PDE3B

and SLFN12. PDE3A and/or B inhibitors which do not cause inhibition of tumor cell proliferation typically do not stabilize the PDE3A- and/or PDE3B-SLFN12 complex.

Some oxadiazinones are known from EP080296 and EP0085227 having cardiotonic and/or antihypertensive activity.

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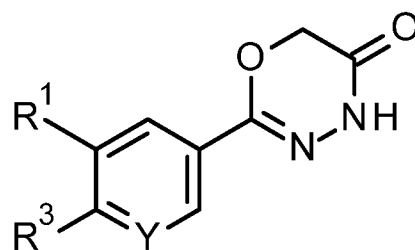
SUMMARY

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

10 In particular, the compounds of the present invention have surprisingly been found to inhibit tumor cell proliferation with IC₅₀ values of < 100 nM in e.g. HeLa cells. Additionally, the compounds do not inhibit enzymatic PDE3A and/or PDE3B at the concentration at which they inhibit tumor cell proliferation but at concentrations where IC₅₀ values for enzymatic PDE3A and/or PDE3B inhibition may be > 10 times higher
15 than IC₅₀ values for tumor cell proliferation. Without wishing to be bound by theory, this distinction in inhibitory properties may be associated with PDE3A- and/or PDE3B-SLFN12 complex induction and/or improved pharmacokinetic parameters *in vitro* or *in vivo* and/or improved physicochemical properties and/or improved safety pharmacological properties. With these advantageous properties, the compounds
20 described herein may therefore be used for the treatment or prophylaxis of hyperproliferative diseases, such as cancer diseases.

The present invention provides compounds of general formula (I) which modulate formation of a PDE3A-SLFN12 complex and/or PDE3B-SLFN12 complex, methods for their preparation, pharmaceutical composition and the use thereof and methods of
25 treatment or prophylaxis of diseases, in particular of hyperproliferative diseases more particularly of cancer diseases. These and other features of the present teachings are set forth herein.

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



formula (I)

wherein

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

5 Y is N, or CR², where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group,

10 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group;

15 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

20 amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

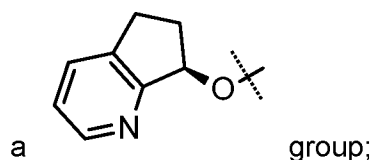
a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and

25 a 5- to 6-membered heteroaryl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded; a 4- to 6-membered

cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;



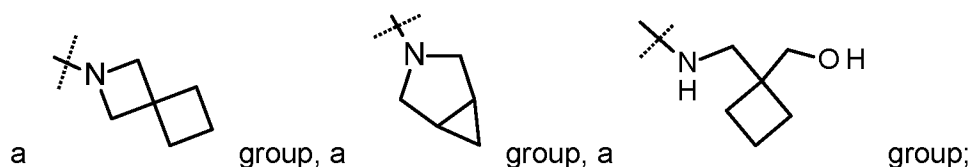
a 4- to 6-membered heterocycloalkoxy group,

5 a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group;

10 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



15 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a cyano group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

20 and

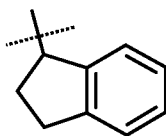
a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

25 a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a 4- to 6-membered heterocycloalkyl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,



a C₅-C₆-cycloalkyl group, a group,

a 4- to 6-membered heterocycloalkyl group, and

5 a C(O)-(C₁-C₆-alkyl) group;

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

In accordance with a further aspect, the present invention includes compounds of general formula (I): wherein

10 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

15 a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

20 a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group;

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

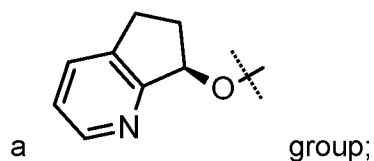
a hydroxy group,

25 a C₁-C₃-alkoxy group,

amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with
 a C₁-C₃-alkyl group, and
 a 5- to 6-membered heteroaryl group,



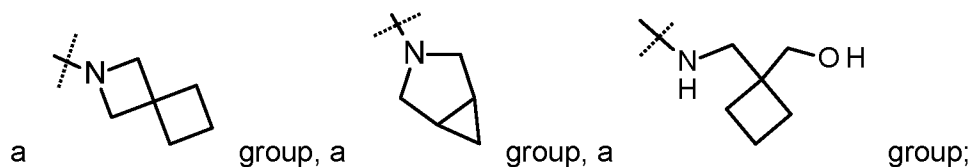
5 a 4- to 6-membered heterocycloalkoxy group,

a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group;

a phenyl group which is substituted one or more times with a group independently
 selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-
 10 haloalkoxy group and a C₁-C₃-haloalkyl group;

a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more
 times with a group independently selected from a halogen atom, a hydroxy
 group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



15 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally
 substituted one or more times with a group independently selected from a C₁-
 C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times
 with a group independently selected from an amino group, a cyano group, a
 20 halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

and

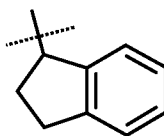
a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

25 a C₁-C₄-alkyl group which is substituted one or more times with a group independently
 selected from a 5- to 6-membered heteroaryl group, a 4- to 6-membered

heterocycloalkyl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl, whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,



5 a C₅-C₆-cycloalkyl group, a group,
a 4- to 6-membered heterocycloalkyl group, and
a C(O)-(C₁-C₆-alkyl) group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same, for use
10 in the prophylaxis and/or treatment of a hyperproliferative disease, particularly cancer, more particularly cervix cancer or melanoma..

DETAILED DESCRIPTION

DEFINITIONS

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

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

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

When groups in the compounds according to the invention are substituted, it is possible for said groups to be mono-substituted or poly-substituted with substituent(s), unless
30 otherwise specified. Within the scope of the present invention, the meanings of all groups

which occur repeatedly are independent from one another. It is possible that groups in the compounds according to the invention are substituted with one, two or three identical or different substituents, particularly with one substituent.

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

The terms “oxo”, “an oxo group” or “an oxo substituent” mean a doubly attached oxygen atom =O. Oxo may be attached to atoms of suitable valency, for example to a saturated carbon atom or to a sulfur atom. For example, but without limitation, one oxo group can be attached to a carbon atom, resulting in the formation of a carbonyl group C(=O) , or two oxo groups can be attached to one sulfur atom, resulting in the formation of a sulfonyl group –S(=O)₂.

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

Should a composite substituent be composed of more than one parts, e.g. (C₁-C₄-alkoxy)-(C₁-C₄-alkyl)-, it is possible for the position of a given part to be at any suitable position of said composite substituent, i.e. the C₁-C₄-alkoxy part can be attached to any carbon atom of the C₁-C₄-alkyl part of said (C₁-C₄-alkoxy)-(C₁-C₄-alkyl)- group. A hyphen at the beginning or at the end of such a composite substituent indicates the point of attachment of said composite substituent to the rest of the molecule. Should a ring, comprising carbon atoms and optionally one or more heteroatoms, such as nitrogen, oxygen or sulfur atoms for example, be substituted with a substituent, it is possible for said substituent to be bound at any suitable position of said ring, be it bound to a suitable carbon atom and/or to a suitable heteroatom.

The term “comprising” and “comprises” when used in the specification can have the meanings ascribed in U.S. Patent Law and can mean “including” or “includes.” The terms “comprising” and “comprises” are open-ended, allowing for the presence of more than that which is recited, and encompasses “consisting of” but is not limited to the scope indicated by “consisting of.”

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

If within the present text any item is referred to as “*supra*” within the description it indicates any of the respective disclosures made within the specification in any of the preceding pages, or above on the same page.

If within the present text any item is referred to as “*infra*” within the description it indicates any of the respective disclosures made within the specification in any of the subsequent pages, or below on the same page.

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

- 5 The term “halogen atom” means a fluorine, chlorine, bromine or iodine atom, particularly a fluorine, or chlorine atom except where halogen is intended to be a leaving group.

The term “C₁-C₈-alkyl-” means a linear or branched, saturated hydrocarbon group having 1, 2, 3, 4, 5, or 6, carbon atoms, such as, for example, a methyl-, ethyl-, propyl-, *iso*-propyl-, *n*-butyl-, *iso*-butyl-, *sec*-butyl-, *tert*-butyl-, *n*-pentyl-, *iso*-pentyl-, 2-methylbutyl-,
 10 1-methylbutyl-, 1-ethylpropyl-, 1,2-dimethylpropyl-, *neo*-pentyl-, 1,1-dimethylpropyl-, *n*-hexyl-, 4-methylpentyl-, 3-methylpentyl-, 2-methylpentyl-, 1-methylpentyl-, 2-ethylbutyl-, 1-ethylbutyl-, 3,3-dimethylbutyl-, 2,2-dimethylbutyl-, 1,1-dimethylbutyl-, 2,3-dimethylbutyl-, 1,3-dimethylbutyl-, 1,2-dimethylbutyl-, Particularly, said group has 1, 2, 3 or 4 carbon atoms (“C₁-C₄-alkyl-”), *e.g.*, a methyl-, ethyl-, *n*-propyl-, *iso*-propyl-, *n*-butyl-,
 15 *iso*-butyl-, *sec*-butyl- or a *tert*-butyl- group, 1, 2 or 3 carbon atoms (“C₁-C₃-alkyl-”), *e.g.*, a methyl-, ethyl-, *n*-propyl- or a *iso*-propyl group, or 1 or 2 carbon atoms (“C₁-C₂-alkyl-”), *e.g.*, a methyl group or an ethyl group.

The same definitions can be applied should the alkyl group be placed within a chain as a bivalent “C₁-C₆-alkylene” moiety. All names as mentioned above then will bear an “ene”
 20 added to the end, thus *e.g.*, a “pentyl” becomes a bivalent “pentylene” group. In addition, the term “C₁-C₆-heteroalkyl” refers to a C₁-C₆-alkyl group in which one or more of the carbon atoms have been replaced with an atom selected from N, O, S, or P, which are substituted as mentioned herein to satisfy atom valency requirements.

The term “C₁-C₆-hydroxyalkyl” means a linear or branched, saturated, monovalent
 25 hydrocarbon group in which the term “C₁-C₆-alkyl” is defined *supra*, and in which 1, 2 or 3 hydrogen atoms are replaced with a hydroxy group, such as, for example, a hydroxymethyl-, 1-hydroxyethyl-, 2-hydroxyethyl-, 1,2-dihydroxyethyl-, 3-hydroxypropyl-, 2-hydroxypropyl-, 1-hydroxypropyl-, 1-hydroxypropan-2-yl-, 2-hydroxypropan-2-yl-, 2,3-dihydroxypropyl-, 1,3-dihydroxypropan-2-yl-, 3-hydroxy-2-methyl-propyl-, 2-hydroxy-2-methyl-propyl-, or a 1-hydroxy-2-methyl-propyl- group.
 30

The term “C₁-C₆-haloalkyl” means a linear or branched, saturated, monovalent hydrocarbon group in which the term “C₁-C₆-alkyl” is as defined *supra*, and in which one or more of the hydrogen atoms are replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine atom. Said C₁-C₆-haloalkyl group is,
 35 for example, a fluoromethyl-, difluoromethyl-, trifluoromethyl-, 2-fluoroethyl-,

2,2-difluoroethyl-, 2,2,2-trifluoroethyl-, pentafluoroethyl-, 3,3,3-trifluoropropyl- or a 1,3-difluoropropan-2-yl group. Particularly haloalkyl is trifluoromethyl or difluoromethyl.

The term "C₁-C₆-alkoxy" means a linear or branched, saturated, monovalent group of formula (C₁-C₆-alkyl)-O-, in which the term "C₁-C₆-alkyl" is as defined *supra*, such as, for example, a methoxy-, ethoxy-, *n*-propoxy-, isopropoxy-, *n*-butoxy-, *sec*-butoxy-, isobutoxy-, *tert*-butoxy-, pentyloxy-, isopentyloxy or a *n*-hexyloxy group, or an isomer thereof.

The term "C₁-C₆-haloalkoxy" means a linear or branched, saturated, monovalent C₁-C₆-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine atom. Said C₁-C₆-haloalkoxy group is, for example, a fluoromethoxy-, difluoromethoxy-, trifluoromethoxy-, 2,2,2-trifluoroethoxy- or a pentafluoroethoxy group.

The term cycloalkoxy means a cycloalkyl group as defined below which is attached to the rest of the molecule via an oxygen atom, e.g. a cyclopropyl-O-, a cyclobutyl-O-, a cyclopentyl-O- or a cyclohexyl-O- group.

Heterocycloalkoxy groups are heterocycloalkyl groups as defined herein attached to the rest of the molecule via an oxygen atom, e.g., a azetidinyloxy-, a oxetanyloxy- or a thietanyloxy-, a tetrahydrofuranyloxy-, a 1,3-dioxolanyloxy-, a thiolanyloxy-, a pyrrolidinyloxy-, a imidazolidinyloxy-, a pyrazolidinyloxy-, a 1,1-dioxidothiolanyloxy-, a 1,2-oxazolidinyloxy-, a 1,3-oxazolidinyloxy- or a 1,3-thiazolidinyloxy-, a tetrahydropyranyloxy-, a tetrahydrothiopyranyloxy-, a piperidinyloxy-, a morpholinylloxy-, a dithianylloxy-, a thiomorpholinylloxy-, a piperazinyloxy-, a 1,3-dioxanyloxy-, a 1,4-dioxanyloxy-, or a 1,2-oxazinanyloxy group.

The term "C₂-C₆-alkenyl" means a linear or branched, monovalent hydrocarbon group, which contains one or two double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("C₂-C₃-alkenyl"), it being understood that in the case in which said alkenyl group contains more than one double bond, then it is possible for said double bonds to be isolated from, or conjugated with, each other. Said alkenyl group is, for example, an ethenyl-, prop-2-enyl-, (*E*)-prop-1-enyl-, (*Z*)-prop-1-enyl-, *iso*-propenyl-, but-3-enyl-, (*E*)-but-2-enyl-, (*Z*)-but-2-enyl-, (*E*)-but-1-enyl-, (*Z*)-but-1-enyl-, 2-methylprop-2-enyl-, 1-methylprop-2-enyl-, 2-methylprop-1-enyl-, (*E*)-1-methylprop-1-enyl-, (*Z*)-1-methylprop-1-enyl-, buta-1,3-dienyl-, pent-4-enyl-, (*E*)-pent-3-enyl-, (*Z*)-pent-3-enyl-, (*E*)-pent-2-enyl-, (*Z*)-pent-2-enyl-, (*E*)-pent-1-enyl-, (*Z*)-pent-1-enyl-, 3-methylbut-3-enyl-, 2-methylbut-3-enyl-, 1-methylbut-3-enyl-, 3-methylbut-2-enyl-, (*E*)-2-methylbut-2-enyl-, (*Z*)-2-methylbut-2-enyl-,

- (E)-1-methylbut-2-enyl-, (Z)-1-methylbut-2-enyl-, (E)-3-methylbut-1-enyl-,
 (Z)-3-methylbut-1-enyl-, (E)-2-methylbut-1-enyl-, (Z)-2-methylbut-1-enyl-,
 (E)-1-methylbut-1-enyl-, (Z)-1-methylbut-1-enyl-, 1,1-dimethylprop-2-enyl-,
 1-ethylprop-1-enyl-, 1-propylvinyl-, 1-isopropylvinyl-, (E)-3,3-dimethylprop-1-enyl-,
 5 (Z)-3,3-dimethylprop-1-enyl-, penta-1,4-dienyl-, hex-5-enyl-, (E)-hex-4-enyl-,
 (Z)-hex-4-enyl-, (E)-hex-3-enyl-, (Z)-hex-3-enyl-, (E)-hex-2-enyl-, (Z)-hex-2-enyl-,
 (E)-hex-1-enyl-, (Z)-hex-1-enyl-, 4-methylpent-4-enyl-, 3-methylpent-4-enyl-,
 2-methylpent-4-enyl-, 1-methylpent-4-enyl-, 4-methylpent-3-enyl-,
 (E)-3-methylpent-3-enyl-, (Z)-3-methylpent-3-enyl-, (E)-2-methylpent-3-enyl-,
 10 (Z)-2-methylpent-3-enyl-, (E)-1-methylpent-3-enyl-, (Z)-1-methylpent-3-enyl-,
 (E)-4-methylpent-2-enyl-, (Z)-4-methylpent-2-enyl-, (E)-3-methylpent-2-enyl-,
 (Z)-3-methylpent-2-enyl-, (E)-2-methylpent-2-enyl-, (Z)-2-methylpent-2-enyl-,
 (E)-1-methylpent-2-enyl-, (Z)-1-methylpent-2-enyl-, (E)-4-methylpent-1-enyl-,
 (Z)-4-methylpent-1-enyl-, (E)-3-methylpent-1-enyl-, (Z)-3-methylpent-1-enyl-,
 15 (E)-2-methylpent-1-enyl-, (Z)-2-methylpent-1-enyl-, (E)-1-methylpent-1-enyl-,
 (Z)-1-methylpent-1-enyl-, 3-ethylbut-3-enyl-, 2-ethylbut-3-enyl-, 1-ethylbut-3-enyl-,
 (E)-3-ethylbut-2-enyl-, (Z)-3-ethylbut-2-enyl-, (E)-2-ethylbut-2-enyl-,
 (Z)-2-ethylbut-2-enyl-, (E)-1-ethylbut-2-enyl-, (Z)-1-ethylbut-2-enyl-,
 (E)-3-ethylbut-1-enyl-, (Z)-3-ethylbut-1-enyl-, 2-ethylbut-1-enyl-, (E)-1-ethylbut-1-enyl-,
 20 (Z)-1-ethylbut-1-enyl-, 2-propylprop-2-enyl-, 1-propylprop-2-enyl-,
 2-isopropylprop-2-enyl-, 1-isopropylprop-2-enyl-, (E)-2-propylprop-1-enyl-,
 (Z)-2-propylprop-1-enyl-, (E)-1-propylprop-1-enyl-, (Z)-1-propylprop-1-enyl-,
 (E)-2-isopropylprop-1-enyl-, (Z)-2-isopropylprop-1-enyl-, (E)-1-isopropylprop-1-enyl-,
 (Z)-1-isopropylprop-1-enyl-, hexa-1,5-dienyl- or a 1-(1,1-dimethylethyl)ethenyl group.
 25 Particularly, said group is a ethenyl- or a prop-2-enyl group.

The same definitions can be applied should the alkenyl group be placed within a chain as a bivalent "C₁-C₆-alkenylene" moiety. All names as mentioned above then will bear a "ene" added to their end, thus e.g., a "pentenyl" becomes a bivalent "pentenylene" group.

- The term "C₃-C₆-cycloalkyl-" means a saturated monocyclic or bicyclic hydrocarbon ring
 30 which contains 3, 4, 5, or 6, carbon atoms ("C₃-C₆-cycloalkyl-"). Said C₃-C₆-cycloalkyl-
 group may be, for example, a monocyclic hydrocarbon ring, such as, for example, a
 cyclopropyl-, cyclobutyl-, cyclopentyl-, cyclohexyl- cycloheptyl ring- a cyclooctyl or a
 cyclononyl ring, or a bicyclic hydrocarbon ring, such as decalinyl ring. Particularly, said
 hydrocarbon ring is monocyclic and contains 5, or 6 carbon atoms ("C₅-C₆-cycloalkyl-"),
 35 such as, for example, cyclopentyl-, or a cyclohexyl ring. A cycloalkyl group may be
 optionally substituted as defined at the respective part wherein such term is used.

The term "C₄-C₆-cycloalkenyl" means a monovalent, mono- or bicyclic hydrocarbon ring which contains 4, 5, or 6 carbon atoms and one double bond. Said C₄-C₆-cycloalkenyl group is, for example, a monocyclic hydrocarbon ring, such as, for example, a cyclobutenyl-, cyclopentenyl-, or a cyclohexenyl-, group. More particularly the
 5 cycloalkenyl group is a C₅-C₆-cycloalkenyl group.

The terms "3- to 9-membered heterocycloalkyl" and "4- to 6-membered heterocycloalkyl" mean a monocyclic, saturated heterocycle with 4, 5, 6, 7, 8 or 9 or, respectively, 4, 5 or 6 ring atoms in total, which contains one or two identical or different ring heteroatoms from the series N, O and S, it being possible for said heterocycloalkyl group to be attached
 10 to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom.

Said heterocycloalkyl group, without being limited thereto, can be a 4-membered ring, such as, for example, a azetidinyl-, oxetanyl- or thietanyl group; or a 5-membered ring, such as a tetrahydrofuranyl-, 1,3-dioxolanyl-, thiolanyl-, pyrrolidinyl-, imidazolidinyl-, pyrazolidinyl-, 1,1-dioxidothiolanyl-, 1,2-oxazolidinyl-, 1,3-oxazolidinyl- or a
 15 1,3-thiazolidinyl group, for example; or a 6-membered ring, such as, for example, a tetrahydropyranyl-, tetrahydrothiopyranyl-, piperidinyl-, morpholinyl-, dithianyl-, thiomorpholinyl-, piperazinyl-, 1,3-dioxanyl-, 1,4-dioxanyl- or a 1,2-oxazinanyl group, for example, or a 7-membered ring, such as an azepanyl-, 1,4-diazepanyl- or a 1,4-oxazepanyl group, for example.

The term a "partially unsaturated 3- to 9-membered heterocycloalkyl" means a monocyclic, unsaturated, non-aromatic heterocycle with 5, 6, 7, 8 or 9 ring atoms in total, which contains one or two double bonds and one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said partially unsaturated heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon
 20 atoms or, if present, a nitrogen atom. The term "partially unsaturated heterocycloalkane", as used herein, refers to a compound consisting of a partially unsaturated heterocycloalkyl group as defined herein, and a hydrogen atom to which said partially unsaturated heterocycloalkyl group is bonded with its one valency.

Said partially unsaturated heterocycloalkyl group is, for example, 4*H*-pyranyl, 2*H*-pyranyl,
 30 3,6-dihydro-2*H*-pyran-4-yl, 5,6-dihydro-2*H*-pyran-3-yl, tetrahydropyridinyl, e.g. 1,2,3,6-tetrahydropyridin-4-yl, or 1-methyl-1,2,3,6-tetrahydropyridin-4-yl, dihydropyridinyl, e.g. 1,6-dihydropyridinyl, 6-oxo-1,6-dihydropyridin-3-yl, 2,5-dihydro-1*H*-pyrrolyl, [1,3]dioxolyl, 4*H*-[1,3,4]thiadiazinyl, 2,5-dihydrofuranyl, 2,3-dihydrofuranyl, 2,5-dihydrothiophenyl, 2,3-dihydrothiophenyl, 4,5-dihydrooxazolyl or 4*H*-[1,4]thiazinyl.

The term “aryl” means a phenyl-, naphthyl-, 5,6-dihydronaphthyl-, 7,8-dihydronaphthyl-, 5,6,7,8-tetrahydronaphthyl-, an indanyl-, or an indenyl group, which is unsubstituted or substituted with one, two, three, four or five substituents, each substituent independently selected from a halogen atom, a cyano group, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, a C₁-C₃-alkoxy group, a C₁-C₃-thioalkyl group, a C₁-C₃-haloalkoxy group, a C₁-C₃-halothioalkyl group, a C₃-C₅-cycloalkyl group, particularly a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, a C₁-C₃-alkoxy group, and a C₁-C₃-haloalkoxy group.

The term “heteroaryl” means a monovalent, monocyclic, bicyclic or tricyclic aromatic ring having 5, 6, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a “5- to 14-membered heteroaryl” group), particularly 5, 6, 9 or 10 ring atoms, more particularly 5 or 6 ring atoms, which contains at least one ring heteroatom and optionally one, two or three further ring heteroatoms from the series: N, O and/or S, and which is bound via a ring carbon atom or optionally via a ring nitrogen atom (if allowed by valency).

Said heteroaryl group can be a 5-membered heteroaryl group, such as, for example, a thienyl-, furanyl-, pyrrolyl-, oxazolyl-, thiazolyl-, imidazolyl-, pyrazolyl-, isoxazolyl-, isothiazolyl-, oxadiazolyl-, triazolyl-, thiadiazolyl- or a tetrazolyl group; or a 6-membered heteroaryl group, such as, for example, a pyridyl-, pyridazinyl-, pyrimidyl-, pyrazinyl- or a triazinyl group; or a benzo-fused 5-membered heteroaryl- group, such as, for example, a benzofuranyl-, benzothienyl-, benzoxazolyl-, benzisoxazolyl-, benzimidazolyl-, benzothiazolyl-, benzotriazolyl-, indazolyl-, indolyl- or a isoindolyl group; or a benzo-fused 6-membered heteroaryl group, such as, for example, a quinolinyl-, quinazolinyl-, isoquinolinyl-, cinnolinyl-, phthalazinyl- or quinoxalinyl-; or another bicyclic group, such as, for example, indoliziny-, purinyl- or a pteridinyl group; or a tricyclic heteroaryl group, such as, for example, a carbazolyl-, acridinyl- or a phenazinyl group; or a 9-membered heteroaryl group, such as, for example, a benzofuranyl-, benzothienyl-, benzoxazolyl-, benzisoxazolyl-, benzimidazolyl-, benzothiazolyl-, benzotriazolyl-, indazolyl-, indolyl-, isoindolyl-, indoliziny- or a purinyl group.

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

The term “C₁-C₆”, as used throughout this text, e.g., in the context of the definition of “C₁-C₆-alkyl-”, “C₁-C₆-haloalkyl-”, “C₁-C₆-alkoxy-” or “C₁-C₆-haloalkoxy-” is to be understood as meaning an alkyl group having a whole number of carbon atoms from 1 to 6, i.e., 1, 2,

3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C₁-C₆" is to be interpreted as disclosing any sub-range comprised therein, e.g. C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; particularly C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more particularly C₁-C₄; in the case of "C₁-C₆-haloalkyl-" or "C₁-C₆-haloalkoxy-" even more particularly C₁-C₂.

Similarly, as used herein, the term "C₂-C₆", as used throughout this text, e.g., in the context of the definitions of "C₂-C₆-alkenyl-" and "C₂-C₆-alkynyl-", is to be understood as meaning an alkenyl- group or an alkynyl group having a whole number of carbon atoms from 2 to 6, i.e., 2, 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C₂-C₆" is to be interpreted as disclosing any sub-range comprised therein, e.g., C₂-C₆, C₃-C₅, C₃-C₄, C₂-C₃, C₂-C₄, C₂-C₅; particularly C₂-C₃.

Further, as used herein, the term "C₃-C₇", as used throughout this text, e.g., in the context of the definition of "C₃-C₇-cycloalkyl-", is to be understood as meaning a cycloalkyl- group having a whole number of carbon atoms of 3 to 7, i.e., 3, 4, 5, 6 or 7 carbon atoms. It is to be understood further that said term "C₃-C₇" is to be interpreted as disclosing any sub-range comprised therein, e.g., C₃-C₆, C₄-C₅, C₃-C₅, C₃-C₄, C₄-C₆, C₅-C₇; particularly C₃-C₆.

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

As used herein, the term "protective group" is a protective group attached to an oxygen or nitrogen atom in intermediates used for the preparation of compounds of the general formula (I). Such groups are introduced e.g., by chemical modification of the respective hydroxy or amino group in order to obtain chemoselectivity in a subsequent chemical reaction. Protective groups for hydroxy and amino groups are described for example in T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 4th edition, Wiley 2006; more specifically, protective groups for amino groups can be selected from substituted sulfonyl groups, such as a mesyl-, tosyl- or a phenylsulfonyl group, acyl

groups such as a benzoyl-, acetyl- or a tetrahydropyranyloxy group, or carbamate based groups, such as a *tert*-butoxycarbonyl group (Boc). Protective groups for hydroxy groups can be selected from acyl groups such as a benzoyl-, acetyl, pivaloyl- or a tetrahydropyranyloxy group, or can include silicon, as in e.g., a *tert*-butyldimethylsilyl-, *tert*-butyldiphenylsilyl-, triethylsilyl- or a triisopropylsilyl group.

The term "substituent" refers to a group "substituted" on, e.g., an alkyl, haloalkyl, cycloalkyl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, aryl, or heteroaryl group at any atom of that group, replacing one or more hydrogen atoms therein. In one aspect, the substituent(s) on a group are independently any one single, or any combination of two or more of the permissible atoms or groups of atoms delineated for that substituent. In another aspect, a substituent may itself be substituted with any one of the above substituents. Further, as used herein, the phrase "optionally substituted" means unsubstituted (e.g., substituted with an H) or substituted.

It will be understood that the description of compounds herein is limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding with regard to valencies, etc. and to give compounds which are not inherently unstable. For example, any carbon atom will be bonded to two, three, or four other atoms, consistent with the four valence electrons of carbon.

By "subject" is meant a mammal, including, but not limited to, a human or non-human mammal, such as a bovine, equine, canine, ovine, rodent, or feline.

An "oxo" substituent in the context of the invention means an oxygen atom, which is bound to a carbon atom via a double bond.

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

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

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

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

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

- With respect to the treatment and/or prophylaxis of the diseases specified herein the
10 isotopic variant(s) of the compounds of general formula (I) particularly contain deuterium (“deuterium-containing compounds of general formula (I)”). Isotopic variants of the compounds of general formula (I) in which one or more radioactive isotopes, such as ^3H or ^{14}C , are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and
15 detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula (I). These isotopic variants of the compounds of general formula (I) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C -containing compounds of general formula (I) can be used in mass spectrometry analyses (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131) in the context of preclinical or clinical
20 studies.

- Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, particularly for a deuterium-containing reagent. Depending on the desired sites of
25 deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds (Esaki et al., Tetrahedron, 2006, 62, 10954; Esaki et al., Chem. Eur. J., 2007, 13, 4052). Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131; J. R. Morandi et al., J. Org. Chem., 1969, 34 (6), 1889) and acetylenic bonds (N. H. Khan, J. Am. Chem. Soc., 1952, 74 (12), 3018; S. Chandrasekhar et al., Tetrahedron Letters, 2011, 52, 3865) is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons (J. G. Atkinson et al., US
30 Patent 3966781). A variety of deuterated reagents and synthetic building blocks are
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commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA. Further information on the state of the art with respect to deuterium-hydrogen exchange is given for example in Hanzlik et al., J. Org. Chem. 55, 3992-3997, 1990; R. P. Hanzlik et al., Biochem. Biophys. Res. Commun. 160, 844, 1989; P. J. Reider et al., J. Org. Chem. 52, 3326-3334, 1987; M. Jarman et al., Carcinogenesis 16(4), 683-688, 1995; J. Atzrodt et al., Angew. Chem., Int. Ed. 2007, 46, 7744; K. Matoishi et al., Chem. Commun. 2000, 1519-1520; K. Kassahun et al., WO2012/112363.

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

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., J. Am. Chem. Soc., 2007, 129, 4490; A. Streitwieser et al., J. Am. Chem. Soc., 1963, 85, 2759;], basicity [C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641; C. L. Perrin, et al., J. Am. Chem. Soc., 2003, 125, 15008; C. L. Perrin in Advances in Physical Organic Chemistry, 44, 144], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102; D. J. Kushner et al., Can. J. Physiol. Pharmacol., 1999, 77, 79). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al.,

Chem. Res. Toxicol., 2013, 26, 410; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208) and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. / Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of general formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium-containing compound(s) of general formula (I) is/are attached to a carbon atom and/or is/are located at those positions of the compound of general formula (I), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P₄₅₀.

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

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

The compounds of the present invention optionally contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. It is possible that one or more asymmetric carbon atoms are present in the (R) or (S) configuration, which can result in racemic mixtures in the case of a single asymmetric centre, and in diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, it is possible that asymmetry also be present due to restricted rotation

about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

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

Preferred isomers are those which produce the more desirable biological activity should they be different for the isomers. These separated, pure or partially purified isomers or
10 racemic mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art including chiral high pressure liquid chromatography (HPLC), the formation and crystallization of chiral salts, or prepared by asymmetric syntheses.

15 The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the
20 basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., HPLC columns using a chiral phase), with or without conventional derivatisation, optimally
25 chosen to maximise the separation of the enantiomers. Suitable HPLC columns using a chiral phase are commercially available, such as those manufactured by Daicel, e.g., Chiracel OD and Chiracel OJ, for example, among many others, which are all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of the present invention can likewise be obtained by chiral
30 syntheses utilizing optically active starting materials.

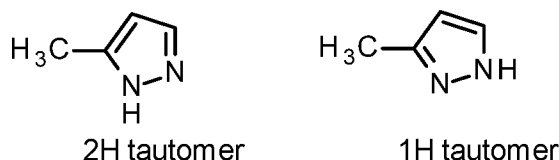
In order to distinguish different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, e.g.
35 (R)- or (S)- isomers, in any ratio. Isolation of a single stereoisomer, e.g. a single

enantiomer or a single diastereomer, of a compound of the present invention can be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, it is possible for the compounds of the present invention to exist as tautomers.

- 5 For example, any compound of the present invention which contains an pyrazol moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, namely :



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

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

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

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

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

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

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

A "pharmaceutically acceptable anion" refers to the deprotonated form of a conventional
25 acid, such as, for example, a hydroxide, a carboxylate, a sulfate, a halide, a phosphate, or a nitrate.

Physiologically acceptable salts of the compounds according to the invention also comprise salts of conventional bases, such as, by way of example and by preference, alkali metal salts (for example lithium, sodium and potassium salts), alkaline earth metal
30 salts (for example calcium, strontium and magnesium salts) or an aluminium salt or a zinc salt, or an ammonium salt derived from ammonia or from an organic primary, secondary or tertiary amine having 1 to 20 carbon atoms, such as by way of example and by preference, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine,
35 dimethylaminoethanol, diethylaminoethanol, tris(hydroxymethyl)aminomethane,

procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, 1,2-ethylenediamine, *N*-methylpiperidine, *N*-methyl-glucamine, *N,N*-dimethyl-glucamine, *N*-ethyl-glucamine, 1,6-hexanediamine, glucosamine, sarcosine, serinol, 2-amino-1,3-propanediol, 3-amino-1,2-propanediol, 4-amino-1,2,3-butanetriol.

- 5 Additionally, the compounds according to the invention may form salts with a quaternary ammonium ion obtainable, *e.g.*, by quaternisation of a basic nitrogen-containing group with agents such as lower alkylhalides, such as alkylchlorides, *e.g.* methylchloride, ethylchloride, propylchloride and butylchloride; such as alkylbromides, *e.g.* methylbromide, ethylbromide, propylbromide and butylbromide; and such as
10 alkyl iodides; *e.g.* methyl iodide, ethyl iodide, propyl iodide and butyl iodide; dialkylsulfates such as dimethylsulfate, diethylsulfate, dibutylsulfate and diamylsulfates, long chain halides such as *e.g.* decylchloride, laurylchloride, myristylchloride and stearylchloride, decylbromide, laurylbromide, myristylbromide and stearyl bromide, decyl iodide, lauryl iodide, myristyl iodide and stearyl iodide, aralkylhalides such as benzylchloride,
15 benzylbromide, benzyl iodide and phenethylbromides and others. Examples of suitable quaternary ammonium ions are tetramethylammonium, tetraethylammonium, tetra(*n*-propyl)ammonium, tetra (*n*-butyl)ammonium, or *N*-benzyl-*N,N,N*-trimethylammonium.

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

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

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

Unless specified otherwise, suffixes to chemical names or structural formulae relating to salts, such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF₃COOH", "x Na⁺", for example, mean a salt form, the stoichiometry of which salt form not being specified.

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

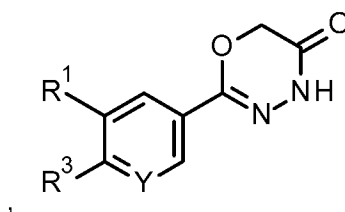
- 5 Solvates and hydrates of disclosed intermediates or example compounds, or salts thereof, which have been obtained, by the preparation and/or purification processes described herein, may be formed in any ratio.

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

Moreover, the present invention also includes prodrugs of the compounds according to the invention. The term “prodrugs” designates compounds which themselves can be biologically active or inactive, but are converted (for example metabolically or hydrolytically) into compounds according to the invention during their residence time in
15 the body. For example, a prodrug may be in the form of an in vivo hydrolysable ester of the specified compound. Derivatives of the compounds of formula (I) and the salts thereof which are converted into a compound of formula (I) or a salt thereof in a biological system (bioprecursors or pro-drugs) are covered by the invention. Said biological system may be, for example, a mammalian organism, particularly a human subject. The bioprecursor
20 is, for example, converted into the compound of formula (I) or a salt thereof by metabolic processes.

DESCRIPTION

In accordance with a first aspect, the present invention includes compounds of general formula (I), *supra*,



formula (I)

wherein

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group,

5 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group;

10 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

15 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

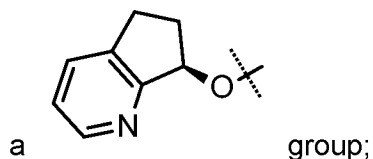
a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and

20 a 5- to 6-membered heteroaryl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded; a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;

25



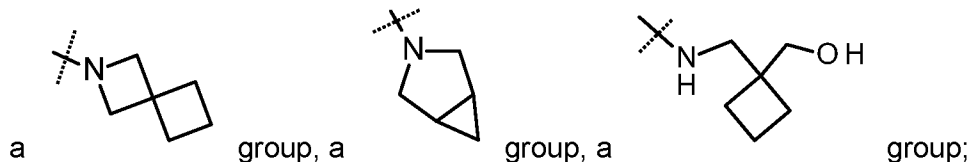
a 4- to 6-membered heterocycloalkoxy group,

a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group;

5 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



10 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a cyano group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

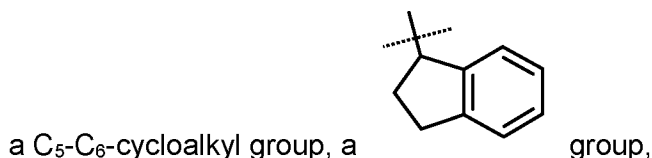
and

15 a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

20 a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a 4- to 6-membered heterocycloalkyl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl, whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,



25 a 4- to 6-membered heterocycloalkyl group, and

a C(O)-(C₁-C₆-alkyl) group;

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

In accordance with a further embodiment of the first aspect, the present invention includes compounds of general formula (I), *supra*, wherein

5 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

10 a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

15 a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group;

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

20 a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

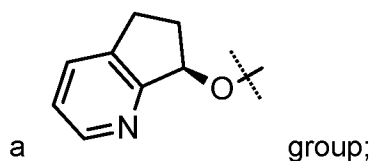
a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

25 a C₁-C₃-alkyl group, and

a 5- to 6-membered heteroaryl group,

with the proviso that R³ as an unsubstituted C₁-C₄-alkyl group or an unsubstituted C₁-C₄-alkoxy group is excluded;

30 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;



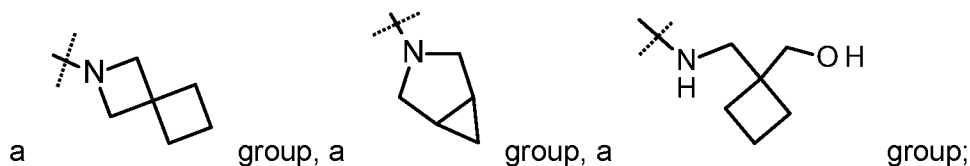
a 4- to 6-membered heterocycloalkoxy group,

a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group;

- 5 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group;

- 10 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

- 15 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a cyano group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

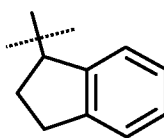
and

a NR⁵R⁶ group,

- 20 R⁵ is a hydrogen atom;

R⁶ is selected from

- 25 a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a 4- to 6-membered heterocycloalkyl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl, whereby said C₃-C₆-cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,



a C₅-C₆-cycloalkyl group, a group,

a 4- to 6-membered heterocycloalkyl group, and

a C(O)-(C₁-C₆-alkyl) group;

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom;

10 R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with

a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

15 a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group,

a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

20 a C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

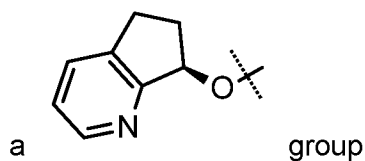
a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

25 a C₁-C₃-alkyl group, and

a 5- to 6-membered heteroaryl group,

with the proviso that an unsubstituted methoxy group is excluded;

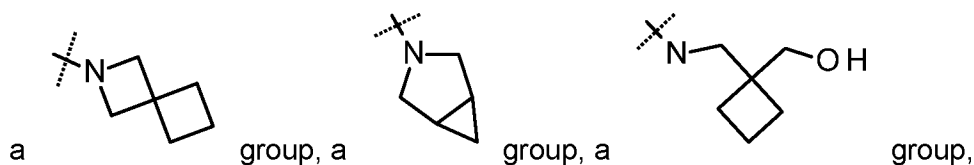
a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,



5 a C₅-C₆-cycloalkenyl group,

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group,

10 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



15 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a cyano group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, and

a NR⁵R⁶ group,

20 R⁵ is a hydrogen atom;

R⁶ is selected from

25 a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a 4- to 6-membered heterocycloalkyl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl group,

whereby said C₃-C₆-cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,

a C₅-C₆-cycloalkyl group,

a 4- to 6-membered heterocycloalkyl group, and

a C(O)-(C₁-C₆-alkyl) group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt

5 of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

10 Y is CR or N, where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group,

15 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group,

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

20 a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

25 amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N,

R³ as an unsubstituted methyl group is excluded; a 4- to 6-membered cycloalkoxy

30 group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,

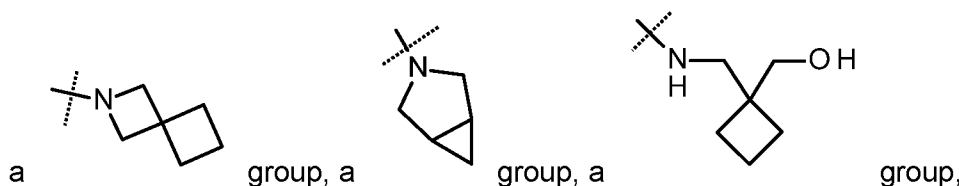
a 4- to 6 membered heterocycloalkoxy group;

a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group,

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group,

5 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



10 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group,

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a cyano group, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, and

a NR⁵R⁶ group,

15 R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

20 a C₅-C₆-cycloalkyl group,

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

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

25 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR or N, where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

30 a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group,

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

with the proviso that R³ as an unsubstituted C₁-C₄-alkyl group or an unsubstituted C₁-C₄-alkoxy group is excluded;

R³ as an unsubstituted methyl group is excluded; a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,

a 4- to 6 membered heterocycloalkoxy group;

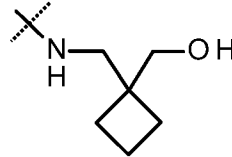
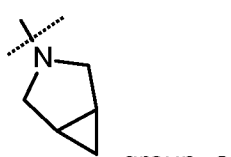
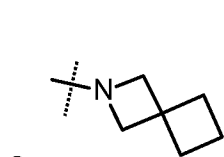
a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group,

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group,

a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group,

a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group,

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a cyano group, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, and

a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

a C₅-C₆-cycloalkyl group,

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR², where R² is a hydrogen atom, or a halogen atom;

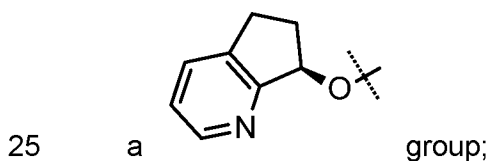
R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and a 5- to 6-membered heteroaryl group;

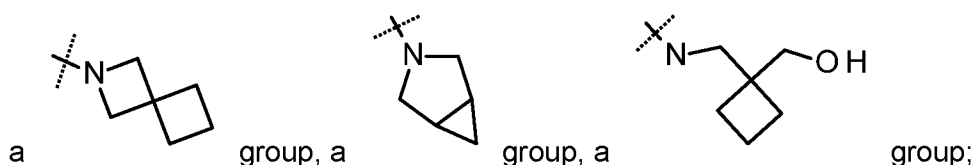
with the proviso that an unsubstituted methoxy group is excluded;

a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;



a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

- 5 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, and a C₁-C₃-haloalkyl group; and

a NR⁵R⁶ group;

R⁵ is a hydrogen atom;

- 10 R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

a C(O)-(C₁-C₆-alkyl) group,

- 15 a C₅-C₆-cycloalkyl group, and

a 4- to 6-membered heterocycloalkyl group;

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR² or N, where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

- 25 a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group, and

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

C₁-C₃-haloalkyl group,

5

a hydroxy group,

a C₁-C₃-alkoxy group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

a C₁-C₃-alkyl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N,

10

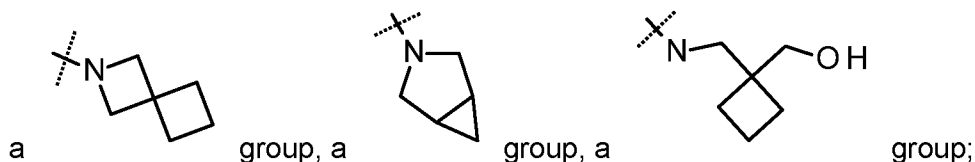
R³ as an unsubstituted methyl group is excluded; a 4- to 6-membered heterocycloalkoxy group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more

15

times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-

20

C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

a NR⁵R⁶ group;

25

R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

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

5 R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;

Y is CR^2 or N , where R^2 is a hydrogen atom, or a halogen atom;

R^3 is selected from

a C_1 - C_6 -alkyl group which is optionally substituted with a group independently selected from

10 a C_1 - C_3 -alkoxy group, and

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C_1 - C_3 -alkyl group;

a C_2 - C_4 -alkenyl group, which is optionally substituted with a C_1 - C_3 -alkoxy group,

a C_1 - C_6 -alkoxy group which is optionally substituted with a group independently selected from

C_1 - C_3 -haloalkyl group,

a hydroxy group,

a C_1 - C_3 -alkoxy group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

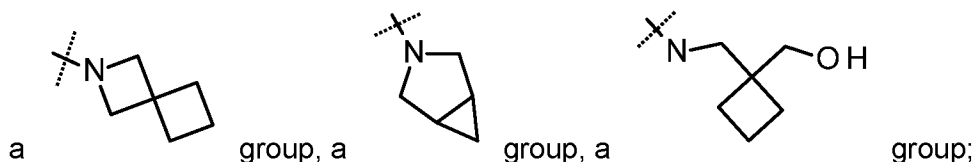
20 a C_1 - C_3 -alkyl group,

with the proviso that R^3 as an unsubstituted C_1 - C_4 -alkoxy group or R^3 as an unsubstituted C_1 - C_4 -alkyl group is excluded;

a 4- to 6-membered heterocycloalkoxy group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C_1 - C_3 -haloalkyl group;

25 a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C_1 - C_3 -alkyl group, and a cyano group;



- a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;
- 5 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and
- a NR⁵R⁶ group;
- R⁵ is a hydrogen atom;
- R⁶ is selected from
- 10 a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.
- 15 In accordance with a further embodiment of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which
- R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;
- Y is CR², where R² is a hydrogen atom, or a halogen atom;
- R³ is selected from
- 20 a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from
- a C₁-C₃-alkoxy group, and
- a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;
- 25 a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,
- a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from
- C₁-C₃-haloalkyl group,
- a hydroxy group,
- 30 a C₁-C₃-alkoxy group,

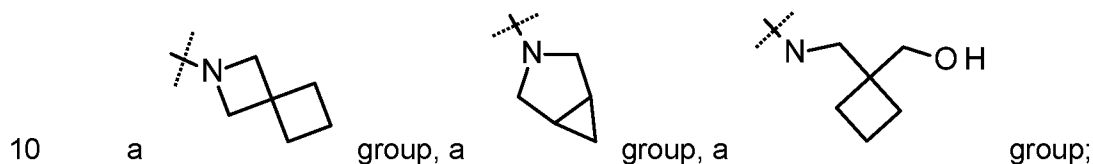
a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

with the proviso that an unsubstituted methoxy group is excluded;

a 4- to 6-membered heterocycloalkoxy group;

5 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

15 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

a NR⁵R⁶ group;

R⁵ is a hydrogen atom;

R⁶ is selected from

20 a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR², where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

5 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

10 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and

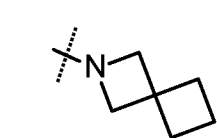
a 5- to 6-membered heteroaryl group,

with the proviso that an unsubstituted methoxy group is excluded;

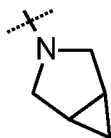
15 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group,

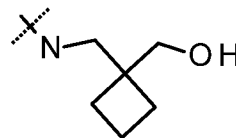
20 a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group,



group, a



group, a



group,

25 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-haloalkyl group,

a NR⁵R⁶ group,

R⁵ is a hydrogen atom

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

a C₅-C₆-cycloalkyl group, and

5 a 4- to 6-membered heterocycloalkyl group;

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

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

10 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR², where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

15 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

20 a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and

a 5- to 6-membered heteroaryl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N,

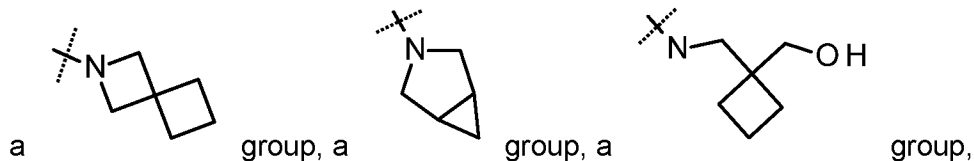
25 R³ as an unsubstituted methyl group is excluded;

a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group,

30

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group,



5 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-haloalkyl group,

a NR⁵R⁶ group,

R⁵ is a hydrogen atom

10 R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

a C₅-C₆-cycloalkyl group, and

15 a 4- to 6-membered heterocycloalkyl group;

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

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

20 R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, or a trifluoromethyl group;

Y is C-R² and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

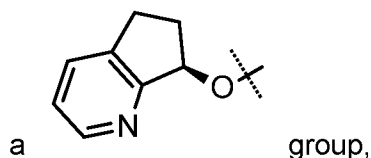
with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time;

25 R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, a -CH₂-N(CH₃)₂ group,

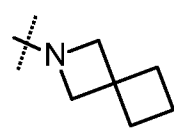
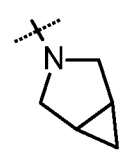
a -CH=C(CH₃)₂ group, a -CH=CH-CH₂-O-CH₃ group, a -CH=CH-CH₂-O-CH₂-CH₃ group,

a cyclopent-1-en-1-yl group,

- a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-(CH₂)₂-C(CH₃)₃ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(pyrazol-3-yl) group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,

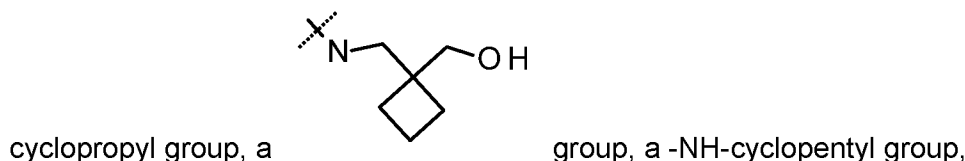


- a 4-chlorophenyl group, a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group, a piperidin-1-yl group, a 3-hydroxy-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-

- hydroxy-3-methylazetidin-1-yl, a  group, a  group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group, a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

- a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-chloro-pyridin-6-yl group, a 3-fluoro-pyrazol-1-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group,

- a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-



- a -NH-(3-tetrahydrofuryl) group,

- a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-(pyrazol-5-yl) group, a -NH-CH₂-pyrazin-2-yl group, and

a -NH-C(O)-CH₂-CH₃ group,

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR² or N where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

10 a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group, and

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

15 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group, and

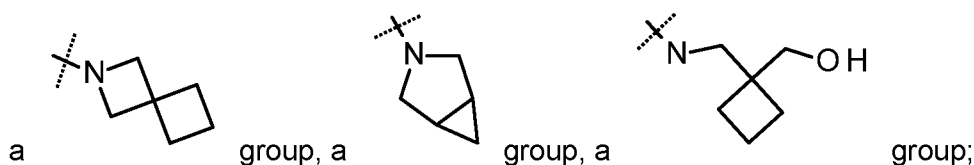
20 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded;

a 4- to 6-membered heterocycloalkoxy group;

25 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

- 5 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

a NR⁵R⁶ group;

R⁵ is a hydrogen atom;

- 10 R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

15

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR² or N where R² is a hydrogen atom, or a halogen atom;

- 20 R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group, and

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

25

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

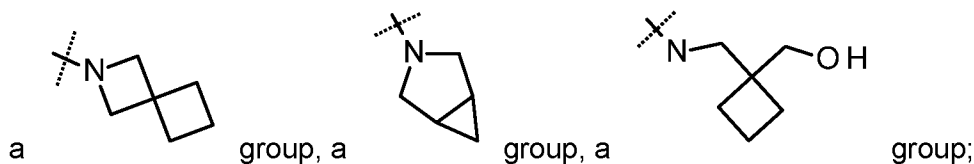
C₁-C₃-haloalkyl group,
 a hydroxy group,
 a C₁-C₃-alkoxy group, and
 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with
 a C₁-C₃-alkyl group,

with the proviso that R³ as an unsubstituted C₁-C₄-alkoxy group or R³ as an unsubstituted C₁-C₄-alkyl group is excluded;

a 4- to 6-membered heterocycloalkoxy group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

a NR⁵R⁶ group;

R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

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

R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, or a trifluoromethyl group;

5 Y is C-R² or N and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

R³ is selected from

a C₁-C₄-alkyl group which is optionally substituted with

a methoxy group,

10 a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

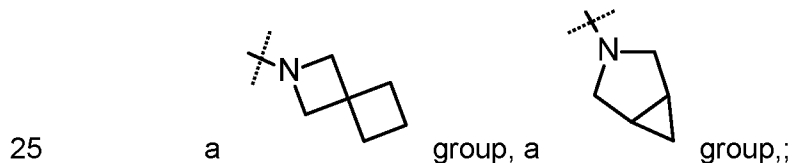
15 a C₁-C₃-alkoxy group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded;

20 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

and

30 a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

- 5 a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

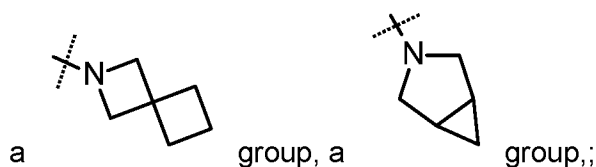
In accordance with a further embodiment of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which:

- 10 R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, or a trifluoromethyl group;

Y is C-R² or N and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

R³ is selected from

- 15 a C₁-C₄-alkyl group which is optionally substituted with
- a methoxy group,
- a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;
- a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from
- 20 a C₁-C₃-haloalkyl group,
- a hydroxy group,
- a C₁-C₃-alkoxy group,
- a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
- 25 with the proviso that R³ as an unsubstituted C₁-C₄-alkoxy group or R³ as an unsubstituted C₁-C₄-alkyl group is excluded;
- a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;
- a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more
- 30 times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

5 and

a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

10 a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

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

R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, or a trifluoromethyl group;

Y is C-R² and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

20 R³ is selected from

a C₁-C₄-alkyl group which is optionally substituted with a group independently selected from

a methoxy group, and

25 a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

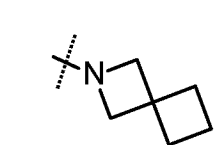
a C₁-C₃-alkoxy group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

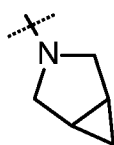
with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



a group, a



group,;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

and

a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

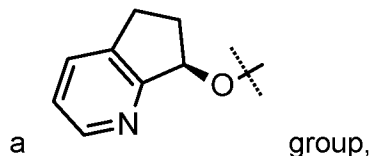
In accordance with a further embodiment of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which:

R¹ is a trifluoromethyl group,

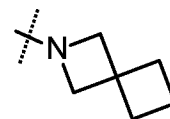
Y is C-R² and R² is a hydrogen atom,

R³ is selected from a -CH₂-(morpholin-4-yl) group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃-CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃

group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,



a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,



a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group, a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-cyclopropyl group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, and a -NH-C(O)-CH₂-CH₃ group;

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

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

R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

Y is C-R² or N and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time;

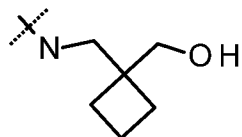
R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group,

- a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,
 a cyclopropyl group,
 a cyclopent-1-en-1-yl group,
 a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃
 5 group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-
 (CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-
 cyclobutyl group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,
 a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-
 trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-
 10 trifluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 3-methyl-
 4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-
 difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl
 group,
 a piperidin-1-yl group, a 1-methyl-piperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group,
 15 a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-
 hydroxy-piperidin-1-yl group, a 3-hydroxy-2-(propan-2-yl)azetidin-1-yl group, a 2-
 hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-



- methylazetidin-1-yl, a group, a group, a pyrrolidin-1-yl
 group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl
 20 group,
 a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-didehydro-1H-pyrrol-3-yl group,
 a 1-methyl-2,5-didehydro-1H-pyrrol-3-yl group;
 a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a
 piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-
 25 ethylparazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethyl-
 pyrazol-1-yl group, a 4-trifluoromethyl-pyrazol-1-yl group, a 3,5-dimethyl-1,2-
 oxazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-
 1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-
 difluoromethyl-1H-1,2,4-triazol-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



group, a -NH-cyclopentyl group,

a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a -NH-C(O)-CH₂-CH₃ group,

a cyano group,

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

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

R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

Y is C-R² or N and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group, a cyclopropyl group,

a cyclopent-1-en-1-yl group,

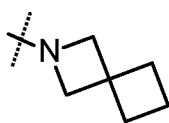
a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-trifluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 3-methyl-4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group,

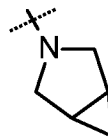
a piperidin-1-yl group, a 1-methyl-piperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3-hydroxy-2-(propan-2-yl)azetidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-

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methylazetidin-1-yl, a



group, a



group, a pyrrolidin-1-yl

group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group,

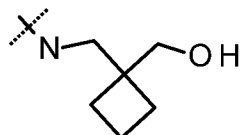
a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-didehydro-1H-pyrrol-3-yl group, a 1-methyl-2,5-didehydro-1H-pyrrol-3-yl group;

10

a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-ethylpyrazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethylpyrazol-1-yl group, a 4-trifluoromethylpyrazol-1-yl group, a 3,5-dimethyl-1,2-oxazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-difluoromethyl-1H-1,2,4-triazol-1-yl group,

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a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



group, a -NH-cyclopentyl group,

20

a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a -NH-C(O)-CH₂-CH₃ group,

a cyano group,

25

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

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

R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

Y is C-R² or N and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

R³ is selected from a a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

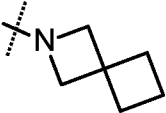
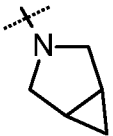
5 a cyclopropyl group,

a cyclopent-1-en-1-yl group,

a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

10 a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-trifluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 3-methyl-4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group,

15 a piperidin-1-yl group, a 1-methyl-piperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3-hydroxy-2-(propan-2-yl)azetidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-

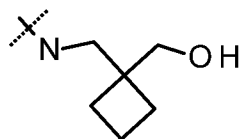
20 methylazetidin-1-yl, a  group, a  group, a pyrrolidin-1-yl group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group,

25 a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-didehydro-1H-pyrrol-3-yl group, a 1-methyl-2,5-didehydro-1H-pyrrol-3-yl group;

30 a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-ethylparazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethylpyrazol-1-yl group, a 4-trifluoromethylpyrazol-1-yl group, a 3,5-dimethyl-1,2-oxazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-

1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-difluoromethyl-1H-1,2,4-triazol-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



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group, a -NH-cyclopentyl group,

a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a -NH-C(O)-CH₂-CH₃ group,

a cyano group,

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

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

R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

15 Y is C-R² and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time;

R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

20 a cyclopropyl group,

a cyclopent-1-en-1-yl group,

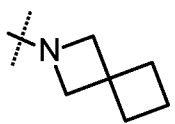
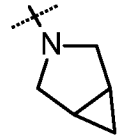
a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-CH₂-(oxolan-2-yl) group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

25

a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-difluoromethylphenyl group, a 2-trifluoromethylphenyl group, a 2-trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-trifluoromethylphenyl group, a 4-chloro-2-

trifluoromethylphenyl group, a 3-methyl-4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methylphenyl group, a 3-fluoro-4-methyl-phenyl group,

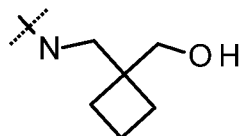
an azepan-4-yl group, a 1,4-oxazepan-4-yl group, a piperidin-1-yl group, a 1-methylpiperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 4-methyl-piperazin-1-yl group, a 3-hydroxy-3-(propan-2-yl)azetidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-

10 methylazetidin-1-yl, a  group, a  group, a pyrrolidin-1-yl group, a 3-hydroxy-3-methyl-pyrrolidine group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group,

a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-dihydro-1H-pyrrol-3-yl group, a 1-methyl-2,5-dihydro-1H-pyrrol-3-yl group;

15 a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-ethylpyrazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethylpyrazol-1-yl group, a 4-trifluoromethyl-pyrazol-1-yl group, a 3,5-dimethyl-1,2-oxazol-4-yl group, a 4-trifluoromethyl-1H-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-2H-1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-difluoromethyl-1H-1,2,4-triazol-1-yl group, a 4-methyl-3-trifluoromethyl-1H-pyrazol-1-yl group,

20 a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



group, a -NH-cyclopentyl group,

25 a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a -NH-C(O)-CH₂-CH₃ group,

a cyano group,

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

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

5 R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

Y is C-R² and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

R³ is selected from a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

10 a cyclopropyl group,

a cyclopent-1-en-1-yl group,

a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-CH₂-(oxolan-2-yl) group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

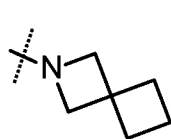
15

a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-difluoromethylphenyl group, a 2-trifluoromethylphenyl group, a 2-trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-trifluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 3-methyl-4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methylphenyl group, a 3-fluoro-4-methyl-phenyl group,

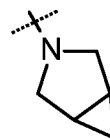
20

an azepan-4-yl group, a 1,4-oxazepan-4-yl group, a piperidin-1-yl group, a 1-methyl-piperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 4-methyl-piperazin-1-yl group, a 3-hydroxy-3-(propan-2-yl)azetidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-

25



methylazetidin-1-yl, a



group, a

pyrrolidin-1-yl

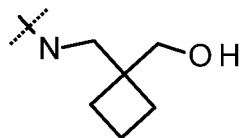
group, a 3-hydroxy-3-methyl-pyrrolidin group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group,

30

a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-dihydro-1H-pyrrol-3-yl group, a 1-methyl-2,5-dihydro-1H-pyrrol-3-yl group;

a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-ethylpyrazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethylpyrazol-1-yl group, a 4-trifluoromethyl-pyrazol-1-yl group, a 3,5-dimethyl-1,2-oxazol-4-yl group, a 4-trifluoromethyl-1H-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-2H-1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-difluoromethyl-1H-1,2,4-triazol-1-yl group, a 4-methyl-3-trifluoromethyl-1H-pyrazol-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



group, a -NH-cyclopentyl group,

a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a -NH-C(O)-CH₂-CH₃ group,

a cyano group,

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

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

R¹ is a hydrogen atom, a fluorine atom or a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom, or a fluorine atom,

R³ is selected from a -CH₂-(morpholin-4-yl) group, a CH₂-N(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group,

a -CH=CH-CH(CH₃)CH₃ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

a cyclopropyl group,

a cyclopentenyl group,

- a 3,4-didehydro-1-methyl-pyrrolidin group,
- a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CH₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-tetrahydropyran-2-yl group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group,
- a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-difluoromethylphenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group, a 2,4-difluorophenyl group, a 4-chloro-2-trifluoromethylphenyl group,
- 2-hydroxymethylazetidin-1-yl, a 3-azabicyclo[3.1.0]hexan-3-yl group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidin group, 3-hydroxypiperidin-1-yl, 4-hydroxy-4-ethyl-piperidin-1-yl, 4,4-difluoropiperidin-1-yl, a 4-methyl-piperazin-1-yl group, a azepan-1-yl group,
- a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethyl-1,2,5-triazol-2-yl group, a 2-methylpyridin-5-yl group,
- a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CH₃ group, a -NH-CH(CH₂OH)CH₂-CH₃ group, a -NH-cyclopentyl group, a -NH-CH₂-C(-CH₂-CH₂-CH₂-)-CH₂-OH group, a -NH-CH₂-(3-pyrazolyl) group and a -NH-CH₂-pyrazin-2-yl group,
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

Y is C-R² or N and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

- with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time;

R³ is selected from a -CH₂-(morpholin-4-yl) group, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

a cyclopropyl group,

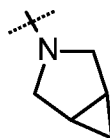
a cyclopent-1-en-1-yl group,

- a 1-methyl-2,5-didehydro-1H-pyrrol-3-yl group

a -O-CH₂-CH₃ group, a -O-CH₂-CHF₂ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-difluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group,

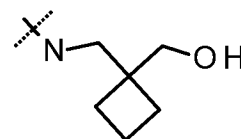
a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 2-



hydroxymethylazetidin-1-yl group, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group, an azepan-1-yl group,

a 6-methyl-pyridin-3-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 3-trifluoromethyl-1,2,5-triazol-2-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CH₃



group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a group, a -NH-cyclopentyl group,

a -NH-CH₂-(pyrazol-3-yl) group, and a -NH-CH₂-pyrazin-2-yl group,

a cyano group,

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

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

R¹ is a hydrogen atom, or a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom,

R³ is selected from a -(CH₂)₃-O-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-tetrahydropyran-2-yl group,

a 2-fluoro-phenyl group,

a 4-methyl-piperazin-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, and a -NH-CH₂-(3-pyrazolyl) group,

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

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

R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

Y is C-R² and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

10 with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time;

R³ is selected from a -CH₂-(morpholin-4-yl) group, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,
a cyclopropyl group,

a cyclopent-1-en-1-yl group,

15 a 1-methyl-2,5-didehydro-1H-pyrrol-3-yl group

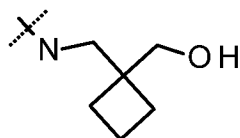
a -O-CH₂-CH₃ group, a -O-CH₂-CHF₂ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-difluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group,
20

a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group, an
25 azepan-1-yl group,

a 6-methyl-pyridin-3-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 3-trifluoromethyl-1,2,5-triazol-2-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CH₃



group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a group,

and a -NH-CH₂-pyrazin-2-yl group,

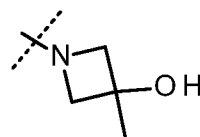
a cyano group,

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

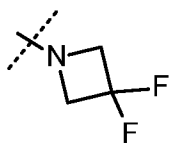
In accordance with a further embodiment of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which

- 10 R¹ is a fluorine atom or a trifluoromethyl group;

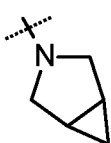
Y is N;



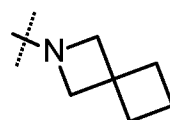
R³ is selected from a NH-(CH₂)₂-O-CH₃ group, a group, a



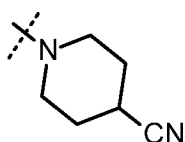
group, a



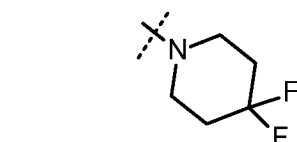
group, a



group, a -NH-cyclopentyl



group, a



group, a



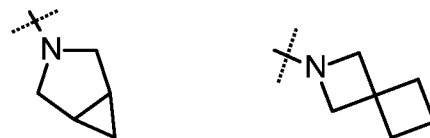
group, a -NH-CH₂-(pyrazol-3-yl) group,

- 15 or a pyrazol-1-yl group, a 3-trifluoromethyl-1-H-pyrazol group or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- 20 R¹ is a hydrogen atom, a trifluoromethyl group;

Y is N;



R^3 is selected from a $\text{NH}-(\text{CH}_2)_2-\text{O}-\text{CH}_3$ group, a group, a group, a $-\text{NH}$ -cyclopentyl group, a $-\text{NH}-\text{CH}_2$ -(pyrazol-3-yl) group, a pyrazol-1-yl group, a 3-trifluoromethyl-1-H-pyrazol group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-
 5 piperidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, a 3-hydroxy-3-methylazetidin-1-yl group, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

In accordance with further embodiments of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which

10 wherein

R^1 is a hydrogen atom or a trifluoromethyl group,

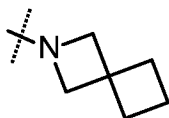
Y is N or C- R^2 and R^2 is a hydrogen atom

R^3 is selected from a $-(\text{CH}_2)_3-\text{OCH}_3$ group, a $-\text{CH}=\text{CH}-\text{CH}_2-\text{O}-\text{CH}_3$ group, a $-\text{O}-(\text{CH}_2)_2-\text{CH}_3$ group, a $-\text{O}-(\text{CH}_2)_3\text{CH}_3$ group, a $-\text{O}-(\text{CH}_2)_2-\text{CF}_3$ group, a $-\text{O}-(\text{CH}_2)_2-\text{O}-\text{CH}_3$
 15 group, a $-\text{O}-\text{CH}_2$ -(tetrahydropyranyl) group,

a 4-fluoro-2-trifluoromethyl-phenyl group,

a 4-methyl-piperazin-1-yl group,

a $-\text{NH}-(\text{CH}_2)_2-\text{O}-\text{CH}_3$ group, a $-\text{NH}-\text{CH}_2-\text{CH}(\text{OH})\text{CF}_3$ group, a $-\text{NH}-\text{CH}_2$ -pyrazol-3-yl



group and a group,

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

In accordance with further embodiments of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which

wherein

25 R^1 is a hydrogen atom or a trifluoromethyl group,

Y is C- R^2 and R^2 is a hydrogen atom

R³ is selected from a $-(CH_2)_3-OCH_3$ group, a $-CH=CH-CH_2-O-CH_3$ group, a $-O-(CH_2)_2-CH_3$ group, a $-O-(CH_2)_3CH_3$ group, a $-O-(CH_2)_2-CF_3$ group, a $-O-(CH_2)_2-O-CH_3$ group, a $-O-CH_2$ -(tetrahydropyranyl) group,

a 4-fluoro-2-trifluoromethyl-phenyl group,

5 a 4-methyl-piperazin-1-yl group,

a $-NH-(CH_2)_2-O-CH_3$ group, a $-NH-CH_2-CH(OH)CF_3$ group, and a $-NH-CH_2$ -pyrazol-3-yl group

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

10 In accordance with further embodiments of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which:

R¹ is a hydrogen atom or a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom

15 R³ is selected from a $-(CH_2)_3-OCH_3$ group, a $-CH=CH-CH_2-O-CH_3$ group, a $-O-(CH_2)_2-CH_3$ group, a $-O-(CH_2)_3CH_3$ group, a $-O-(CH_2)_2-CF_3$ group, a $-O-(CH_2)_2-O-CH_3$ group, a $-O-CH_2$ -(tetrahydropyranyl) group,

a 4-fluoro-2-trifluoromethyl-phenyl group,

a 4-methyl-piperazin-1-yl group,

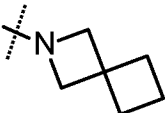
20 a $-NH-(CH_2)_2-O-CH_3$ group, a $-NH-CH_2-CH(OH)CF_3$ group, and a $-NH-CH_2$ -pyrazol-3-yl group

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

25 In accordance with further embodiments of the first aspect, the present invention includes compounds of general formula (I), *supra*, in which

R¹ is a hydrogen atom or a trifluoromethyl group,

Y is N;

R³ is a  group,

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR², where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

10 a C₁-C₆-alkyl group which is optionally substituted with a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

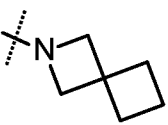
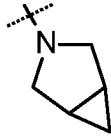
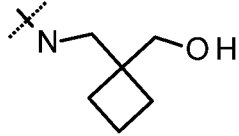
a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, a 4- to 6-membered heterocycloalkyl group which itself can be substituted with
15 a C₁-C₃-alkyl group, and a 5- to 6-membered heteroaryl group,

with the proviso that an unsubstituted methoxy group is excluded;

a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,

20 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group,

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group,

25 a  group, a  group, a  group,

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-haloalkyl group,

a NR⁵R⁶ group,

R⁵ is a hydrogen atom

R⁶ is selected from

- 5 a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl, a C₅-C₆-cycloalkyl group, and a 4- to 6-membered heterocycloalkyl group;

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

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

R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, or a trifluoromethyl group;

Y is C-R² and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

- 15 with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time;

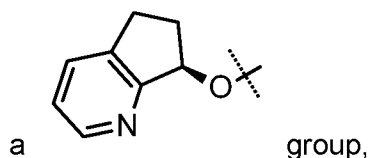
R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-CH₂-O-CH₃ group, a -CH=CH-CH₂-O-CH₂-CH₃ group,

- 20 a cyclopent-1-en-1-yl group,

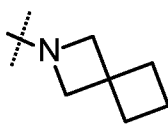
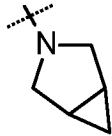
a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-(CH₂)₂-C(CH₃)₃ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(pyrazol-3-yl) group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl,

- 25 a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,

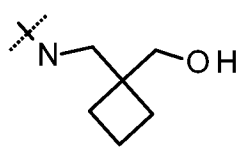


a 4-chlorophenyl group, a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,

a piperidin-1-yl group, a 3-hydroxy-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-

5 hydroxy-3-methylazetidin-1-yl, a  group, a  group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group, a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

10 a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-chloro-pyridin-6-yl group, a 3-fluoro-pyrazol-1-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group, a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-

 group, a  group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-(pyrazol-5-yl) group, a -NH-CH₂-pyrazin-2-yl group, and a -NH-C(O)-CH₂-CH₃ group;

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

20

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

R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, or a trifluoromethyl group;

25 Y is C-R² and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

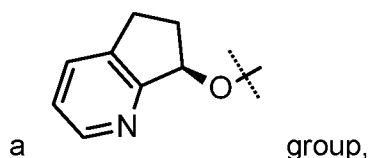
R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, a -CH₂-N(CH₃)₂ group,

a $-\text{CH}=\text{C}(\text{CH}_3)_2$ group, a $-\text{CH}=\text{CH}-\text{CH}_2-\text{O}-\text{CH}_3$ group, a $-\text{CH}=\text{CH}-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_3$ group,

a cyclopent-1-en-1-yl group,

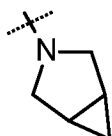
5 a $-\text{O}-(\text{CH}_2)_2-\text{CH}_3$ group, a $-\text{O}-(\text{CH}_2)_3\text{CH}_3$ group, a $-\text{O}-\text{CH}_2-(\text{CH}_3)_2$ group, a $-\text{O}-(\text{CH}_2)_2-\text{C}(\text{CH}_3)_3$ group, a $-\text{O}-\text{CH}_2-\text{CF}_3$ group, a $-\text{O}-(\text{CH}_2)_2-\text{CF}_3$ group, a $-\text{O}-(\text{CH}_2)-\text{CH}(\text{CH}_3)-\text{OH}$ group, a $-\text{O}-(\text{CH}_2)-\text{C}(\text{CH}_3)_2-\text{OH}$ group, a $-\text{O}-(\text{CH}_2)_2-\text{O}-\text{CH}_3$ group, a $-\text{O}-\text{CH}_2$ -cyclopropyl group, a $-\text{O}-\text{CH}_2$ -cyclobutyl group, a $-\text{O}-(\text{methyl-oxetan-3-yl})$ group, a $-\text{O}-\text{CH}_2$ -tetrahydrofuran-2-yl group, a $-\text{O}-\text{CH}_2$ -(methyl-azetidin-2-yl)- group, a $-\text{O}-\text{CH}_2$ -(pyrazol-3-yl) group, a $-\text{O}-\text{CH}_2$ -(4H)-pyrazol-3-yl, a $-\text{O}-\text{CH}_2$ -pyrazin-2-yl,

10 a $-\text{O}-(3\text{-methylcyclobutyl})$ group, a $-\text{O}-(\text{cyclopentyl})$ group,



a 4-chlorophenyl group, a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,

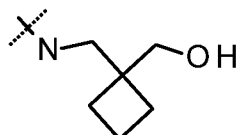
15 a piperidin-1-yl group, a 3-hydroxy-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-

hydroxy-3-methylazetidin-1-yl, a  group, a  group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group,

20 a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-chloro-pyridin-6-yl group, a 3-fluoro-pyrazol-1-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group,

a $-\text{NH}-(\text{CH}_2)_2-\text{O}-\text{CH}_3$ group, a $-\text{NH}-\text{CH}_2-\text{CH}(\text{OH})\text{CF}_3$ group, a $-\text{NH}-\text{CH}(\text{CH}_3)-$

25 cyclopropyl group, a  group, a $-\text{NH}$ -cyclopentyl group, a $-\text{NH}$ -

(3-tetrahydrofuryl) group, -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-(pyrazol-5-yl) group, a -NH-CH₂-pyrazin-2-yl group, and

a -NH-C(O)-CH₂-CH₃ group;

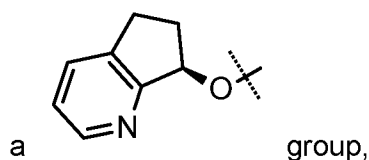
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

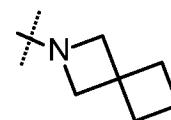
R¹ is a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom,

R³ is selected from a -CH₂-(morpholin-4-yl) group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,



a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,



a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group,

a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-cyclopropyl group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, and;

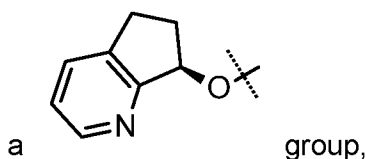
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

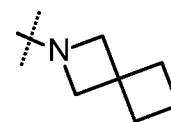
5 R¹ is a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom,

R³ is selected from a -CH₂-(morpholin-4-yl) group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃-CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,



15 a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,



a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group,

20 a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-cyclopropyl group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, and

25

a -NH-C(O)-CH₂-CH₃ group;

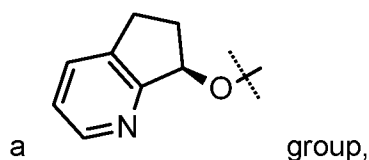
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

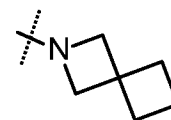
R¹ is a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom,

- 5 R³ is selected from a -CH₂-(morpholin-4-yl) group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(4H)-
 10 pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,



a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,



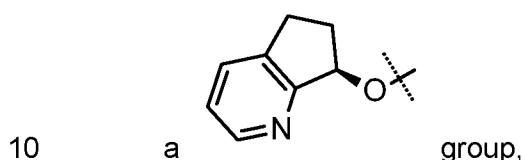
- 15 a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group, a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,
- 20 a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-cyclopropyl group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, and a -NH-C(O)-CH₂-CH₃ group;
- 25 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

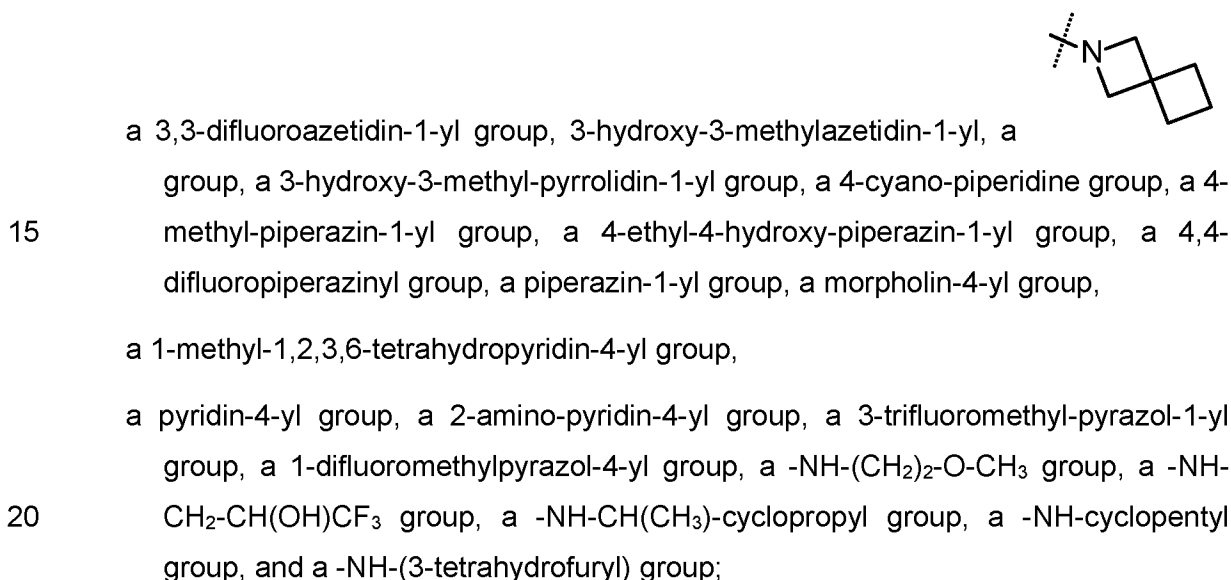
R¹ is a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom,

R³ is selected from a -CH₂-(morpholin-4-yl) group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,



a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,



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

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

R¹ is a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom,

R³ is a -NH-C(O)-CH₂-CH₃ group;

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

- 5 In accordance with a further embodiment of the first aspect, the present invention includes compounds of general formula (I), *supra*, selected from

2-(4'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(2',4'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(2,4'-difluoro-2'-methyl[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(4'-fluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(2,2',4'-trifluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(2,4'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(cyclopent-1-en-1-yl)-3-fluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[2'-(difluoromethyl)-2-fluoro[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[2',4'-difluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4'-fluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(2-methylprop-1-en-1-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[2'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4'-fluoro-2'-methyl-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[2'-(difluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[2'-fluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4'-fluoro-2'-methoxy-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[3-fluoro-4-(6-methylpyridin-3-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(3,5-dimethyl-1,2-oxazol-4-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4'-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,

2-[4-(6-methylpyridin-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(E)-2-ethoxyethenyl]-3-fluorophenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{3-fluoro-4-[(1E)-3-methoxyprop-1-en-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-chloro-2-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]-3-fluorophenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2-fluoro-2'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(3,5-dimethyl-1,2-oxazol-4-yl)-3-fluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
5-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]pyridine-2-carbonitrile,
2-{4-[(1E)-3-methoxyprop-1-en-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1-methyl-1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1-ethyl-1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-(2,2'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(2-methoxyethyl)amino]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1,4-oxazepan-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(azepan-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2R)-3,3,3-trifluoro-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-3,3,3-trifluoro-2-methoxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2R)-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,

2-{3-(trifluoromethyl)-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[3-(difluoromethyl)-1H-1,2,4-triazol-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{3-(trifluoromethyl)-4-[4-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[3-methyl-4-(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{3-(trifluoromethyl)-4-[3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{3-(trifluoromethyl)-4-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{3-(trifluoromethyl)-4-[4-(trifluoromethyl)-2H-1,2,3-triazol-2-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{3-fluoro-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-fluoro-4-(2-methoxyethoxy)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,,
2-[4-{{(1H-pyrazol-3-yl)methyl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one
1-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]piperidine-4-carbonitrile,
2-{4-[(3S)-3-hydroxypiperidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(3-azabicyclo[3.1.0]hexan-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(4-ethyl-4-hydroxypiperidin-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-({[1-(hydroxymethyl)cyclobutyl]methyl}amino)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-{{(pyrazin-2-yl)methyl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(3R)-3-hydroxy-3-methylpyrrolidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,

2-{4-[(2S)-2-(hydroxymethyl)azetidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(3S)-3-hydroxy-3-methylpyrrolidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-1-hydroxybutan-2-yl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[3-hydroxy-3-(propan-2-yl)azetidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2R)-1-hydroxybutan-2-yl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(2R)-2-(hydroxymethyl)azetidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(1S)-2,3-dihydro-1H-inden-1-yl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(morpholin-4-yl)methyl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(dimethylamino)methyl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(piperidin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[5-fluoro-6-(3-hydroxy-3-methylazetidin-1-yl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-(3-azabicyclo[3.1.0]hexan-3-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-(cyclopentylamino)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-[(2-methoxyethyl)amino]-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-[(1H-pyrazol-3-yl)methyl]amino]-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[5-(trifluoromethyl)-6-[3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-(3,3-difluoroazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,

1-[5-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-3-(trifluoromethyl)pyridin-2-yl]piperidine-4-carbonitrile,
 2-[6-(4,4-difluoropiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[6-(2-azaspiro[3.3]heptan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[3-(trifluoromethyl)-4-(3,3,3-trifluoropropoxy)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-propoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-[(2S)-oxolan-2-yl]methoxy]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-butoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(cyclopropyloxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-[(oxetan-3-yl)oxy]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(cyclobutyloxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-ethoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(2,2-difluoroethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-cyclopropyl-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(3-fluoro-4-[(2S)-oxolan-2-yl]methoxy)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-[2-(dimethylamino)ethoxy]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)benzonitrile,
 2-[4-(2-hydroxyethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(3-fluoro-4-propoxyphenyl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-(4-cyclopropyl-3-fluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(2,5-dihydro-1H-pyrrol-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one—hydrogen chloride (1/1),
 2-[4-(3-methoxypropyl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[3-fluoro-4-(3-methoxypropyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(2-methylpropyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(1-methylpiperidin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,

2-[4-(2-methoxyethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(4,4-difluoropiperidin-1-yl)-3,5-difluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[3-fluoro-4-(morpholin-4-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one, and
 2-[4-(morpholin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

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

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

- 5 R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;
 Y is N, or CR^2 , and R^2 is a hydrogen atom, or a halogen atom;

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

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

R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;
 Y is N;

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

- 15 In some further embodiments of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;
 Y is CR^2 , and R^2 is a hydrogen atom, or a halogen atom;

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

In some further embodiments of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;
 Y is CR^2 , and R^2 is a hydrogen atom, or a halogen atom;

- 25 R^2 is a hydrogen atom, or a halogen atom;

with the proviso that both, R^1 and R^2 , may not be a hydrogen atom at the same time;

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

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

R^1 is a hydrogen atom, a fluorine atom, a methyl group, or a trifluoromethyl group;

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

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

R^1 is a hydrogen atom or a fluorine atom or a trifluoromethyl group;

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

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

R^1 is a hydrogen atom or a fluorine atom or a trifluoromethyl group;
Y is C- R^2 or N and R^2 is a hydrogen atom or a fluorine atom,

with the proviso that both, R^1 and R^2 , may not be a hydrogen atom at the same time;

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

In some further embodiments of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^1 is a hydrogen atom or a fluorine atom or a trifluoromethyl group;
Y is C- R^2 and R^2 is a hydrogen atom or a fluorine atom,

25 with the proviso that both, R^1 and R^2 , may not be a hydrogen atom at the same time;

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

5 a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group which itself is optionally substituted with a C₁-C₃-alkyl group,

10 whereby said C₁-C₃-alkyl group is optionally substituted with an amino group,

which is substituted once or twice with a C₁-C₃-alkyl group

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

20 R³ is a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

25 a 4- to 6-membered heterocycloalkyl group which itself is optionally substituted with a C₁-C₃-alkyl group,

whereby said C₁-C₃-alkyl group is optionally substituted with an amino group,

which is substituted once or twice with a C₁-C₃-alkyl group ,

30 with the proviso that if Y is N, R³ as an unsubstituted methyl group is excluded;

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

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

- 5 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;
Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

- a C₁-C₃-alkoxy group,
- 10 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and
- a 4- to 6-membered heterocycloalkyl group which itself is optionally substituted with a C₁-C₃-alkyl group,
- whereby said C₁-C₃-alkyl group is optionally substituted with an amino
- 15 group,
- which is substituted once or twice with a C₁-C₃-alkyl group ,
- with the proviso that if Y is N, R³ as an unsubstituted C₁-C₄-alkyl group is excluded;

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;
Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

- 25 R³ is a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- 30 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

- 5 a C₁-C₃-haloalkyl group,
 - a hydroxy group,
 - a C₁-C₃-alkoxy group,
 - a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
 - a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and
 - 10 a 5- to 6-membered heteroaryl group,
- with the proviso that an unsubstituted methoxy group is excluded;

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

- 20 a C₁-C₃-haloalkyl group,
 - a hydroxy group,
 - a C₁-C₃-alkoxy group,
 - a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
 - a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and
 - 25 a 5- to 6-membered heteroaryl group,
- with the proviso that an unsubstituted C₁-C₄-alkoxy group is excluded;

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

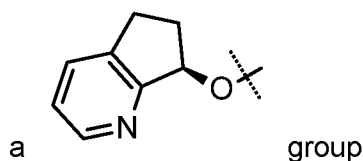
- 30 In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;

5 or



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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a heterocycloalkoxy group,

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

20 R³ is a C₃-C₆-cycloalkyl group,

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

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

25 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a C₅-C₆-cycloalkenyl group,

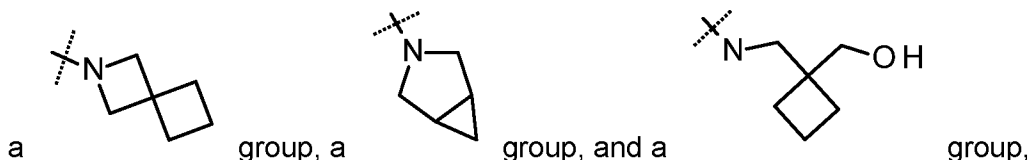
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- 5 R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;
 Y is N, or CR^2 , where R^2 is a hydrogen atom, or a halogen atom; and
 R^3 is a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1 - C_3 -alkyl group, and a C_1 - C_3 -haloalkyl group,
 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt
 10 of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;
 Y is N, or CR^2 , where R^2 is a hydrogen atom, or a halogen atom; and
 15 R^3 is selected from a 4- to 6-membered heterocycloalkyl group
 which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C_1 - C_3 -alkyl group, and a cyano group;



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

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

- R^1 is a hydrogen atom, a halogen atom, a C_1 - C_3 -alkyl group, or a C_1 - C_3 -haloalkyl group;
 25 Y is N, or CR^2 , where R^2 is a hydrogen atom, or a halogen atom; and
 R^3 is selected from a 4- to 6-membered partially unsaturated heterocycloalkyl group

which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a NR⁵R⁶ group,

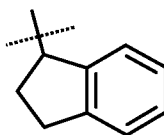
- 10 R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a 4- to 6-membered heterocycloalkyl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

15

whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,



a C₅-C₆-cycloalkyl group, a group,

a 4- to 6-membered heterocycloalkyl group, and

- 20 a C(O)-(C₁-C₆-alkyl) group;

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

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

- 25 R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group,

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

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

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

10 Y is N, or CR², where R² is a hydrogen atom, or a halogen atom; and

R³ is a NR⁵R⁶ group,

R⁵ is a hydrogen atom

R⁶ is selected from

15 a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

whereby said C₁-C₃-cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,

a C₅-C₆-cycloalkyl group,

20 a 4- to 6-membered heterocycloalkyl group; and

a C(O)-(C₁-C₆-alkyl) group,

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

25 In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which for the embodiments disclosed herein:

Y is CR²,

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

In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which for the embodiments disclosed herein:

Y is N,

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

10 R² is a hydrogen atom

R³ is a C₁-C₆-alkyl group which is optionally substituted with

a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl
group, and

15 a 4- to 6-membered heterocycloalkyl group which itself is optionally substituted
with a C₁-C₃-alkyl group,

whereby said C₁-C₃-alkyl group is optionally substituted with an amino
group,

which is substituted once or twice with a C₁-C₃-alkyl group

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

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

R¹ is a trifluoromethyl group

25 Y is a CR² group;

R² is a hydrogen atom

R³ is a C₁-C₆-alkyl group which is optionally substituted with a group independently
selected from

a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4 to 6-membered heterocycloalkyl group which itself is optionally substituted with a C₁-C₃-alkyl group,

5 whereby said C₁-C₃-alkyl group is optionally substituted with an amino group,

 which is substituted once or twice with a C₁-C₃-alkyl group

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

10

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

R¹ is a trifluoromethyl group

Y is a CR² group;

15 R² is a hydrogen atom

R³ is a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

 a C₁-C₃-haloalkyl group,

 a hydroxy group,

20 a C₁-C₃-alkoxy group,

 a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

 a C₁-C₃-alkyl group, and

 a 5- to 6-membered heteroaryl group,

25 with the proviso that an unsubstituted methoxy group is excluded;

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

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

30 R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

R³ is a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

- a C₁-C₃-haloalkyl group,
 - 5 a hydroxy group,
 - a C₁-C₃-alkoxy group,
 - a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
 - a 4- to 6-membered heterocycloalkyl group which itself can be substituted with
 - a C₁-C₃-alkyl group, and
 - 10 a 5- to 6-membered heteroaryl group,
- with the proviso that an unsubstituted C₁-C₄-alkoxy group is excluded;

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

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

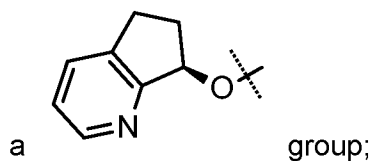
R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

20 R³ is a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;

or



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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

R³ is a 4- to 6-membered heterocycloalkoxy group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

- 10 R³ is a C₃-C₆-cycloalkyl group;

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

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

- 15 R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

R³ is a C₃-C₆-cycloalkenyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

- 25 R² is a hydrogen atom

R³ is a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

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

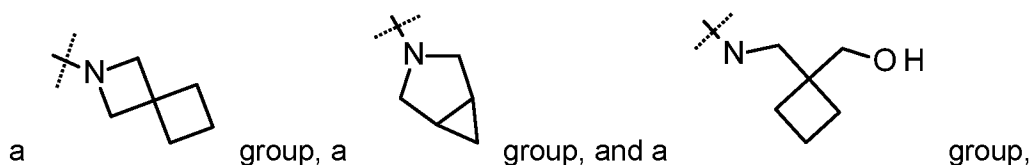
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R¹ is a trifluoromethyl group

Y is a CR² group;

5 R² is a hydrogen atom

R³ is selected from a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



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

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

R¹ is a trifluoromethyl group

15 Y is a CR² group;

R² is a hydrogen atom

R³ is a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

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

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

R¹ is a trifluoromethyl group

25 Y is a CR² group;

R² is a hydrogen atom

R³ is a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

10 R² is a hydrogen atom

R³ is a 5- to 6-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

20 R² is a hydrogen atom

R³ is a NR⁵R⁶ group,

R⁵ is a hydrogen atom

R⁶ is selected from

25 a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,

a C₅-C₆-cycloalkyl group,

30 a 4- to 6-membered heterocycloalkyl group; and

a C(O)-(C₁-C₆-alkyl) group,

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

R³ is a NR⁵R⁶ group,

10 R⁵ is a hydrogen atom

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently
selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a
hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

15 whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl
group,

a C₅-C₆-cycloalkyl group, and

a 4- to 6-membered heterocycloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

25 R² is a hydrogen atom

R³ is a NR⁵R⁶ group,

R⁵ is a hydrogen atom

R⁶ is a C(O)-(C₁-C₆-alkyl) group,

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

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

5 R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

R³ is a NR⁵R⁶ group,

R⁵ is a hydrogen atom

10 R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

15 whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,

and

a C₅-C₆-cycloalkyl group,

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

20

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

R¹ is a trifluoromethyl group

Y is a CR² group;

25 R² is a hydrogen atom

R³ is a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

5 R² is a hydrogen atom

R³ is a phenyl group which is substituted one or more times with halogen atom;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

15 R³ is a phenyl group which is substituted one or more times with a group independently selected from C₁-C₃-alkyl group;

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

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

20 R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

R³ is a phenyl group which is substituted one or more times with a group independently selected from a C₁-C₃-haloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

R³ is a phenyl group which is substituted one or more times with a group independently selected from C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

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

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

R¹ is a trifluoromethyl group

- 10 Y is a CR² group;

R² is a hydrogen atom

R³ is a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and C₁-C₃-alkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

- 20 R² is a hydrogen atom

R³ is a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

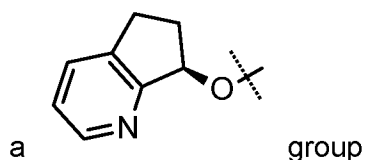
R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

5 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and a 5- to 6-membered heteroaryl group,

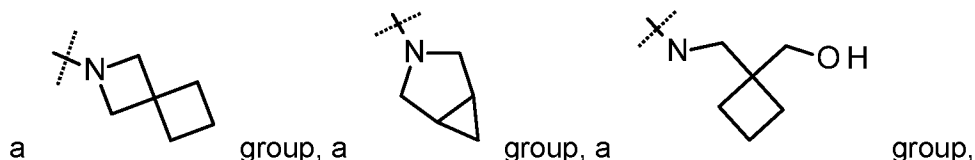
with the proviso that an unsubstituted methoxy group is excluded;

10 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,



15 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group,

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group,



20 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group

a 5 to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-haloalkyl group,

25

a NR⁵R⁶ group;

R⁵ is a hydrogen atom

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

5 a C(O)-(C₁-C₆-alkyl) group,

a C₅-C₆-cycloalkyl group, and

a 4- to 6-membered heterocycloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

15 R³ is selected from

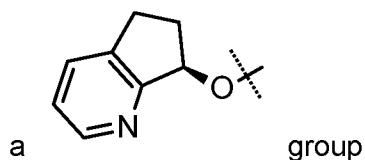
a C₁-C₆-alkyl group which is optionally substituted with a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a

20 a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and a 5- to 6-membered heteroaryl group,

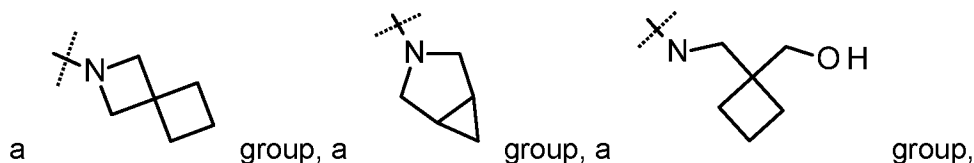
with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded;

25 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,



a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group,

- 5 a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group,



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group

- 10 a -5 to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-haloalkyl group,

a NR⁵R⁶ group;

R⁵ is a hydrogen atom

- 15 R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

a C(O)-(C₁-C₆-alkyl) group,

- 20 a C₅-C₆-cycloalkyl group, and

a 4- to 6-membered heterocycloalkyl group;

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

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

R¹ is a trifluoromethyl group

Y is a CR² group;

R² is a hydrogen atom

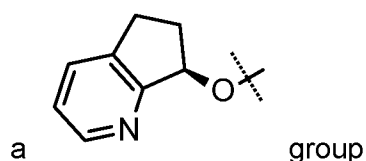
R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

5 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and a 5- to 6-membered heteroaryl group,

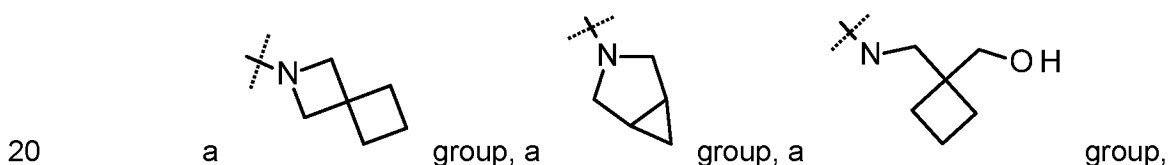
10 with the provisos that R³ as an unsubstituted C₁-C₄-alkoxy group is excluded and if Y is N, R³ as an unsubstituted C₁-C₄-alkyl group is excluded;

a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,



15 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group,

a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group,



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group

25 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-haloalkyl group,

a NR⁵R⁶ group;

R⁵ is a hydrogen atom

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

a C(O)-(C₁-C₆-alkyl) group,

a C₅-C₆-cycloalkyl group, and

a 4- to 6-membered heterocycloalkyl group;

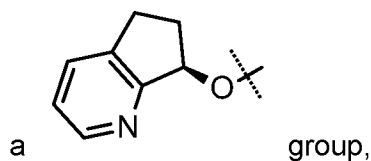
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

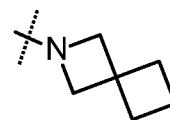
R¹ is a trifluoromethyl group

R² is a hydrogen atom

R³ is selected from a -CH₂-(morpholin-4-yl) group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃-CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,



a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,



a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-

methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group,
 a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,
 a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl
 5 group, a 1-difluoromethylpyrazol-4-yl group, a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-cyclopropyl group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, and
 a -NH-C(O)-CH₂-CH₃ group;

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

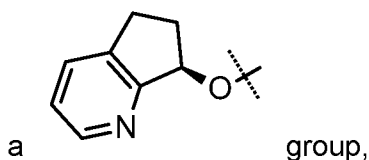
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R¹ is a trifluoromethyl group

Y is a CR² group;

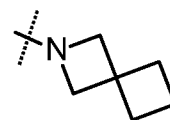
15 R² is a hydrogen atom

R³ is selected from a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -
 20 O-CH₂-(methyl-azetidin-2-yl)- group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,



a 4-fluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group,

25 a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-



- methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group,
- a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,
- a 2-amino-pyridin-4-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-cyclopropyl group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, and
- a -NH-C(O)-CH₂-CH₃ group;
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group; or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, a trifluoromethyl group; or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, a trifluoromethyl group; with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time; or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R² is a hydrogen atom, a halogen atom;

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

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

R² is a hydrogen atom, a fluorine atom, a chlorine atom;

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

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

R¹ is a trifluormethyl group;

R² is; a hydrogen atom

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

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

20 R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with

a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl
group,

25 a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted
with a C₁-C₃-alkyl group;

a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group;

a C₁-C₆-alkoxy group which is optionally substituted with a group independently
selected from

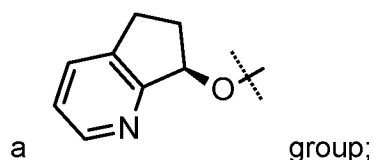
30 a C₁-C₃-haloalkyl group,

a hydroxy group,

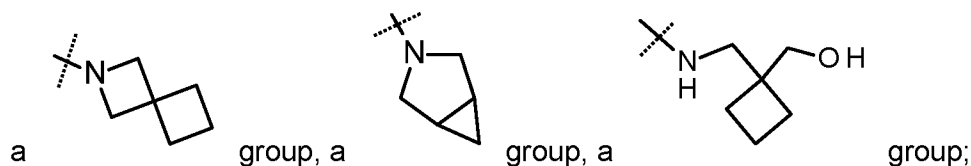
- 5 a C₁-C₃-alkoxy group,
 amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,
 a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with
 a C₁-C₃-alkyl group, and
 a 5- to 6-membered heteroaryl group,

with the proviso that an unsubstituted methoxy group is excluded;

- 10 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more
 times with a group independently selected from a halogen atom, and a C₁-C₃-
 haloalkyl group;



- a 4- to 6-membered heterocycloalkoxy group,
 a C₃-C₆-cycloalkyl group;
 15 a C₅-C₆-cycloalkenyl group;
 a phenyl group which is substituted one or more times with a group independently
 selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-
 haloalkoxy group and a C₁-C₃-haloalkyl group;
 20 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more
 times with a group independently selected from a halogen atom, a hydroxy
 group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



- a partially unsaturated 4 to 6-membered heterocycloalkyl group which is optionally
 substituted one or more times with a group independently selected from a C₁-
 C₃-alkyl group and a C₁-C₃-haloalkyl group;
 25 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times
 with a group independently selected from an amino group, a cyano group, a
 halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

and

a NR^5R^6 group,

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

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

R^3 is selected from

a $\text{C}_1\text{-C}_6$ -alkyl group which is optionally substituted with a group independently selected from

- 10 a $\text{C}_1\text{-C}_3$ -alkoxy group,

an amino group which is optionally substituted once or twice with a $\text{C}_1\text{-C}_3$ -alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a $\text{C}_1\text{-C}_3$ -alkyl group;

- 15 a $\text{C}_2\text{-C}_6$ -alkenyl group, which is optionally substituted with a $\text{C}_1\text{-C}_3$ -alkoxy group;

a $\text{C}_1\text{-C}_6$ -alkoxy group which is optionally substituted with a group independently selected from

a $\text{C}_1\text{-C}_3$ -haloalkyl group,

a hydroxy group,

- 20 a $\text{C}_1\text{-C}_3$ -alkoxy group,

amino group which is optionally substituted once or twice with a $\text{C}_1\text{-C}_3$ -alkyl group,

a $\text{C}_3\text{-C}_6$ -cycloalkyl group which itself can be substituted with a $\text{C}_1\text{-C}_3$ -alkyl group,

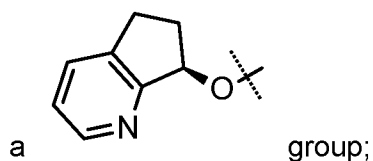
a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

- 25 a $\text{C}_1\text{-C}_3$ -alkyl group, and

a 5- to 6-membered heteroaryl group,

with the provisos that R^3 as an unsubstituted methoxy group is excluded and if Y is N, R^3 as an unsubstituted methyl group is excluded;

- 30 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a $\text{C}_1\text{-C}_3$ -haloalkyl group;



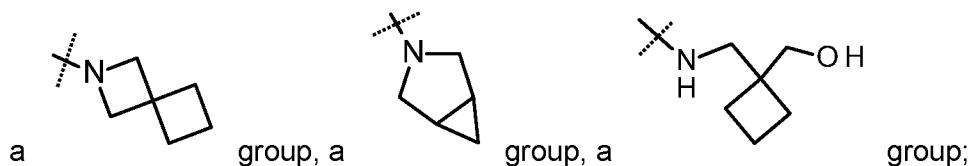
a 4- to 6-membered heterocycloalkoxy group,

a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group;

- 5 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group;

- 10 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

- 15 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a cyano group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

and

a NR⁵R⁶ group,

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

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

R³ is selected from

- 25 a C₁-C₆-alkyl group which is optionally substituted with
a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

5 a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group;

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

10 a C₁-C₃-alkoxy group,

amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

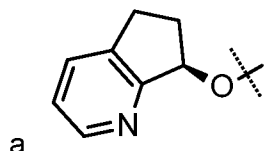
a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

15 a C₁-C₃-alkyl group, and

a 5- to 6-membered heteroaryl group,

with the proviso that R³ as an unsubstituted C₁-C₄-alkoxy group and if Y is N, R³ as an unsubstituted C₁-C₄-alkyl group is excluded;

20 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;



group;

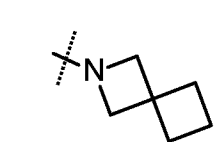
a 4- to 6-membered heterocycloalkoxy group,

a C₃-C₆-cycloalkyl group;

25 a C₅-C₆-cycloalkenyl group;

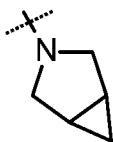
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group;

a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;

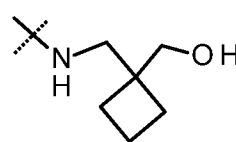


a

group, a



group, a



group;

5 a partially unsaturated 4 to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

10 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a cyano group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

and

a NR⁵R⁶ group,

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

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

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with

a C₁-C₃-alkoxy group,

20 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group,

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

25 a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from

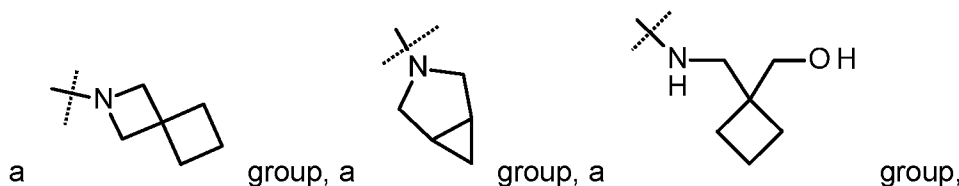
a C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

30 amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

- a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
 with the proviso that an unsubstituted methoxy group is excluded;
 a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more
 5 times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,
 a 4- to 6 membered heterocycloalkoxy group;
 a C₃-C₆-cycloalkyl group;
 a C₅-C₆-cycloalkenyl group,
 10 a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group,
 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group,
 15 a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



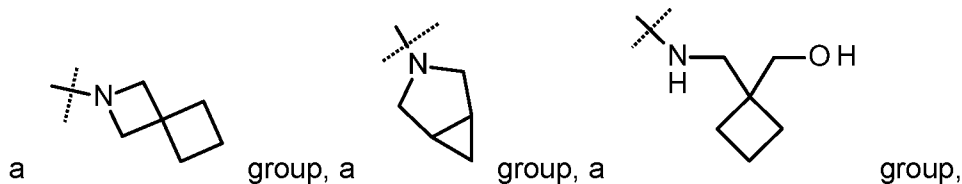
- a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group,
 20 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a cyano group, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, and
 a NR⁵R⁶ group,
 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt
 25 of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R³ is selected from

- a C₁-C₆-alkyl group which is optionally substituted with a group independently selected
 30 from
 a C₁-C₃-alkoxy group,

- an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,
- a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group,
- 5 a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,
- a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from
- a C₁-C₃-haloalkyl group,
- a hydroxy group,
- 10 a C₁-C₃-alkoxy group,
- amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,
- a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
- with the provisos that R³ as an unsubstituted methoxy group and if Y is N R³ as an
- 15 unsubstituted methyl group is excluded;
- a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,
- a 4- to 6 membered heterocycloalkoxy group;
- 20 a C₃-C₆-cycloalkyl group;
- a C₅-C₆-cycloalkenyl group,
- a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group,
- 25 a 4 to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



- a partially unsaturated 4 to 6-membered heterocycloalkyl group which is optionally
- 30 substituted one or more times with a group independently selected from a C₁-C₃-alkyl group,

- a 5 to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a cyano group, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, and a NR⁵R⁶ group,
- 5 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

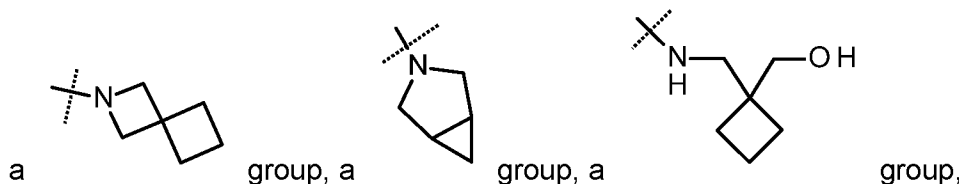
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R³ is selected from

- 10 a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from
- a C₁-C₃-alkoxy group,
 - an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and
- 15 a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group,
- a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,
 - a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from
- 20 a C₁-C₃-haloalkyl group,
- a hydroxy group,
 - a C₁-C₃-alkoxy group,
 - amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,
 - a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a
- 25 C₁-C₃-alkyl group,
- with the provisos that R³ as an unsubstituted C₁-C₄-alkoxy group and if Y is N R³ as an unsubstituted C₁-C₄-alkyl group is excluded;
 - a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl
- 30 group,
- a 4- to 6 membered heterocycloalkoxy group;
 - a C₃-C₆-cycloalkyl group;
 - a C₅-C₆-cycloalkenyl group,

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group,

5 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



10 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group,

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a cyano group, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, and

a NR⁵R⁶ group,

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

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

R³ is selected from

20 a C₁-C₆-alkyl group which is optionally substituted with

a C₁-C₃-alkoxy group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

25 a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

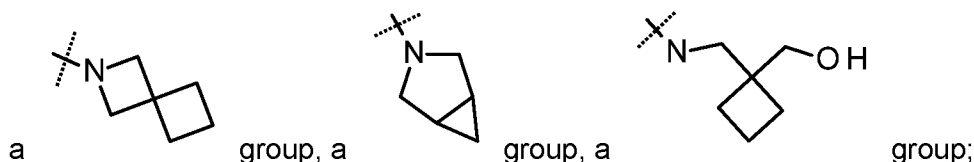
30 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

with the proviso that an unsubstituted methoxy group is excluded;

a 4- to 6-membered heterocycloalkoxy group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

- 5 a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



- 10 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

- 15 a NR⁵R⁶ group;

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

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

- 20 R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with

a C₁-C₃-alkoxy group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

- 25 a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

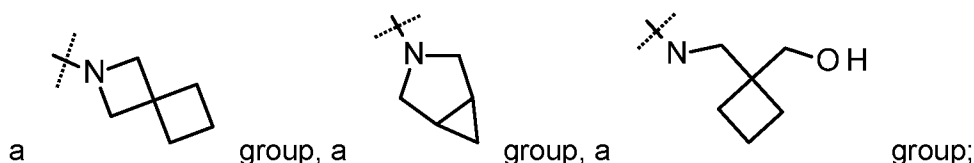
a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

5 with the provisos that R³ as an unsubstituted methoxy group and if Y is N, R³ as an unsubstituted methyl group is excluded;

a 4- to 6-membered heterocycloalkoxy group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

10 a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



15 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

a NR⁵R⁶ group;

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

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

R³ is selected from

25 a C₁-C₆-alkyl group which is optionally substituted with

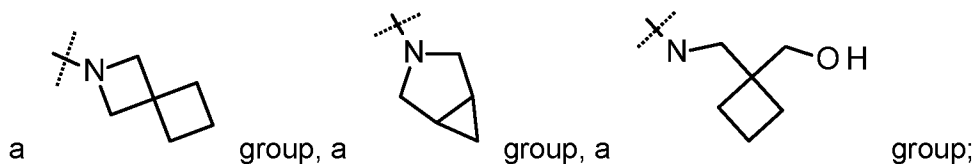
a C₁-C₃-alkoxy group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

- a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from
- C₁-C₃-haloalkyl group,
- a hydroxy group,
- 5 a C₁-C₃-alkoxy group,
- a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
- with the provisos that R³ as an unsubstituted C₁-C₄-alkoxy group and if Y is N, R³ as an unsubstituted C₁-C₄-alkyl group is excluded;

- 10 a 4- to 6-membered heterocycloalkoxy group;
- a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;
- a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group,
- 15 a C₁-C₃-alkyl group, and a cyano group;



- a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;
- 20 a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

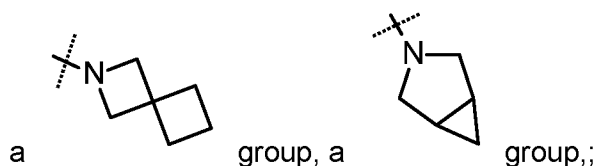
- a NR⁵R⁶ group;
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt
- 25 of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R³ is selected from

a C₁-C₄-alkyl group which is optionally substituted with

- a methoxy group,
- a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;
- a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from
- a C₁-C₃-haloalkyl group,
- a hydroxy group,
- a C₁-C₃-alkoxy group,
- a 4 to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
- with the proviso that an unsubstituted methoxy group is excluded;
- a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;
- a 4 to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



- a 5 to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

and

a NR⁵R⁶ group,

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

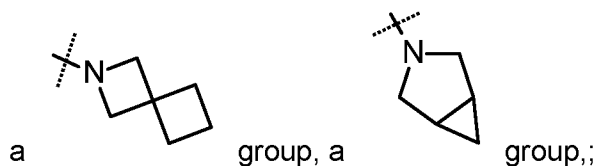
- In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R³ is selected from

a C₁-C₄-alkyl group which is optionally substituted with

a methoxy group,

- a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;
- a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from
- 5 a C₁-C₃-haloalkyl group,
 a hydroxy group,
 a C₁-C₃-alkoxy group,
 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
- 10 with the proviso that R³ as an unsubstituted methoxy group and if Y is N, R³ as an unsubstituted methyl group is excluded;
- a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;
- a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more
- 15 times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



- a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;
- 20

and

a NR⁵R⁶ group,

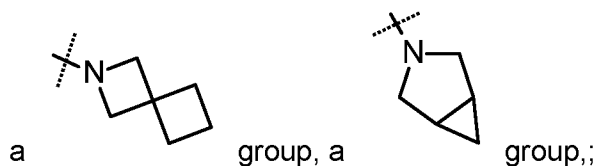
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R³ is selected from

a C₁-C₄-alkyl group which is optionally substituted with
 a methoxy group,

- a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;
- a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from
- 5 a C₁-C₃-haloalkyl group,
 a hydroxy group,
 a C₁-C₃-alkoxy group,
 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
- 10 with the proviso that R³ as an unsubstituted C₁-C₄-alkoxy group and if Y is N, R³ as an unsubstituted C₁-C₄-alkyl group is excluded;
- a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;
- a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more
- 15 times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



- a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;
- 20

and

a NR⁵R⁶ group,

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

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

R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

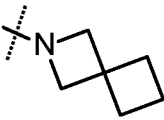
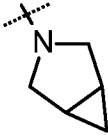
- 30 a cyclopropyl group,

a cyclopent-1-en-1-yl group,

a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-trifluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 3-methyl-4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group,

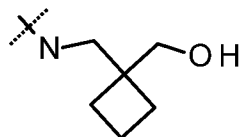
a piperidin-1-yl group, a 1-methyl-piperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3-hydroxy-2-(propan-2-yl)azetidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-

methylazetidin-1-yl, a  group, a  group, a pyrrolidin-1-yl group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group,

a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-didehydro-1H-pyrrol-3-yl group, a 1-methyl-2,5-didehydro-1H-pyrrol-3-yl group;

a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-ethylpyrazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethylpyrazol-1-yl group, a 4-trifluoromethylpyrazol-1-yl group, a 3,5-dimethyl-1,2-oxazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-difluoromethyl-1H-1,2,4-triazol-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



group, a -NH-cyclopentyl group,

a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a -NH-C(O)-CH₂-CH₃ group,

a cyano group,

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

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

R³ is selected from a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group,

a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

15 a cyclopropyl group,

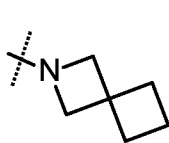
a cyclopent-1-en-1-yl group,

a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

20 a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-trifluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 3-methyl-4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group,

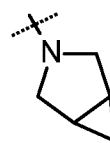
25 a piperidin-1-yl group, a 1-methyl-piperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3-hydroxy-2-(propan-2-yl)azetidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-

30



methylazetidin-1-yl, a

group, a



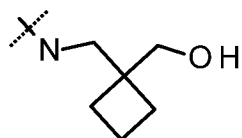
group, a pyrrolidin-1-yl

group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group,

5 a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-didehydro-1H-pyrrol-3-yl group, a 1-methyl-2,5-didehydro-1H-pyrrol-3-yl group;

a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-ethylparazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethylpyrazol-1-yl group, a 4-trifluoromethyl-pyrazol-1-yl group, a 3,5-dimethyl-1,2-oxazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-difluoromethyl-1H-1,2,4-triazol-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



15

group, a -NH-cyclopentyl group,

a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a -NH-C(O)-CH₂-CH₃ group,

a cyano group,

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

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

R³ is selected from

25 2-methylpropyl, (morpholin-4-yl)methyl, (dimethylamino)methyl, (piperidin-1-yl)methyl, 3-methoxypropyl, 2-methylprop-1-en-1-yl, (E)-2-ethoxyethenyl, (1E)-3-methoxyprop-1-en-1-yl,

- ethoxy, propoxy, 4-butoxy, 2-hydroxyethoxy, 2-methoxyethoxy, 2,2-difluoroethoxy, 3,3,3-trifluoropropoxy, (2S)-oxolan-2-yl]methoxy, (dimethylamino)ethoxy, cyclopropyloxy, cyclobutyloxy, (oxetan-3-yl)oxy,
- 5 cyclopropyl, cyclopent-1-en-1-yl, 2-fluorophenyl, 4-fluorophenyl, 2-(difluoromethyl)phenyl, 2-(trifluoromethyl)phenyl, 4-fluoro-2-methoxyphenyl, 2-(trifluoromethoxy)phenyl, 3-fluoro-4-(2-methoxyethoxy)phenyl, 2,4-difluorophenyl, 4-fluoro-2-methylphenyl, 2-(difluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-chloro-2-(trifluoromethyl)phenyl,
- 10 1,4-oxazepan-4-yl, azapan-1-yl, 4-cyano-piperidin-1-yl, 4-methylpiperazin-1-yl, (3S)-3-hydroxypiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-ethyl-4-hydroxypiperidin-1-yl, 1-methylpiperidin-4-yl, (3R)-3-hydroxy-3-methylpyrrolidin-1-yl, (3S)-3-hydroxy-3-methylpyrrolidin-1-yl, (2S)-2-(hydroxymethyl)azetidin-1-yl, (2R)-2-(hydroxymethyl)azetidin-1-yl, 3-hydroxy-3-methylazetidin-1-yl, 3-hydroxy-3-(propan-2-yl)azetidin-1-yl, 3,3-difluoroazetidin-1-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 2-azaspiro[3.3]heptan-2-yl, morpholin-4-yl,
- 15 1-methyl-1,2,3,6-tetrahydropyridin-4-yl, 2,5-dihydro-1H-pyrrol-3-yl, 1-methyl-2,5-dihydro-1H-pyrrol-3-yl, 1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 1-ethyl-1H-pyrazol-4-yl, 1-(difluoromethyl)-1H-pyrazole-4-yl, 3-(trifluoromethyl)-1H-pyrazol-1-yl, 4-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl, 4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl, 3-methyl-4-(trifluoromethyl)-1H-pyrazol-1-yl, 3-(difluoromethyl)-1H-1,2,4-triazol-1-yl, 3-(trifluoromethyl)-1H-1,2,4-triazol-
- 20 1-yl, 4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl, 3,5-dimethyl-1,2-oxazol-4-yl, 6-methylpyridin-3-yl)phenyl, 2-cyano-pyridin-5-yl, (2-methoxyethyl)amino, (2R)-3,3,3-trifluoro-(2-hydroxypropyl)amino, (2S)-3,3,3-trifluoro-(2-methoxypropyl)amino, (2S)-(2-hydroxypropyl)amino, (2R)-(2-hydroxypropyl)amino, (2S)-1-hydroxybutan-2-yl]amino, (2R)-1-hydroxybutan-2-yl]amino, [1-(hydroxymethyl)cyclobutyl]methyl}amino, cyclopentylamino, [1H-pyrazol-3-yl)methyl]amino, [(pyrazin-2-yl)methyl]amino, [(1S)-2,3-dihydro-1H-inden-1-yl]amino and cyano
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt
- 35 of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R³ is a C₁-C₆-alkyl group which is optionally substituted with

a C₁-C₃-alkoxy group,

5 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself is optionally substituted with a C₁-C₃-alkyl group,

10 whereby said C₁-C₃-alkyl group is optionally substituted with an amino group,

which is substituted once or twice with a C₁-C₃-alkyl group

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

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

R³ is a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

20 a C₁-C₃-alkoxy group,

a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, and

a 5- to 6-membered heteroaryl group,

25 with the proviso that an unsubstituted methoxy group is excluded;

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

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

30 R³ is a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,
 a C₁-C₃-alkoxy group,
 a C₄-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a
 5 C₁-C₃-alkyl group, and
 a 5- to 6-membered heteroaryl group,

with the proviso that an unsubstituted methoxy group is excluded;

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

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

R³ is a C₁-C₆-alkoxy group which is optionally substituted with a group independently
 selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a C₄-
 C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group, a 4 to
 15 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-
 alkyl group, and a 5 to 6-membered heteroaryl group,

with the proviso that an unsubstituted methoxy group is excluded;

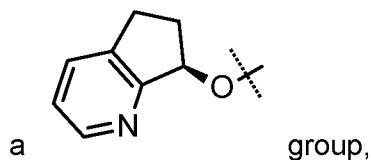
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt
 of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

20

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

R³ is a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-
 (CH₂)₂-C(CH₃)₃ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂-
 25 CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -
 O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl)
 group, a -O-CH₂-tetrahydrofuran-2-yl group, a -O-CH₂-(methyl-azetidin-2-yl)- group,
 a -O-CH₂-(pyrazol-3-yl) group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl,
 a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,

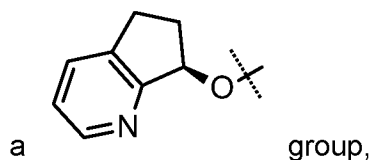
30



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

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

- 5 R^3 is -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-(CH₃)₂ group, a -O-CH₂-CF₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)-CH(CH₃)-OH group, a -O-(CH₂)-C(CH₃)₂-OH group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-cyclopropyl group, a -O-CH₂-cyclobutyl group, a -O-(methyl-oxetan-3-yl) group, a -O-CH₂-(methyl-azetidin-2-yl)-group, a -O-CH₂-(4H)-pyrazol-3-yl, a -O-CH₂-pyrazin-2-yl, a -O-(3-methylcyclobutyl) group, a -O-(cyclopentyl) group,
- 10



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

- In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:
- 15

R^3 is a 4 to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,

- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.
- 20

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

R^3 is a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group,

- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.
- 25

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

R^3 is a phenyl group which is substituted one or more times with a halogen atom,

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

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

- 5 R^3 is a phenyl group which is substituted one or more times with a group selected from a C_1 - C_3 -alkyl group, and a C_1 - C_3 -haloalkyl group
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^3 is a phenyl group which is substituted one or more times with a C_1 - C_3 -alkyl group
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^3 is a phenyl group which is substituted one or more times with a C_1 - C_3 -haloalkyl group
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- R^3 is a phenyl group which is substituted one or more times with a group selected from a fluorine atom, a chlorine atom, a methyl group, a trifluoromethyl group, and a difluoromethyl group
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt
25 of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

- R^3 is a phenyl group which is substituted one or more times with a group selected from a fluorine atom, a chlorine atom, a methyl group, and a trifluoromethyl group,
30 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R³ is a phenyl group which is substituted one or more times with a group selected from a fluorine atom, and a chlorine atom,

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

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

R³ is a phenyl group which is substituted one or more times with a fluorine atom,

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

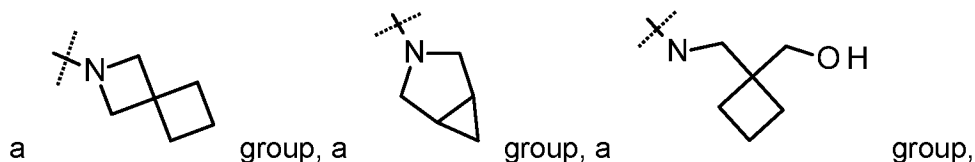
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R³ is a phenyl group which is substituted one or more times with a trifluoromethyl group,

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

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

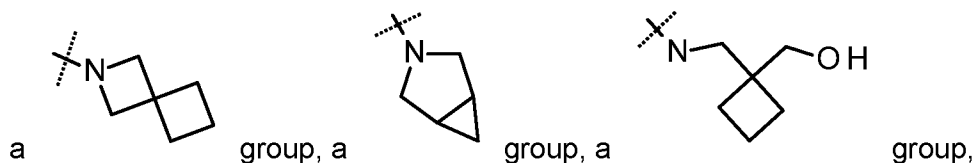
- 20 R³ is a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



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

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

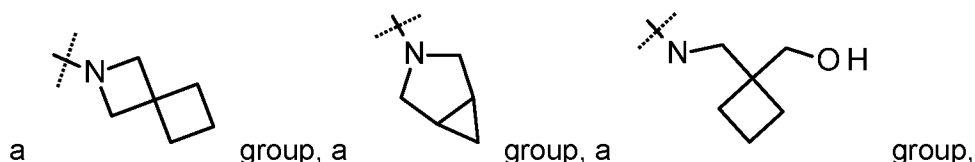
R³ is a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group,



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

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

R^3 is a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, a methyl group, an ethyl group, a hydroxymethyl group and a cyano group,



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

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

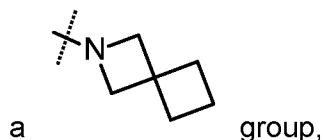
R^3 is a piperidin-1-yl group, which is optionally substituted one or more times with a group
15 independently selected from a hydroxy group, a halogen atom and a C_1 - C_3 -alkyl group;

a azetidin-1-yl group, which is optionally substituted one or more times with a group independently selected from a hydroxy group, a halogen atom and a C_1 - C_3 -alkyl group;

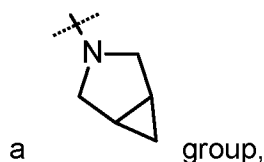
20 a pyrrolidin-1-yl group, which is optionally substituted one or more times with a group independently selected from a hydroxy group, a halogen atom and a C_1 - C_3 -alkyl group;

a piperidine group, which is optionally substituted one or more times with a group independently selected from a cyano group, a hydroxy group, a halogen atom
25 and a C_1 - C_3 -alkyl group;

a piperazin-1-yl group which is optionally substituted one or more times with a group independently selected from a hydroxy group, a halogen atom and a C₁-C₃-alkyl group;



5



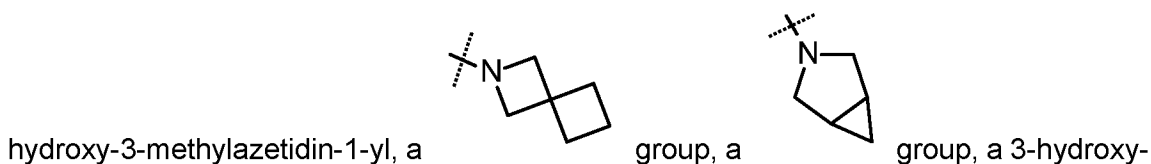
a morpholin-4-yl group, and

a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

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

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

R³ is a piperidin-1-yl group, a 3-hydroxy-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-

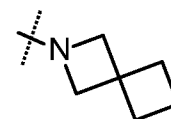


- 15 3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group, and a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

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

20

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



R³ is a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidine group, a 4-methyl-piperazin-1-yl group, a 4-ethyl-4-hydroxy-piperazin-1-yl group, a 4,4-difluoropiperazinyl group, a piperazin-1-yl group, a morpholin-4-yl group,

5 a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group,

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

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

10 R³ is a a 5 to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group,

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

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

R³ is a 5 to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a halogen atom, a C₁-C₃-haloalkyl group,

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

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

25 R³ is a pyridin-4-yl group, which is optionally substituted one or more times with a group independently selected from a amino group, and a halogen atom;

a pyrazol-1-yl group, which is optionally substituted one or more times with a group independently selected from a trifluoromethyl group and a halogen atom

a pyrazol-1-yl group, which is optionally substituted one or more times with a halogen atom, a trifluoromethyl group and a difluoromethyl group,

a 4-trifluoromethyl-1,2,3-triazol-2-yl group,

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

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

R³ is a a pyridin-4-yl group, a 2-amino-pyridin-4-yl group, a 3-chloro-pyridin-6-yl group, a 3-fluoro-pyrazol-1-yl group, a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a 4-trifluoromethyl-1,2,3-triazol-2-yl group,

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

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

- 15 R³ is a NR⁵R⁶ group, and

R⁵ is a hydrogen atom;

R⁶ is selected from

- a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5 to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,

a C₅-C₆-cycloalkyl group,

a 4- to 6-memberd heterocycloalkyl group; and

- 25 a -C(O)-(C₁-C₆-alkyl) group,

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

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

- 30 R³ is a NR⁵R⁶ group, and

R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

a -C(O)-(C₁-C₆-alkyl) group,

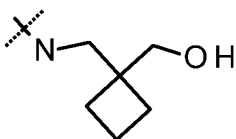
a C₅-C₆-cycloalkyl group, and

a 4- to 6-membered heterocycloalkyl group;

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

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

R³ is selected from a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-



CH(CH₃)-cyclopropyl group, a group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-(pyrazol-5-yl) group, and a -NH-CH₂-pyrazin-2-yl group,

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

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

R³ is selected from a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH(CH₃)-cyclopropyl group, a -NH-cyclopentyl group, a -NH-(3-tetrahydrofuryl) group, and a -NH-C(O)-CH₂-CH₃ group,

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

In further embodiments, the present invention includes compounds of formula (II), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

In further embodiments, the present invention includes compounds of formula (I), or a tautomer, an N-oxide, or a salt thereof or a salt of a tautomer or a salt of an N-oxide or a mixture of same

5 In further embodiments, the present invention includes compounds of formula (I), or a tautomer, or a salt thereof, or a salt of a tautomer, or a mixture of same

In yet further embodiments, the present invention includes compounds of formula (I), or a salt thereof or a mixture of same

In further embodiments, the present invention includes compounds of formula (I), which are salts.

10 In further embodiments, the present invention includes compounds of formula (I), which are amine salts or salts with organic acids.

In further embodiments, the present invention includes compounds of formula (I), which are salts with organic acids particularly formed with pharmaceutically acceptable organic acids.

15 In further embodiments, the present invention includes compounds of formula (I), which are amine salts, particularly formed with pharmaceutically acceptable amines.

In further embodiments, the present invention includes compounds of formula (I), which are a tautomer, or a salt thereof or a salt of a tautomer or a mixture of same

20 In further embodiments, the present invention includes compounds of formula (I), which are an N-oxide, or a salt thereof or a salt of an N-oxide or a mixture of same

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

25 Furthermore it is understood that the invention includes any subcombination of the disclosed single embodiments herein for certain residues or combined with a subcombination of residues of formula (I) as outlined in the claims.

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

30 The present invention includes any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of general formula (IV).

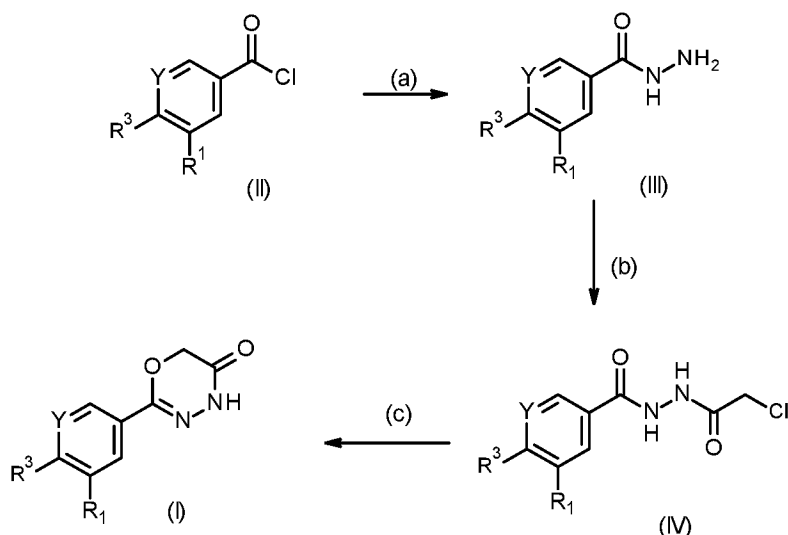
The present invention includes the compounds of general formula (I) which are disclosed in the Example Section of this text, *infra*.

General synthesis of compounds of general formula (I)**A. General Synthesis Route**

- The compounds according to the invention of general formula (I) can be prepared according to the following schemes 1, 2, 3, 4, 5, 6 and 7. The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in schemes 1, 2, 3, 4, 5, 6 and 7 can be modified in various ways. The order of transformations exemplified in these schemes is therefore not intended to be limiting. In addition, interconversion of any of the substituents, R^1 , Y, and R^3 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.
- Five routes for the preparation of compounds of general formula (I) are described in schemes 1, 2, 3, 4, 5, 6 and 7.

Synthesis Routes

Route 1



Scheme 1

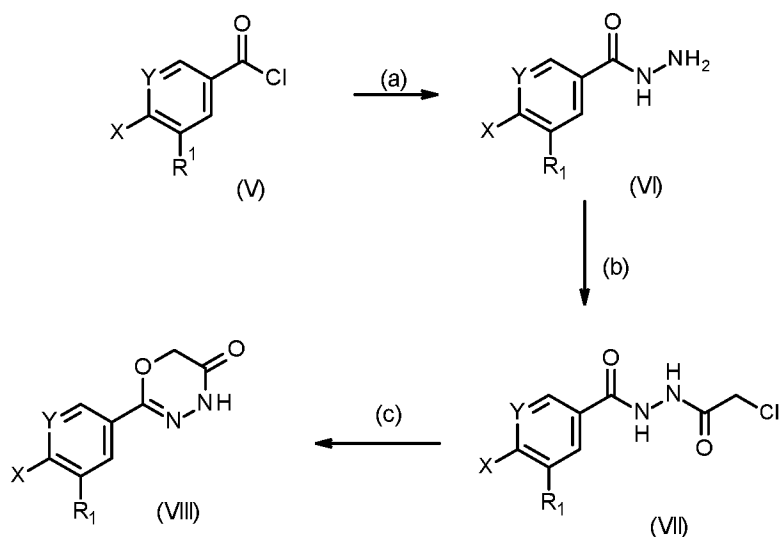
- 5 *Scheme 1*: Route for the preparation of compounds of general formula (I) from compounds of formulae (II), in which R¹, Y, and R³ have the meaning as defined *supra*. Compounds of formulae (II) are known to the person skilled in the art and can be readily prepared from commercially available precursors by known methods. It may be advantageous to protect reactive functional groups in R³ to obtain compounds of formula (I) bearing a protecting group. The protecting group can be readily deprotected using a method known to the person skilled in the art to obtain compounds of the invention.

(a) hydrazine hydrate, DCM, 0 °C, 1h; (b) chloroacetyl chloride, EtOAc, 60 °C, 0.5h; (c) NaHCO₃, DMF, 60 °C – 100 °C, 1h – 24h

- Compounds of formula (I) containing chiral centers can be optionally separated by methods known to the person skilled in the art, such as e.g. chiral chromatography, to obtain individual enantiomers or diastereomers.

Route 2: Alternative synthesis of a subset of compounds of general formula (I), compounds of general formula (Ia)

Part I: Synthesis of intermediate compounds of formula (VIII)

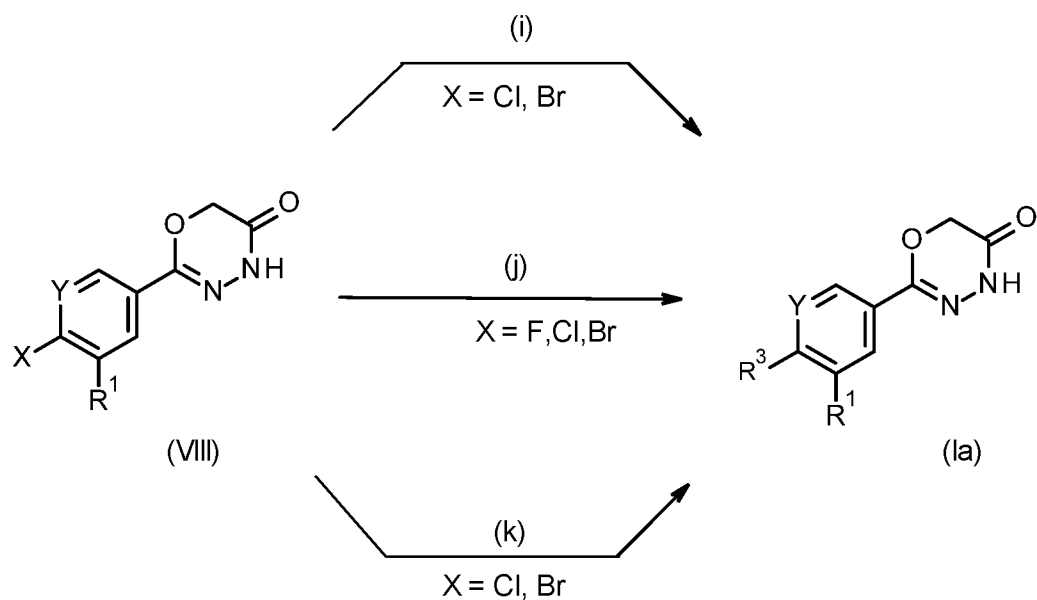


Scheme 2

Scheme 2: Route for the preparation of intermediate compounds of formula (VIII), in which R^1 and Y have the meaning as defined *supra*; the meaning of X is as defined below in context of Scheme 3 and the paragraphs (i), (j), (k) for compounds of formula (VIII).

(a) hydrazine hydrate, DCM, 0 °C, 1h; (b) chloroacetyl chloride, EtOAc, 60 °C, 0.5h; (c) NaHCO_3 , DMF, 60 °C – 100 °C, 1h – 24h

10 Part II: Conversion of the intermediate compounds of formula (VI) into compounds of general formula (Ia):



Scheme 3

(i): R^3 = a substituted methyl group, an optionally substituted alkenyl group, a cycloalkenyl group, a substituted phenyl group, a substituted heteroaryl group, a partially saturated heterocycloalkyl group

5 (j), (k): R^3 = NR^5R^6 , opt. subst. N-linked heterocycloalkyl or N-linked heteroaryl

Scheme 3: Route for the preparation of compounds of general formula (I) via formula (VI) in which R^1 and Y have the meaning as defined *supra*, in which R^3 in general formula (Ia) is a substituted methyl group, an optionally substituted alkenyl group, a cycloalkenyl
 10 group, a substituted phenyl group, a substituted heteroaryl group, a partially saturated heterocycloalkyl group as defined in more detail below in paragraph (i); or R^3 is NR^5R^6 , opt. subst. N-linked heterocycloalkyl, N-linked heteroaryl or N-linked heterocycloalkyl, as defined in more detail below in paragraph (j) and (k), respectively; and in which the terms
 15 "N-linked heterocycloalkyl", "N-linked, partially unsaturated heterocycloalkyl" and "N-linked heteroaryl" refer to a 4- to 6-membered heterocycloalkyl, a 5- to 6-membered partially unsaturated heterocycloalkyl, or a heteroaryl group, as defined for R^3 *supra*, which is bonded to the rest of the molecule *via* a nitrogen atom which constitutes a ring atom of said heterocycloalkyl, partially unsaturated heterocycloalkyl or heteroaryl group.

20 (i) Route 2 *via* Suzuki coupling with organoboron compounds

Compounds of general formula (I), in which R^3 is R^x as defined below for the formulae (IXa), (IXb), and (IXc), can be obtained by reacting intermediate compounds of formula (VIII), in which

X is Cl, Br, (as reflected in scheme 3), or a group selected from (C₁-C₄-alkylsulfonyl)oxy,
 25 (C₁-C₄-fluoroalkylsulfonyl)oxy and (phenylsulfonyl)oxy, the phenyl present in (phenylsulfonyl)oxy being optionally substituted with one, two, three, four or five substituents, each of them independently selected from halogen, nitro, cyano, C₁-C₄-alkyl and C₁-C₄-alkoxy;

R^1 is as defined *supra* but different from Cl, Br, I,

30 Y is as defined *supra* but different from C-Cl, C-Br, C-I and with boronic acids $R^xB(OH)_2$ (formula (IXa)), or boronic esters $R^xB(OR^y)_2$ (formula (IXb)), or tetrafluoroborate salts R^xBF_4 (formula (IXc)),
 in the presence of

a base, such as potassium carbonate or potassium acetate,
 35 a palladium catalyst, such as dichlorobis(triphenylphosphine)palladium, tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate/triscyclohexylphosphine,

tris(dibenzylideneacetone)dipalladium, bis(diphenylphosphineferrocenyl)palladium(II) chloride, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene(1,4-naphthoquinone) palladium dimer, allyl(chloro)(1,3-dimesityl-1,3-dihydro-2H-imidazol-2-ylidene)palladium, palladium(II) acetate/dicyclohexyl(2',4',6'-triisopropyl-biphenyl-2-yl)phosphine, [1,1-bis(diphenylphosphino)ferrocene]palladium(II) chloride monodichloromethane adduct, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II), palladium (II) acetate and (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II), particularly chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II),, and, optionally, an additional ligand, such as 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl, in a solvent, such as dioxane, toluene, or water, or a mixture thereof, under nitrogen or argon atmosphere, at 80 °C-120 °C, for 2h-7d;

whereby

R^x is

a methyl group which is substituted one or more times with a group selected from a C₁-C₃-alkyl group, a C₁-C₃-alkoxy group, a heterocycloalkyl group, and an amino group which is substituted with a C₁-C₃-alkyl group,

a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

a C₅-C₆-cycloalkenyl group,

a phenyl group which is substituted one or more times with a group selected from a fluorine atom, a chlorine atom, a methyl group, a trifluoromethyl group,

a 5 to 10-membered heteroaryl group which is optionally substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluoromethyl group, and a difluoromethyl group,

R^y is C₁-C₆-alkyl, or the two residues R^y together are a C₂-C₆-alkylene group, particularly -C(CH₃)₂-C(CH₃)₂- to form a pinacol ester.

As readily understood by the person skilled in the art, compounds of general formula (I) prepared e.g. by a Suzuki coupling, in which R³ features a group comprising an olefinic double bond (e.g. if R³ is alkenyl, cycloalkenyl or partially unsaturated heterocycloalkyl), can be readily converted into compounds in which R³ features the corresponding saturated group (e.g. alkyl, cycloalkyl, heterocycloalkyl) by methods known to the person

skilled in the art, such as catalytic hydrogenolysis using a suitable catalyst, such as palladium on carbon.

(j) **Route 2 via nucleophilic aromatic substitution to introduce R³ substituents**
 5 **selected from -NR⁵R⁶, a N-linked heterocycloalkyl group, and a N-linked**
 heteroaryl group, whereby the term “N-linked” is to be understood as described
 in context of Scheme 3.

Compounds of general formula (I), in which

R³ is selected from -NR⁵R⁶, a N-linked 4- to 6-membered heterocycloalkyl group, and a
 10 N-linked heteroaryl group, whereby the term “N-linked” is to be understood as
 described in context of Scheme 3, and in which the terms “4- to 6-membered
 heterocycloalkyl”, and “heteroaryl” are constituted and optionally substituted as
 defined for R³, *supra*,

can be obtained by reacting intermediate compounds of formula (VI), in which

15 X is F, Cl, or Br (as reflected in scheme 3), and if X is Cl or Br, R¹ can not be F and
 Y can not be C-F; particularly X is F;

R¹ and Y have the meaning as defined *supra*, with the proviso that if X is Cl or Br,
 R¹ can not be F and Y can not be C-F, and with the proviso that at least one of R¹
 and Y exerts an electron withdrawing effect; particularly, R¹ is selected from
 20 fluorine, and -CF₃, and Y is C-H or C-F or N; more particularly, R¹ is -CF₃ and Y is
 C-H or N;

with a corresponding amine, optionally as a free base or as a salt, such as a hydrochloride
 salt, selected from HNR⁵R⁶ and a cyclic amine featuring one N-H as a ring atom, said
 cyclic amine being selected from a 4- to 6-membered heterocycloalkane, and a
 25 heteroarene containing one N-H as a ring atom, respectively,
 optionally in the presence of a base, such as triethylamine, DIPEA, or cesium carbonate,
 in an inert solvent, such as THF, CH₃CN, DMF, DMA, or DMSO, at optionally elevated
 temperatures ranging from RT to 160 °C, particularly from 60°C to 150 °C, for 2h-7d;
 whereby

30 R⁵ is H, and R⁶ is selected from

 a C₁-C₃-alkyl group which is substituted one or more times with a group independently
 selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a
 hydroxy group, a C₁-C₃-haloalkyl group, and a C₄-C₆-cycloalkyl group which itself
 is optionally substituted with a C₁-C₃-hydroxyalkyl group, and

35 a C₅-C₆-cycloalkyl group;

(k) **Alternative Route *via* transition metal catalyzed, particularly palladium catalyzed amination, to introduce R³ substituents selected from -NR⁵R⁶, a N-linked heterocycloalkyl group, and a N-linked heteroaryl group, whereby**
 5 the term "N-linked" is to be understood as described in context of Scheme 3,.

Compounds of general formula (I), in which R³ is selected from -NR⁵R⁶, a N-linked 4- to 6-membered heterocycloalkyl group, and a N-linked heteroaryl group, whereby the term "N-linked" is to be understood as described in context of Scheme 3, and in which the
 10 terms "4- to 6-membered heterocycloalkyl", and "heteroaryl" are constituted and optionally substituted as defined for R³, *supra*,
 can be obtained by reacting intermediate compounds of formula (VI), in which
 X is Cl, Br, (as reflected in scheme 3), or a group selected from (C₁-C₄-alkylsulfonyl)oxy,
 (C₁-C₄-fluoroalkylsulfonyl)oxy and (phenylsulfonyl)oxy, the phenyl present in
 15 (phenylsulfonyl)oxy being optionally substituted with one, two, three, four or five substituents, each of them independently selected from halogen, nitro, cyano, C₁-C₄-alkyl and C₁-C₄-alkoxy;

R¹ is as defined *supra* but is different from Cl, Br, I;

Y is as defined *supra* but is different from C-Cl, C-Br, C-I; particularly, R¹ is -CF₃ and Y
 20 is C-H;

with a corresponding amine, optionally as a free base or as a salt, such as a hydrochloride salt, selected from HNR⁵R⁶ and a cyclic amine featuring one N-H as a ring atom, said cyclic amine being selected from a 4- to 6-membered heterocycloalkane, and a heteroarene containing one N-H as a ring atom, respectively,

25 in the presence of a base, such as potassium phosphate or cesium carbonate, a palladium catalyst, such as tris(dibenzylideneacetone)dipalladium(0), a ligand, such as 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl or 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene, in an inert solvent, such as dioxane or toluene, at elevated temperatures ranging from 60-160 °C, for 2h-7d;

30 whereby

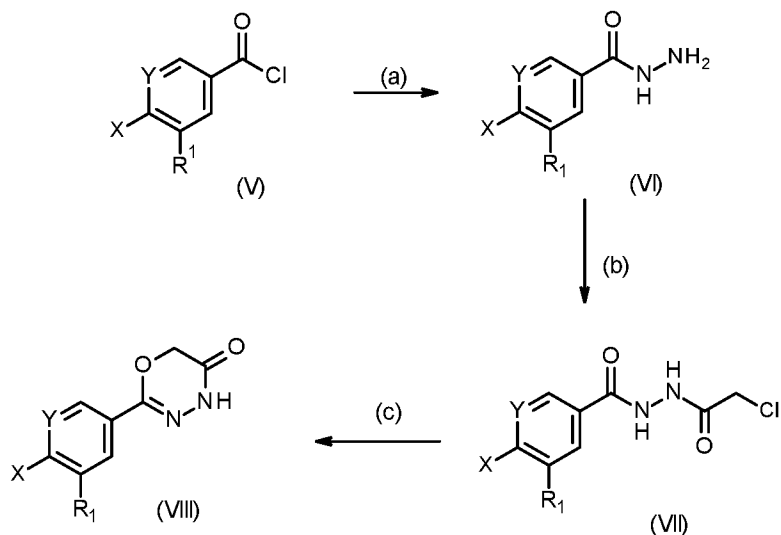
R⁵ is H, and R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5 to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₄-C₆-cycloalkyl group which itself
 35 is optionally substituted with a C₁-C₃-hydroxyalkyl group, and
 a C₅-C₆-cycloalkyl group;

The thus obtained compounds of formula (I) containing chiral centers can be optionally separated by chiral chromatography to obtain individual enantiomers or diastereomers.

**Route 3: Alternative synthesis of a subset of compounds of general formula (I),
5 compounds of general formula (Ib)**

Part I: Synthesis of intermediate compounds of formula (VIII)

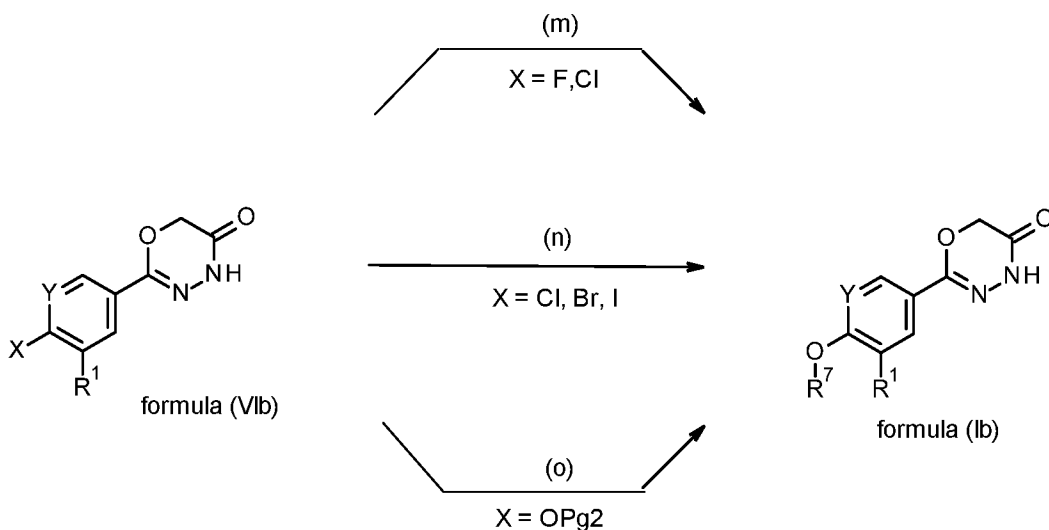


Scheme 4

Scheme 4: Route for the preparation of intermediate compounds of formula (VIII), in
10 which R¹ and Y have the meaning as defined *supra*; the meaning of X is as defined above
in context of Scheme 3 and the paragraphs (i), (j), (k) for compounds of formula (VIII).

(a) hydrazine hydrate, DCM, 0 °C, 1h; (b) chloroacetyl chloride, EtOAc, 60 °C, 0.5h; (c)
NaHCO₃, DMF, 60 °C – 100 °C, 1h – 24h

Part II: Conversion of the intermediate compounds of formula (VIII) into compounds of general formula (Ib):



5

Scheme 5

R^7 = a C_1 - C_6 -alkyl group which is optionally substituted with a group selected from C_1 - C_3 -haloalkyl group, a hydroxy group, a C_1 - C_3 -alkoxy group, a C_4 - C_6 -cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group, with the proviso that an unsubstituted methyl group is excluded; and Pg_2 is a protecting group suitable for hydroxy groups, e.g. a benzyl group.

Scheme 5: Route for the preparation of compounds of general formula (Ib) via formula (VIIIb) in which R^1 and Y have the meaning as defined *supra*, in which R^7 in general formula (Ib) is a C_1 - C_6 -alkyl group which is optionally substituted with a group selected from C_1 - C_3 -haloalkyl group, a hydroxy group, a C_1 - C_3 -alkoxy group, a C_4 - C_6 -cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group, with the proviso that an unsubstituted methyl group is excluded.

(m) Route 3 via nucleophilic aromatic substitution to introduce R^3 substituents

Compounds of general formula (Ib), can be obtained by reacting intermediate compounds of formula (VIIIb), in which

X is F, Cl, or Br (as reflected in scheme 3), and if X is Cl or Br, R^1 can not be F and Y can not be C-F; particularly X is F;

R^1 and Y have the meaning as defined *supra*, with the proviso that if X is Cl or Br, R^1 can not be F and Y can not be C-F, and with the proviso that at least one of R^1 and Y exerts an electron withdrawing effect; particularly, R^1 is selected from

fluorine, and $-\text{CF}_3$, and Y is C-H or C-F or N; more particularly, R^1 is $-\text{CF}_3$ and Y is C-H;

with a corresponding alcohol $\text{R}^7\text{-OH}$, optionally as the alcohol or as an alkoxide salt, such as a sodium or potassium salt,

- 5 optionally in the presence of a strong base, such as potassium tert-butoxide, or sodium hydride, or sodium metal,
optionally in an inert solvent, such as THF or DMF,
optionally in the presence of a base, such as cesium carbonate, in a solvent, such as DMSO, optionally at elevated temperatures ranging from RT to 160 °C, particularly from
10 60°C to 150 °C, for 2h-7d;
whereby

- R^5 is a $\text{C}_1\text{-C}_6$ -alkyl group which is optionally substituted with a group selected from $\text{C}_1\text{-C}_3$ -haloalkyl group, a hydroxy group, a $\text{C}_1\text{-C}_3$ -alkoxy group, a $\text{C}_4\text{-C}_6$ -cycloalkyl group, a 4 to 6-membered heterocycloalkyl group, a 5 to 6-membered heteroaryl group, with
15 the proviso that an unsubstituted methyl group is excluded.

(n) Alternative Route *via* transition metal catalyzed, particularly palladium catalyzed amination, to introduce R^3 substituents

- Compounds of general formula (Ib), can be obtained by reacting intermediate compounds
20 of formula (VIIIb), in which

- X is Cl, Br, (as reflected in scheme 5), or a group selected from ($\text{C}_1\text{-C}_4$ -alkylsulfonyl)oxy, ($\text{C}_1\text{-C}_4$ -fluoroalkylsulfonyl)oxy and (phenylsulfonyl)oxy, the phenyl present in (phenylsulfonyl)oxy being optionally substituted with one, two, three, four or five substituents, each of them independently selected from halogen, nitro, cyano, $\text{C}_1\text{-C}_4$ -alkyl and $\text{C}_1\text{-C}_4$ -alkoxy;
25

R^1 is as defined *supra* but is different from Cl, Br, I;

Y is as defined *supra* but is different from C-Cl, C-Br, C-I; particularly, R^1 is $-\text{CF}_3$ and Y is C-H;

with a corresponding alcohol $\text{R}^7\text{-OH}$,

- 30 in the presence of a base, such as potassium phosphate or cesium carbonate, a palladium catalyst, such as [(2-Di-*tert*-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate or [(2-Di-*tert*-butylphosphino-3-methoxy-6-methyl-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2-aminobiphenyl)]palladium(II) methanesulfonate, optionally a ligand, such as 2-Di(*tert*-butyl)phosphino-2',4',6'-triisopropyl-3-methoxy-6-methylbiphenyl or 2-(Di-*tert*-
35

butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl, in an inert solvent, such as dioxane or toluene, at elevated temperatures ranging from 60-160 °C, for 2h-7d; whereby

5 R^7 = is a C₁-C₆-alkyl group which is optionally substituted with a group selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a C₄-C₆-cycloalkyl group, a 4 to 6-membered heterocycloalkyl group, a 5 to 6-membered heteroaryl group, with the proviso that an unsubstituted methyl group is excluded.

The thus obtained compounds of formula (I) containing chiral centers can be optionally separated by chiral chromatography to obtain individual enantiomers or diastereomers.

10

(o) Alternative Route *via* Mitsunobu reaction, to introduce R³ substituents

Compounds of general formula (Ib), can be obtained in a two step procedure (o-1 (Removal of the protecting group Pg₂), followed by o-2 (Mitsunobu reaction)).

15 (o-1) Compounds of general formula (VIII), where X is -OH, can be obtained by reacting intermediate compounds of formula (VI), in which X is OPg₂, where Pg₂ is a protecting group suitable for hydroxy groups, e.g. a benzyl group;

R¹ has the meaning as defined *supra*,

Y has the meaning as defined *supra* but is different from N,

20

with hydrogen gas, in the presence of a palladium catalyst, such as Palladium on carbon, in a solvent, such as ethanol, at temperatures ranging from room temperature to 60 °C, for 2h-3d, at hydrogen pressure ranging from 1 bar to 10 bar, particularly 1 bar.

25 (o-2) Compounds of general formula (Ib), can be obtained by reacting intermediate compounds of formula (VIII), in which X is -OH,

R¹ has the meaning as defined *supra*,

Y has the meaning as defined *supra* but is different from N,

with a corresponding alcohol R⁷-OH,

30 in the presence of an dialkylazodicarboxylate, particularly diisopropylazodicarboxylate, a phosphine, such as tri-n-butylphosphine, in an inert solvent, such as THF, at temperatures ranging from 0 °C to room temperature, for 2h-3d;

whereby

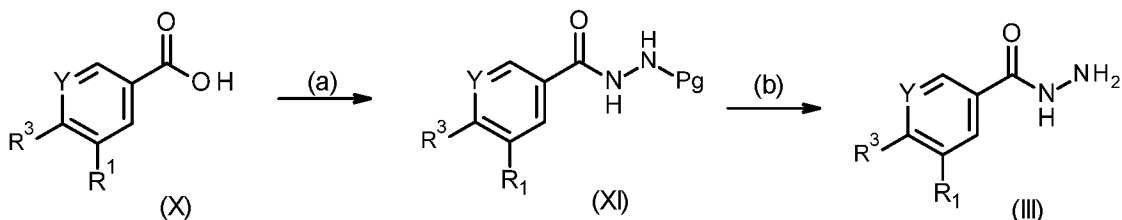
35 R^7 = is a C₁-C₆-alkyl group which is optionally substituted with a group selected from C₁-C₃-haloalkyl group, a hydroxy group, a C₁-C₃-alkoxy group, a C₄-C₆-cycloalkyl group, a

4 to 6-membered heterocycloalkyl group, a 5 to 6-membered heteroaryl group, with the proviso that an unsubstituted methyl group is excluded.

The thus obtained compounds of formula (I) containing chiral centers can be optionally separated by chiral chromatography to obtain individual enantiomers or diastereomers.

5

Route 4: Alternative synthesis of compounds of general formula (III)



Scheme 6

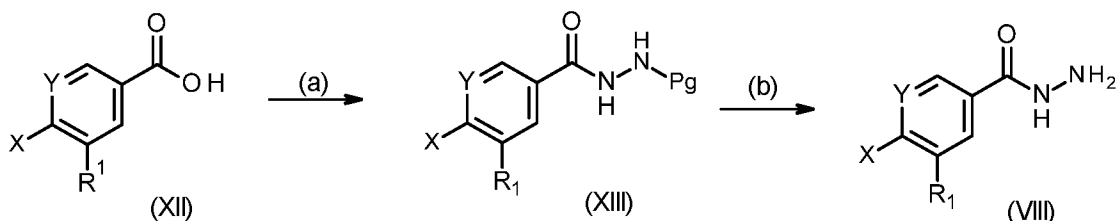
Scheme 6: Route for the preparation of compounds of general formula (III) from compounds of formulae (X), in which R¹, Y, and R³ have the meaning as defined *supra* and Pg is a protecting group suitable for a hydrazide, such as tert-butylcarbamate (BOC). Compounds of formulae (X) are known to the person skilled in the art and can be readily prepared from commercially available precursors by known methods. It may be advantageous to protect reactive functional groups in R³ to obtain compounds of formula (I) bearing a protecting group. The protecting group can be readily deprotected using a method known to the person skilled in the art to obtain compounds of the invention.

15

(a) T3P, tert-butyl hydrazinecarboxylate, in a solvent, such as DCM or EtOAc, at a temperature range of 0 °C to RT, for 1h-24 h, in the presence of a base, such as triethylamine; (b) TFA, DCM or HCl, dioxane

20

Route 5: Alternative synthesis of compounds of general formula (VIII)



Scheme 7

Scheme 7: Route for the preparation of compounds of general formula (VIII) from compounds of formulae (XII), in which R¹ and Y have the meaning as defined *supra* and Pg is a protecting group suitable for a hydrazide, such as tert-butylcarbamate (BOC).

25

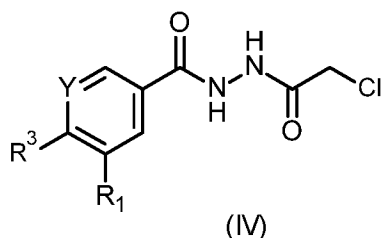
Compounds of formulae (XII) are known to the person skilled in the art and can be readily prepared from commercially available precursors by known methods. It may be advantageous to protect reactive functional groups in R^3 to obtain compounds of formula (I) bearing a protecting group. The protecting group can be readily deprotected using a method known to the person skilled in the art to obtain compounds of the invention.

(a) T3P, tert-butyl hydrazinecarboxylate, in a solvent, such as DCM or EtOAc, at a temperature range of 0 °C to RT, for 1h-24 h, in the presence of a base, such as triethylamine; (b) TFA, DCM or HCl, dioxane

Compounds of formula (I) containing chiral centers can be optionally separated by methods known to the person skilled in the art, such as *e.g.* chiral chromatography, to obtain individual enantiomers or diastereomers.

The present invention provides methods of preparing compounds of the present invention of general formula (I), said methods comprising the steps as described in the Experimental Section herein.

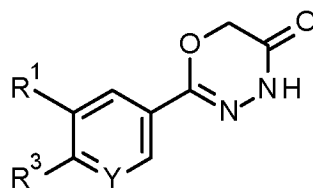
In accordance with a second aspect, the present invention includes methods of preparing compounds of general formula (I) as defined *supra*, said methods comprising the step of allowing an intermediate compound of general formula (IV) :



in which R^1 , R^3 , and Y are as defined for the compound of general formula (I) according to any of the claims 1-8,

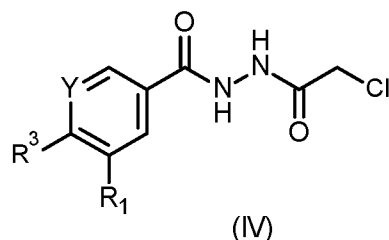
to react in

with sodium bicarbonate, in DMF, at a temperature range of about 50 °C – 100 °C, thereby giving a compound of general formula (I)



in which R¹, Y, and R³ are as defined according to anyone of claims 1-8.

In accordance with a third aspect, the present invention includes methods of preparing
 5 compounds of general formula (I) as defined *supra*, said methods comprising the step of
 allowing an intermediate compound of general formula (IV) :

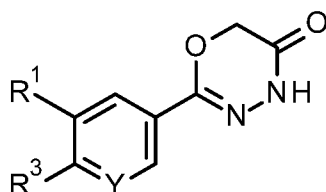


in which R¹, R³, and Y are as defined for the compound of general formula (I) according
 to any of the claims 1-8,

10 to react in

with sodium bicarbonate, in DMF, at a temperature range of about 50 °C – 100 °C,

thereby giving a compound of general formula (I)



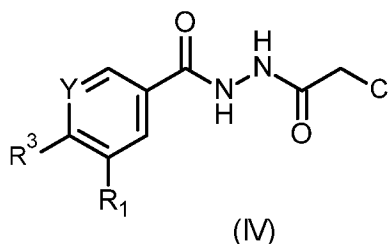
15 in which R¹, Y, and R³ are as defined according to anyone of claims 1-8.

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

The present invention includes methods of preparing compounds of the present invention
 of general formula (I), said methods comprising the steps as described in the
 20 Experimental Section herein.

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

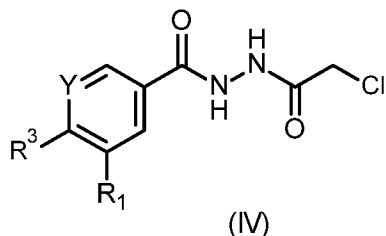
Particularly, the inventions includes the intermediate compounds of general formula (IV) :



in which R¹, R³, and Y are as defined for the compound of general formula (I) formula (I) *supra*.

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

Particularly, the inventions includes the use of intermediate compounds of general formula (IV) :



in which R¹, R³, and Y are as defined for the compound of general formula (I) formula (I) *supra*.

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

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

The present invention includes any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of general formula (IV) *supra*.

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

Methods and Administration

Compounds of general formula (I) of the present invention demonstrate a valuable pharmacological spectrum of action, which could not have been predicted. Compounds of the present invention have surprisingly been found to effectively inhibit cell proliferation and it is likely therefore that said compounds may be used for the treatment or prophylaxis of diseases, preferably hyperproliferative diseases in humans and animals.

More particularly the compounds of formula (I) are suitable for the treatment of a patient having a cancer that is sensitive to treatment with a phosphodiesterase 3A/B (PDE3A/B)-SLF12 complex modulator by detecting co-expression of *PDE3A* and / or PDE3B and *Schlafen 12* (*SLFN12*) and / or SLFN12L mRNA, polynucleotides or polypeptides and/or a lack of decrease in expression of *CREB3L1* mRNA, polynucleotides or polypeptides in a cancer cell derived from such patients. The compounds of formula (I) are selective for cancer cell killing while minimizing enzymatic inhibition of PDE3A and PDE3B

Compounds of the present invention can be utilized to to inhibit tumor growth by inducing a SLFN12 complex formation.. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of general formula (I) of the present invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof, which is effective to treat the disease.

Further Definitions

By "alteration" is meant a change (increase or decrease) in the expression levels, structure or activity of a gene or polypeptide as detected by standard art known methods such as those described herein. As used herein, in one embodiment an alteration includes an about 10% change in expression levels, preferably an about 25% change, more preferably an about 40% change, and most preferably an about 50% or greater change in expression levels. In certain embodiments an alteration includes a 10% or less (including 10 %) change in expression levels, preferably a 25% or less (including 25%) change, more preferably a 40% or less (including 40%) change, and most preferably a 50% or less (including 50%) or greater change in expression levels. In other embodiments

an alteration includes a 9% - 11% (including 9% and 11 %) change in expression levels, preferably a 10%-25% (including 10% and 25%) change, more preferably a 25% - 40% (including 25% and 40%) change, and most preferably a 40%-50% (including 40% - 50%) or greater than 50% (including 50%) change in expression levels. In other certain

5 embodiments an alteration includes a 9% - 11% (including 9% and 11 %) change in expression levels, preferably a 22%-28% (including 22% and 28%) change, more preferably a 35% - 45% (including 35% and 45%) change, and most preferably a 45%-55% (including 45% - 55%) or a greater or equal to 55% change in expression levels

By "fragment" is meant a portion of a polypeptide or nucleic acid molecule. This portion

10 contains, preferably, at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90% of the entire length of the reference nucleic acid molecule or polypeptide. In certain embodiments this portion contains, preferably, at least 9%-11% (including 9% and 11%), 18%-22% (including 18% and 22%), 27%-33% (including 27% and 33%), 36%-44% (including 36% and 44%), 45%-

15 55% (including 45% and 55%), 54%-66% (including 54% and 66%), 63%-77% (including 63% and 77%), 72%-88% (including 72% and 88%), or 81%-99% (including 81% and 99%) of the entire length of the reference nucleic acid molecule or polypeptide. A fragment may contain about 10, about 20, about 30, about 40, about 50, about 60, about 70, about

20 80, about 90, about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, or about 1000 nucleotides or amino acids. In certain embodiments a fragment may contain 9-11, about 18-22, 27-33, 36-44, 45-55, 54-66, 63-77, 72-88, 81-99, 90-110, 180-220, 270-330, 360-440, 450-550, 540-660, 630-770, 720-880, 810-990, or 900-1100 nucleotides or amino acids (including for each the mentioned limitation e.g. for "9-11" means including 9 and 11).

25 By "modulator" is meant any agent that binds to a polypeptide and alters a biological function or activity of the polypeptide. A modulator includes, without limitation, agents that reduce or eliminate a biological function or activity of a polypeptide (e.g., an "inhibitor"). For example, a modulator may inhibit a catalytic activity of a polypeptide. A modulator includes, without limitation, agents that increase or decrease binding of a

30 polypeptide to another agent. For example, a modulator may promote binding of a polypeptide to another polypeptide. In some embodiments, the modulator of PDE3A/PDE3B polypeptide is a compound of formula (I).

By "hyperproliferative disease" is meant a disease, such as cancer, associated with inappropriately high levels of cell division, inappropriately low levels of apoptosis, or both.

Hyperproliferative diseases include, but are not limited to, hematopoietic and benign hyperproliferative diseases.

“Hematopoietic hyperproliferative diseases” also known as myeloproliferative diseases include e.g. polycythemia vera, essential thrombocythosis, thrombocythosis, primary
5 myelofibrosis, and others.

“Benign hyperproliferative diseases” include for example, endometriosis, leiomyoma and benign prostate hyperplasia.

Hyperproliferative diseases include, but are not limited to, for example : psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid
10 tumours, such as cancers of the brain, breast, digestive tract, eye, head and neck, liver, respiratory tract, reproductive organs, skin, thyroid, parathyroid, urinary tract, and their distant metastases. Those diseases also include leukaemias, lymphomas, and sarcomas.

“Solid tumours” are such as e.g. cancers of the breast, brain, digestive tract, eye, head
15 and neck, liver, parathyroid, reproductive organs, respiratory tract, skin, thyroid, urinary tract, and their distant metastases. Those diseases also include lymphomas, sarcomas, and leukaemias.

Examples of *breast* cancers include, but are not limited to, invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma *in situ*, and lobular carcinoma *in situ*.

20 Examples of *brain* cancers include, but are not limited to, brain stem and hypothalamic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

Tumours of the *digestive tract* include, but are not limited to, anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland
25 cancers.

Eye cancers include, but are not limited to, intraocular melanoma and retinoblastoma.

Head-and-neck cancers include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell.

Examples of *liver* cancers include, but are not limited to, hepatocellular carcinoma (liver
30 cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Examples of cancers of the *respiratory tract* include, but are not limited to, small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

5 Tumours of the *male reproductive organs* include, but are not limited to, prostate and testicular cancer.

Tumours of the *female reproductive organs* include, but are not limited to, endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumours of the *urinary tract* include, but are not limited to, bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

10 *Skin* cancers include, but are not limited to, squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Leukemias include, but are not limited to, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia. More particularly *Leucemias* include, but are not limited to acute lymphoblastic
15 leukemia, acute myeloid leukemia, (acute) T-cell leukemia, acute lymphoblastic leukemia, acute lymphocytic leukemia (ALL), acute monocytic leukemia (AML), acute promyelocytic leukemia (APL), bisphenotypic B myelomonocytic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), large granular lymphocytic leukemia, plasma
20 cell leukemia and also myelodysplastic syndrome (MDS), which can develop into an acute myeloid leukemia.

Lymphomas include, but are not limited to, AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system. Particularly *Lymphomas* include, but are not
25 limited to, AIDS-related lymphoma, chronic lymphocytic lymphoma (CLL), non-Hodgkin's lymphoma (NHL), T-non-Hodgkin lymphoma (T-NHL), subtypes of NHL such as Diffuse Large Cell Lymphoma (DLBCL), activated B-cell DLBCL, germinal center B-cell lymphoma DLBCL, double-hit lymphoma and double-expressor lymphoma; anaplastic large cell lymphoma, B-cell lymphoma, cutaneous T-cell lymphoma, Burkitt's lymphoma,
30 follicular lymphoma, hairy cell lymphoma, Hodgkin's disease, mantle cell lymphoma (MCL), lymphoma of the central nervous system, small lymphocytic lymphoma and chronic lymphocytic lymphoma and Sezary syndrome.

Sarcomas include, but are not limited to, sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

5 The term "treating" or "treatment" as stated throughout this document is used conventionally, and includes for example the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, and/or improving the condition of a disease or disease, such as a carcinoma. These diseases have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention. It will be appreciated that, although not precluded, treating a disease or condition does not require that the
10 disease, condition or symptoms associated therewith be completely eliminated.

By "subject" is meant a mammal, including, but not limited to, a human or non-human mammal, such as a bovine, equine, canine, ovine, or feline.

The term "treating" or "treatment" as stated throughout this document is used conventionally, for example the management or care of a subject for the purpose of
15 combating, alleviating, reducing, relieving, improving the condition of a disease or disease, such as a carcinoma.

The compounds of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

20 Generally, the use of chemotherapeutic agents and/or anti-cancer agents in combination with a compound or pharmaceutical composition of the present invention will serve to:

1. yield better efficacy in reducing the growth of a tumour or even eliminate the tumour as compared to administration of either agent alone,
2. provide for the administration of lesser amounts of the administered chemo-
25 therapeutic agents and/or anti-cancer agents,
3. provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,
4. provide for treating a broader spectrum of different cancer types in mammals,
30 especially humans,
5. provide for a higher response rate among treated patients,
6. provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

7. provide a longer time for tumour progression, and/or
8. yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other anti-cancer agent combinations produce antagonistic effects.

5 In addition, the compounds of general formula (I) of the present invention can also be used in combination with radiotherapy and/or surgical intervention.

In a further embodiment of the present invention, the compounds of general formula (I) of the present invention may be used to sensitize a cell to radiation, *i.e.* treatment of a cell with a compound of the present invention prior to radiation treatment of the cell renders the cell more susceptible to DNA damage and cell death than the cell would be
10 in the absence of any treatment with a compound of the present invention. In one aspect, the cell is treated with at least one compound of general formula (I) of the present invention.

Thus, the present invention also provides a method of killing a cell, wherein a cell is administered one or more compounds of the present invention in combination with
15 conventional radiation therapy.

The present invention also provides a method of rendering a cell more susceptible to cell death, wherein the cell is treated with one or more compounds of general formula (I) of the present invention prior to the treatment of the cell to cause or induce cell death.

20 In one aspect, after the cell is treated with one or more compounds of general formula (I) of the present invention, the cell is treated with at least one compound, or at least one method, or a combination thereof, in order to cause DNA damage for the purpose of inhibiting the function of the normal cell or killing the cell.

In other embodiments of the present invention, a cell is killed by treating the cell with at least one DNA damaging agent, *i.e.* after treating a cell with one or more compounds of
25 general formula (I) of the present invention to sensitize the cell to cell death, the cell is treated with at least one DNA damaging agent to kill the cell. DNA damaging agents useful in the present invention include, but are not limited to, chemotherapeutic agents (*e.g.* cis platin), ionizing radiation (X-rays, ultraviolet radiation), carcinogenic agents, and
30 mutagenic agents.

In other embodiments, a cell is killed by treating the cell with at least one method to cause or induce DNA damage. Such methods include, but are not limited to, activation of a cell signalling pathway that results in DNA damage when the pathway is activated, inhibiting of a cell signalling pathway that results in DNA damage when the pathway is inhibited,

and inducing a biochemical change in a cell, wherein the change results in DNA damage. By way of a non-limiting example, a DNA repair pathway in a cell can be inhibited, thereby preventing the repair of DNA damage and resulting in an abnormal accumulation of DNA damage in a cell.

- 5 In one aspect of the invention, a compound of general formula (I) of the present invention is administered to a cell prior to the radiation or other induction of DNA damage in the cell. In another aspect of the invention, a compound of general formula (I) of the present invention is administered to a cell concomitantly with the radiation or other induction of DNA damage in the cell. In yet another aspect of the invention, a compound of general
10 formula (I) of the present invention is administered to a cell immediately after radiation or other induction of DNA damage in the cell has begun.

In another aspect, the cell is in vitro. In another embodiment, the cell is in vivo.

- Thus in some embodiments, the present invention includes a method of inhibiting proliferation of a cell and/or the induction of apoptosis in a cell, comprising contacting the
15 cell with a compound of formula (I) according to any one of claims 1-8.

- Compounds of the present invention can be utilized to inhibit tumor growth by inducing a SLFN12 complex formation. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or
20 ester thereof; which is effective to treat the disease.

The present invention also includes methods of treating hyperproliferative diseases, cancer diseases.

- These diseases have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical
25 compositions of the present invention.

The compounds of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of hyperproliferative diseases, cancer diseases.

- Another aspect of the invention is a method for controlling cancer (*e.g.*, through treatment and/or prophylaxis) in a subject (*e.g.*, human, other mammal, such as rat, etc.) by
30 administering an effective amount of at least one compound of general formula (I), or a pharmaceutically acceptable salt, polymorph, metabolite, hydrate, solvate or ester thereof to the subject.

Particularly in some embodiments, the present invention includes a method of treating a hyperproliferative disease, more particularly cancer, comprising administering an

effective amount of at least one compound of general formula (I) according to any one of claims 1-8.

A method of inhibiting hyperproliferation of a cancer cell is also provided, wherein the method comprises contacting a cancer cell with a compound of general formula (I). The cancer cell may be *in vitro* or *in vivo*.

In accordance with a further aspect, the present invention includes a method of treatment or prophylaxis of diseases, in particular hyperproliferative diseases, particularly cancer diseases, more particularly cervix cancer or melanoma, using an effective amount of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

In a further embodiment the present invention includes all compounds of formula (I) including the disclaimed compounds for use in the treatment of a hyperproliferative disease, particularly cancer, more particularly cervix cancer or melanoma.

In accordance with a further aspect, the present invention includes a method for controlling hyperproliferation in humans and animals comprising administering to a human or animal subject an effective amount of at least one compound of any one of claims 1 to 8, or of a composition as defined herein.

In accordance with a further aspect, the present invention includes a method of treating a hyperproliferative disease, more particularly cancer, in a subject comprising administering to a subject an effective amount of at least one compound of general formula (I) according to any one of claims 1-8.

In some embodiments, the method of treatment and/or prophylaxis of a hyperproliferative disease in a subject may comprise administering to the subject an effective amount of a compound of general formula (I). The hyperproliferative disease may be, for example, cancer (such as e.g., tumors of the anus, the brain, the breast, the bones, the central and peripheral nervous system, the colon, the eye, the kidney, the endocrine glands (e.g., thyroid and adrenal cortex), the endometrium, the esophagus, the gastrointestinal tract (including gastrointestinal stromal tumors), the germ cells, the head and the neck, the kidney, the liver, the larynx and hypopharynx, the lung, the mesothelioma, the pancreas, the prostate, the rectum, the reproductive organs (e.g., cervix, ovary, prostate), the respiratory tract, the small intestine, the skin, the soft tissue, the stomach, the testis, the thyroid gland, the parathyroid gland, ureter, the urogenital tract, vagina and vulva and the

connective tissue and metastases of these tumors. Malignant neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor. etc.).

In some embodiments, the method of treatment and/or prophylaxis of a hyperproliferative disease in a subject may comprise administering to the subject an effective amount of a
5 compound of general formula (I). The hyperproliferative disease may be, for example, cancer (such as e.g., cervix cancer and melanoma etc.).

Furthermore in some embodiments, the present invention includes a method of treating cancer, particularly tumors of the anus, the brain, the breast, the bones, the central and peripheral nervous system, the colon, the eye, the kidney, the endocrine glands (e.g.,
10 thyroid and adrenal cortex), the endometrium, the esophagus, the gastrointestinal tract (including gastrointestinal stromal tumors), the germ cells, the head and the neck, the kidney, the liver, the larynx and hypopharynx, the lung, the mesothelioma, the pancreas, the prostate, the rectum, the reproductive organs (e.g., cervix, ovary, prostate), the respiratory tract, the small intestine, the skin, the soft tissue, the stomach, the testis, the
15 thyroid gland, the parathyroid gland, ureter, the urogenital tract, vagina and vulva and the connective tissue and metastases of these tumors. Malignant neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor. comprising administering an effective amount of at least one compound of formula (I) according to any one of claims 1-8.

20 Furthermore in some embodiments, the present invention includes a method of treating cancer, particularly cervix cancer and melanoma comprising administering an effective amount of at least one compound of formula (I) according to any one of claims 1-8.

Furthermore in some embodiments, the present invention includes a method of treating cancer, particularly tumors of the anus, the brain, the breast, the bones, the central and
25 peripheral nervous system, the colon, the eye, the kidney, the endocrine glands (e.g., thyroid and adrenal cortex), the endometrium, the esophagus, the gastrointestinal tract (including gastrointestinal stromal tumors), the germ cells, the head and the neck, the kidney, the liver, the larynx and hypopharynx, the lung, the mesothelioma, the pancreas, the prostate, the rectum, the reproductive organs (e.g., cervix, ovary, prostate), the
30 respiratory tract, the small intestine, the skin, the soft tissue, the stomach, the testis, the thyroid gland, the parathyroid gland, ureter, the urogenital tract, vagina and vulva and the connective tissue and metastases of these tumors. Malignant neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor. comprising administering an effective amount of at least one compound of formula (I) according to
35 any one of claims 1-8.

Furthermore in some embodiments, the present invention includes a method of treating cancer, particularly cervix cancer and melanoma comprising administering an effective amount of at least one compound of formula (I) according to any one of claims 1-8.

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

10 In some embodiments, the present invention includes a method of using a compound of general formula (I) for the treatment of diseases.

The pharmaceutical activity of the compounds according to the invention can be explained by their activity as SLFN12 complex inducer.

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

20 In accordance with a further aspect, the present invention includes the use of a compound of formula (I), described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of diseases, in particular hyperproliferative diseases, particularly cancer diseases.

25 In accordance with a further aspect, the present invention includes the use of compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, in a method of treatment or prophylaxis of diseases, in particular hyperproliferative diseases, particularly cancer diseases.

30 In some embodiments, the present invention includes use of the compounds of general formula (I) for the manufacture of a medicament for the treatment of a hyperproliferative disease, particularly cancer and more particularly tumors of the anus, the brain, the breast, the bones, the central and peripheral nervous system, the colon, the eye, the kidney, the endocrine glands (e.g., thyroid and adrenal cortex), the endometrium, the esophagus, the gastrointestinal tract (including gastrointestinal stromal tumors), the germ cells, the head and the neck, the kidney, the liver, the larynx and hypopharynx, the lung,

the mesothelioma, the pancreas, the prostate, the rectum, the reproductive organs (e.g., cervix, ovary, prostate), the respiratory tract, the small intestine, the skin, the soft tissue, the stomach, the testis, the thyroid gland, the parathyroid gland, ureter, the urogenital tract, vagina and vulva and the connective tissue and metastases of these tumors.

- 5 Malignant neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor..

In some embodiments, the present invention includes use of the compounds of general formula (I) for the manufacture of a medicament for the treatment of a hyperproliferative disease, particularly cancer and more particularly cervix cancer and melanoma.

- 10 In some embodiments, the present invention includes a compound of general formula (I) for use in a method of inhibiting proliferation of a cell and/or the induction of apoptosis in a cell, comprising contacting the cell with a compound of formula (I) according to any one of claims 1-8.

- 15 In some embodiments, the present invention includes compound of general formula (I) according to any one of claims 1 to 6 for use in a method of treatment or prophylaxis of a disease.

- Particularly in some embodiments, the present invention includes compounds of general formula (I) for use in a method of treating a hyperproliferative disease, more particularly wherein the hyperproliferative disease is cancer, and yet even more particularly wherein
20 the cancer disease is cervix cancer and melanoma.

In some embodiments the present invention provides for compounds of general formula (I) for use in a method of treating cancer, particularly where the cancer disease is cervix cancer and melanoma.

- 25 In accordance with a further aspect, the present invention includes use of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the preparation of a pharmaceutical composition, preferably a medicament, for the prophylaxis or treatment of diseases, in particular hyperproliferative diseases, particularly cancer diseases.

- 30 In accordance with a further aspect, the present invention includes pharmaceutical compositions, in particular a medicament, comprising a compound of general formula (I), as described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, a salt thereof, particularly a pharmaceutically acceptable salt, or a mixture of same, and one or more excipients), in particular one or more pharmaceutically acceptable

excipient(s). Conventional procedures for preparing such pharmaceutical compositions in appropriate dosage forms can be utilized.

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

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

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

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

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

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

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

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

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

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

- 30 In accordance with another aspect, the present invention includes pharmaceutical combinations, in particular medicaments, comprising at least one compound of general formula (I) of the present invention and at least one or more further active ingredients, in

particular for the treatment and/or prophylaxis of a hyperproliferative disease, e.g. cancer.

Particularly, the present invention includes a pharmaceutical combination, which comprises:

- 5
- one or more first active ingredients, in particular compounds of general formula (I) as defined *supra*, and
 - one or more further active ingredients, in particular anti-cancer agent(s).

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

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

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

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also
30 includes such pharmaceutical combinations. For example, the compounds of the present invention can be combined with known anti-cancer agents.

Examples of anti-cancer agents include:

¹³¹I-chTNT, abarelix, abemaciclib, abiraterone, acalabrutinib, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab,

alendronic acid, alitretinoin, altretamine, amifostine, aminogluthethimide, hexyl
 aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione,
 anetumab ravtansine, angiotensin II, antithrombin III, apalutamide, aprepitant,
 arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, avelumab,
 5 axicabtagene ciloleucel, axitinib, azacitidine, basiliximab, belotecan, bendamustine,
 besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin,
 blinatumomab, bortezomib, bosutinib, buserelin, brentuximab vedotin, brigatinib,
 busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolate,
 capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur,
 10 carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil,
 chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid,
 clofarabine, cobimetinib, copanlisib, crisantaspase, crizotinib, cyclophosphamide,
 cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa,
 dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftiox,
 15 denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium
 chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron,
 doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, durvalumab, eculizumab,
 edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, enasidenib, endostatin,
 enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin
 20 zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine,
 ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim,
 fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane,
 fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid
 meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib,
 25 gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron,
 granulocyte colony stimulating factor, histamine dihydrochloride, histrelin,
 hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan,
 ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic
 acid, ingenol mebutate, inotuzumab ozogamicin, interferon alfa, interferon beta,
 30 interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan,
 Itraconazole, ixabepilone, ixazomib, lanreotide, lansoprazole, lapatinib, lasocholine,
 lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, levamisole,
 levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, lutetium
 Lu 177 dotatate, masoprocyl, medroxyprogesterone, megestrol, melarsoprol, melphalan,
 35 mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen,
 methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine,

- midostaurin, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, mvasi, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine,
- 5 neratinib, neridronic acid, netupitant/palonosetron, nivolumab, pentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nintedanib, niraparib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotinod, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel,
- 10 palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pembrolizumab, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor,
- 15 plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib, regorafenib,
- 20 ribociclib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, rucaparib, samarium (153Sm) lexidronam, sargramostim, sarilumab, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin,
- 25 technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tisagenlecleucel, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin,
- 30 trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.
- 35 Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyperproliferative diseases, such as e.g. cancer diseases, by standard

toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the compounds of the present invention can readily
5 be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

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

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

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION - NMR SPECTRA

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

- 5 Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (300 or 400 MHz ^1H , 75 or 101 MHz ^{13}C) spectrometer. Proton, fluorine, and carbon chemical shifts are reported in ppm (δ) referenced to the NMR solvent. Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz).
- 10 The ^1H -NMR data of selected compounds are listed in the form of ^1H -NMR peaklists. Therein, for each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, a peaklist is described by the general form: δ_1 (intensity₁), δ_2 (intensity₂), ... , δ_i (intensity_i), ... , δ_n (intensity_n).
- 15 The intensity of a sharp signal correlates with the height (in cm) of the signal in a printed NMR spectrum. When compared with other signals, this data can be correlated to the real ratios of the signal intensities. In the case of broad signals, more than one peak, or the center of the signal along with their relative intensity, compared to the most intense signal displayed in the spectrum, are shown. A ^1H -NMR peaklist is similar to a classical
- 20 ^1H -NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation. Moreover, similar to classical ^1H -NMR printouts, peaklists can show solvent signals, signals derived from stereoisomers of the particular target compound, peaks of impurities, ^{13}C satellite peaks, and/or spinning sidebands. The peaks of stereoisomers, and/or peaks of impurities are typically displayed with a lower intensity
- 25 compared to the peaks of the target compound (e.g., with a purity of >90%). Such stereoisomers and/or impurities may be typical for the particular manufacturing process, and therefore their peaks may help to identify a reproduction of the manufacturing process on the basis of "by-product fingerprints". An expert who calculates the peaks of the target compound by known methods (MestReC, ACD simulation, or by use of
- 30 empirically evaluated expectation values), can isolate the peaks of the target compound as required, optionally using additional intensity filters. Such an operation would be similar to peak-picking in classical ^1H -NMR interpretation. A detailed description of the reporting of NMR data in the form of peaklists can be found in the publication "Citation of NMR Peaklist Data within Patent Applications" (cf.
- 35 <http://www.researchdisclosure.com/searching-disclosures>, Research Disclosure

Database Number 605005, 2014, 01 Aug 2014). In the peak picking routine, as described in the Research Disclosure Database Number 605005, the parameter "MinimumHeight" can be adjusted between 1% and 4%. However, depending on the chemical structure and/or depending on the concentration of the measured compound it may be reasonable to set the parameter "MinimumHeight" <1%.

Chemical names were generated using the ACD/Name software from ACD/Labs. In some cases generally accepted names of commercially available reagents were used in place of ACD/Name generated names.

EXPERIMENTAL SECTION - ABBREVIATIONS

The following table 1 lists the abbreviations used in this paragraph and in the Examples section as far as they are not explained within the text body. Other abbreviations have their meanings customary *per se* to the skilled person.

Table 1: Abbreviations

The following table lists the abbreviations used herein.

[α]	specific rotation value
d	doublet (NMR coupling pattern)
CDI	1,1'-Carbonyldiimidazole
DAD	Diode array detector
DIPEA	N,N-diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ESI	electrospray ionisation (MS)
EtOAc	Ethyl acetate
EtOH	Ethanol
LC-MS	liquid chromatography coupled to mass spectrometry
M	Molar or molecular Mass
m	multiplet (NMR coupling pattern)
Me	Methyl
MeOH	methanol
MeOH	methanol
MHz	Megahertz
MS	mass spectrometry
NMR	nuclear magnetic resonance

pH	Potential of Hydrogen
q	quartet (NMR coupling pattern)
R _t	retention time
RT	room temperature
s	singlet (NMR coupling pattern)
t	triplet (NMR coupling pattern)
tBuOH	<i>tert</i> -butanol
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
UPLC	Ultra Performance Liquid Chromatography
UPLC-MS	Ultra High Performance Liquid Chromatography Mass Spectroscopy
UV	ultraviolet
WL	wavelength
δ	NMR shift in ppm

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

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

5 EXPERIMENTAL SECTION - GENERAL PART

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art. Reactions were set up and started, *e.g.* by the addition of reagents, at temperatures as specified in the protocols; if
10 no temperature is specified, the respective working step was performed at ambient temperature, *i.e.* between 18 and 25 °C.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some
15 cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, *e.g.* Biotage SNAP cartridges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system

(SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or DCM/methanol.

In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

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

Analytical LC-MS Methods:

Method 1:

Instrument: Waters Acquity UPLC-MS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 50x2.1mm; eluent A: water + 0.1 vol % formic acid (99%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 2:

Instrument: Waters Acquity UPLC-MS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 50x2.1mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 3:

Instrument: SHIMADZU LCMS - UFLC 20-AD - LCMS 2020 MS detector; Column: Waters Atlantis dC18 3 μ m, 2.1 x 100 mm; eluent A: water + 0.1 % formic acid (v/v), eluent B: acetonitrile + 0.1% formic acid (v/v); gradient: 0-5.00 min 5-100% B 5.00-5.40 min 100% B; flow: 0.6 mL/min; temperature: 40°C; PDA scan: 210 - 420 nm.

- 5 Method 4: Instrument Waters Acquity UPLCMS SingleQuad; Column: Phenomenex Kinetix-XB C18 1.7 μ m, 2.1 x 100mm; eluent A: water + 0.1% formic acid (v/v), eluent B: acetonitrile + 0.1% formic acid (v/v); gradient: 0-5.30 min 5-100% B, 5.30-5.80 min 100% B; flow: 0.6 mL/min; temperature: 40 °C; PDA scan: 200-400 nm.

Method 5:

- 10 LCMS instrument type: SHIMADZU LCMS-2020; column: Kinetex EVO C18 30*2.1mm, 5 μ m; mobile phase A: 0.0375% TFA in water (v/v), B: 0.0188% TFA in Acetonitrile (v/v); gradient: 0.00 min 5% B $\rightarrow$ 0.80 min 95% B $\rightarrow$ 1.20 min 95% B $\rightarrow$ 1.21 min 5% B $\rightarrow$ 1.55 min 5% B; flow rate: 1.5 mL/min; column temperature: 50 °C; detector: 220 nm & 254 nm;

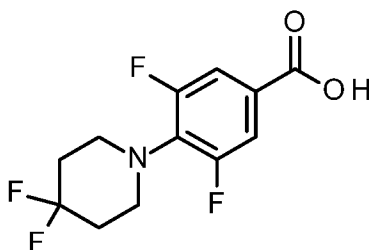
Method 6:

- 15 Instrument type: Agilent 1200; column: Kinetex EVO C18 30*2.1mm, 5 μ m; mobile phase A: 0.0375% TFA in water (v/v), B: 0.1% TFA in Acetonitrile; gradient: 0.00 min 5% B $\rightarrow$ 1.5 min 95% B; flow rate: 1.5 mL/min; oven temperature: 50°C; UV: 220nm&254nm.

20 **EXPERIMENTAL SECTION – INTERMEDIATES**

Intermediate 1

4-(4,4-difluoropiperidin-1-yl)-3,5-difluorobenzoic acid



- 25 3,4,5-trifluorobenzoic acid (2.0 g, 11.4 mmol) and 4,4-difluoropiperidine hydrochloride (1.37 g, 11.4 mmol) were dissolved in DMSO (10 mL) and DIPEA (4.4 mL, 25.0 mmol) was added. The resulting mixture was split in two and heated in two sealed tubes at 140 °C for 3 days. The reaction was cooled to RT and poured in to water (200 mL) and the

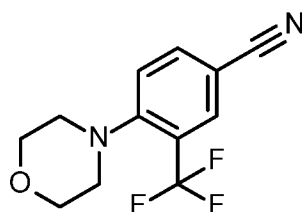
mixture was then acidified with 1M aq. HCl (35 mL) and the product precipitated as an off white solid. This was dried then purified via Biotage Isolera chromatography (eluting with a gradient of eluents; 1:1 heptane:EtOAc to 100% EtOAc) giving the desired product (1.54 g, 41% yield) as an off white solid.

- 5 ¹H NMR (250 MHz, Chloroform-d) δ 7.61 (d, J = 10.1 Hz, 2H), 3.52 - 3.35 (m, 4H), 2.25 - 2.00 (m, 4H).

LC-MS (Method 3): R_t = 1.05 min; MS (ESIpos): m/z = 278 [M+H]⁺

Intermediate 2

4-(morpholin-4-yl)-3-(trifluoromethyl)benzonitrile



10

A mixture of 4-fluoro-3-(trifluoromethyl)benzonitrile (600mg, 3.17mmol) and morpholine (0.97ml, 11.1mmol) in N,N-Dimethylacetamide (3ml) was heated at 100°C for 18h. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with sat. NaHCO₃(aq) and brine. The organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was purified by Biotage Isolera™ chromatography (silica gel, 25g kp-Sil, eluting with heptanes-EtOAc, 1:0 to 1:1) to afford 608mg (75% yield) of the title compound as a white solid.

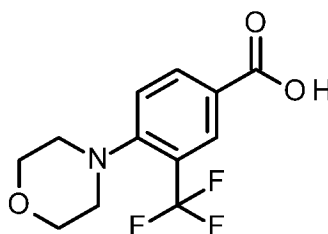
15

LCMS (Method 3) 100% @ R_t = 1.14 min, MS (ESIpos): m/z = 257 (M+H)⁺. ¹H NMR (250 MHz, Chloroform-d) δ 2.99 - 3.10 (m, 4H), 3.79 - 3.89 (m, 4H), 7.32 (d, J = 8.5 Hz, 1H), 7.78 (dd, J = 8.5, 2.0 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H).

20

Intermediate 3

4-(morpholin-4-yl)-3-(trifluoromethyl)benzoic acid

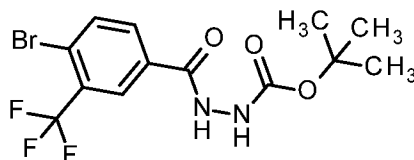


A suspension of 4-(morpholin-4-yl)-3-(trifluoromethyl)benzonitrile (600mg, 2.34mmol, Intermediate 2) and Hydrochloric acid (12M, 8ml) was heated at 100°C for 2h. The reaction mixture was cooled to room temperature and rigorously evaporated under vacuum to afford 730mg (90% yield, estimated 80% purity) of the title compound as a white solid.

LCMS (Method 3) 87% @ Rt = 1.06 min, MS (ESIpos): m/z = 276 (M+H)⁺. ¹H NMR (250 MHz, DMSO-d₆) δ 2.91 - 3.01 (m, 4H), 3.66 - 3.79 (m, 4H), 7.57 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 7.8 Hz, 2H).

Intermediate 4

tert-butyl 2-[4-bromo-3-(trifluoromethyl)benzoyl]hydrazine-1-carboxylate

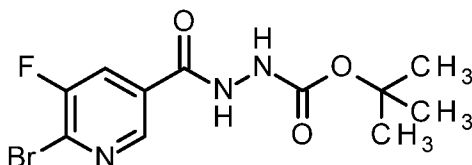


A mixture of 4-bromo-3-(trifluoromethyl)benzoic acid (1.15g, 4.28mmol), tert-butyl hydrazinecarboxylate (0.68g, 5.13mmol), Triethylamine (1.5ml, 1.07mmol) and T3P (50% in ethyl acetate) (3.3ml, 5.56mmol) in Dichloromethane (20ml) was stirred at room temperature for 30mins. The reaction mixture was quenched with sat. NaHCO₃(aq) and the phases separated. The aqueous phase was extracted with dichloromethane and the combined organic layers dried over sodium sulfate and evaporated under vacuum. The residue was purified by Biotage Isolera™ chromatography (silica gel, 50g kp-Sil, eluting with heptanes-EtOAc, 1:0 to 0:1) to afford 1.128g (69% yield) of the title compound as a white solid.

LCMS (Method 3) 94% @ Rt = 1.15min, MS (ESI_{neg}): m/z = 381/383 (M-H)⁻. ¹H NMR (500 MHz, Chloroform-d) δ 1.51 (s, 9H), 6.71 (s, 1H), 7.74 - 7.82 (m, 2H), 8.11 (s, 1H), 8.41 (s, 1H).

Intermediate 5

tert-butyl 2-(6-bromo-5-fluoropyridine-3-carbonyl)hydrazine-1-carboxylate



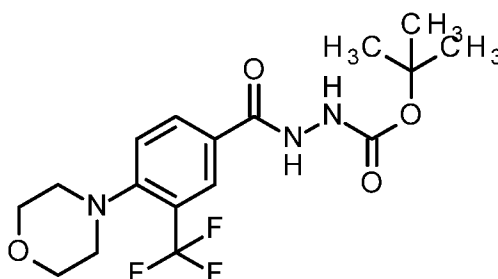
T3P (50% in ethyl acetate) (19.7 mL of a 50% solution in EtOAc, 33.1 mmol) was added dropwise to a stirred solution of 6-bromo-5-fluoropyridine-3-carboxylic acid (4.9 g, 22.0 mmol), tert-butyl hydrazinecarboxylate (3.5 g, 26.5 mmol) and triethylamine (7.7 mL, 55.1 mmol) dissolved in DCM (200 mL). After the addition was complete the mixture was stirred at RT overnight. The following day crude NMR showed conversion to the desired product. The organic layers were washed with water (3 x 50 mL) and the product precipitated as a white solid. This was filtered and dried giving the desired product (5.04 g, 68% yield) as a white solid. This was used in the next step without any further purification.

¹H NMR (250 MHz, DMSO-d₆) δ 10.63 (s, 1H), 9.09 (s, 1H), 8.72 (s, 1H), 8.23 (dd, J = 8.6, 1.8 Hz, 1H), 1.42 (s, 9H).

LC-MS (Method 3): R_t = 0.98 min; MS (ESIpos): m/z = 334 [M+H]⁺

Intermediate 6

tert-butyl 2-[4-(morpholin-4-yl)-3-(trifluoromethyl)benzoyl]hydrazine-1-carboxylate

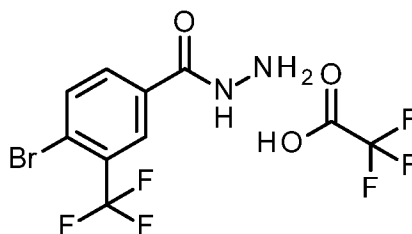


15 Synthesized in analogy to Intermediate 5 from Intermediate 3.

LCMS (Method 3) 98% @ R_t = 1.10 min, MS (ESIpos): m/z = 390 (M+H)⁺. ¹H NMR (250 MHz, Chloroform-d) δ 1.50 (s, 9H), 2.92 - 3.04 (m, 4H), 3.78 - 3.90 (m, 4H), 5.77 (s, 1H), 6.70 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.95 (dd, J = 8.4, 2.0 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H).

20 Intermediate 7

trifluoroacetic acid—4-bromo-3-(trifluoromethyl)benzohydrazide (1/1)

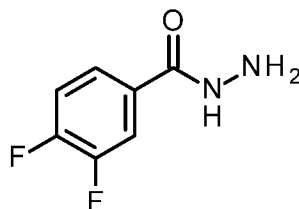


A mixture of tert-butyl 2-[4-bromo-3-(trifluoromethyl)benzoyl]hydrazinecarboxylate (1.128g, 2.944ml, Intermediate 4) and Trifluoroacetic acid (5ml) in Dichloromethane (15ml) was stirred at room temperature for 1.5h, then rigorously evaporated under vacuum to afford 1.20g (quantitative yield, estimated 96% purity) of the title compound as a white solid.

LCMS (Method 3) 99% @ $R_t = 0.96\text{min}$, MS (ESIpos): $m/z = 283/285$ (M+H)⁺. ¹H NMR (250 MHz, DMSO-d₆) δ 8.00 - 8.16 (m, 2H), 8.26 (d, J = 1.7 Hz, 1H).

Intermediate 8

3,4-difluorobenzohydrazide



10

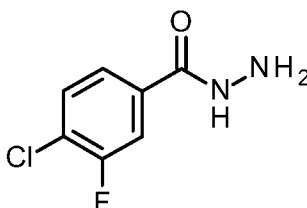
3,4-Difluorobenzoyl chloride (15.6 g, 88.4 mmol) was dissolved in DCM (100 mL) and added dropwise to hydrazine hydrate (50% aq. solution, 21.5 ml, 220 mmol) in DCM (200 mL) at 0 °C. The mixture was then allowed to warm to room temperature giving a white precipitate. The was then filtered and washed with water (300 mL) and TBME (300 mL) and dried giving the desired product (10.7 g, 50% purity, 35% yield) as a white solid. NMR and LCMS showed the product contained ~50% of the bis-acylated product. The mixture was used without further purification.

15

LC-MS (Method 3): $R_t = 0.63\text{ min}$; MS (ESIpos): $m/z = 173$ [M+H]⁺

Intermediate 9

20 4-chloro-3-fluorobenzohydrazide



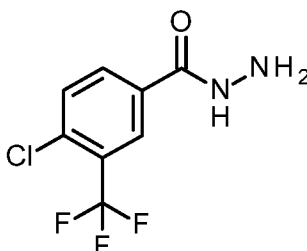
Synthesized in analogy to Intermediate 8.

LC-MS (Method 3): $R_t = 0.71\text{ min}$; MS (ESIpos): $m/z = 189$ [M+H]⁺

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 4.559 (3.70), 7.675 (1.10), 7.679 (1.24), 7.696 (16.00), 7.700 (6.71), 7.708 (6.99), 7.729 (1.38), 7.790 (5.80), 7.813 (4.69), 7.817 (4.51), 9.947 (2.80).

Intermediate 10

- 5 4-chloro-3-(trifluoromethyl)benzohydrazide



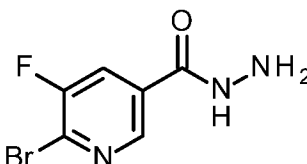
Synthesized in analogy to Intermediate 8

LC-MS (Method 3): *R*_t = 0.89 min; MS (ESIpos): *m/z* = 239 [M+H]⁺

- 10 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.906 (0.41), 2.518 (6.17), 2.522 (3.93), 4.673 (2.82), 7.842 (12.24), 7.863 (14.42), 7.943 (0.41), 7.964 (0.46), 8.097 (8.58), 8.102 (9.05), 8.118 (7.34), 8.123 (7.82), 8.250 (16.00), 8.255 (15.20), 8.359 (0.50), 10.117 (7.06).

Intermediate 11

6-bromo-5-fluoropyridine-3-carbohydrazide



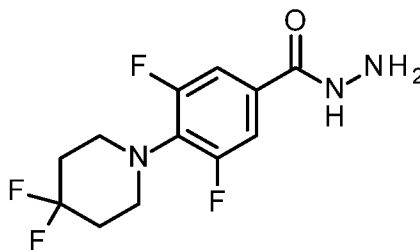
- 15 Synthesized in analogy to Intermediate 7 from Intermediate 5.

¹H NMR (250 MHz, DMSO-d₆) δ 10.10 (s, 1H), 8.68 (dd, *J* = 1.9, 0.8 Hz, 1H), 8.17 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.64 (s, 2H).

LC-MS (Method 3): *R*_t = 0.68 min; MS (ESIpos): *m/z* = 234 [M+H]⁺

Intermediate 12

- 20 4-(4,4-difluoropiperidin-1-yl)-3,5-difluorobenzohydrazide



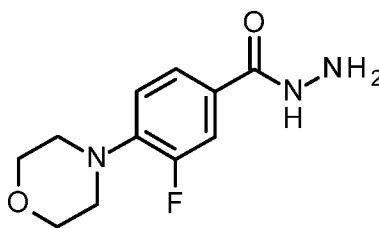
Synthesized in analogy to Intermediate 8 from Intermediate 1.

¹H NMR (500 MHz, Methanol-d₄) δ 7.46 - 7.32 (m, 4H), 3.43 - 3.30 (m, 12H), 2.22 - 1.93 (m, 4H)

- 5 LCMS (Method 3) Rt=1.00 mins, MS (ESI^{Pos}): m/z = 291.9 (M+H)⁺

Intermediate 13

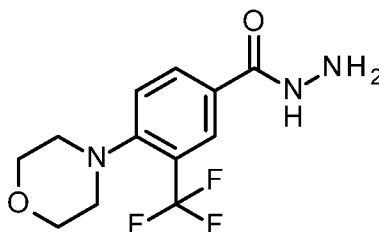
3-fluoro-4-(morpholin-4-yl)benzohydrazide



Synthesized in analogy to Intermediate 8 from 3-fluoro-4-(morpholin-4-yl)benzoic acid.

Intermediate 14

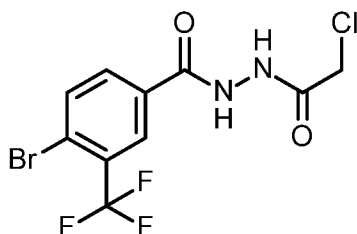
4-(morpholin-4-yl)-3-(trifluoromethyl)benzohydrazide



Synthesized in analogy to Intermediate 7 from Intermediate 6.

Intermediate 15

- 15 4-bromo-N'-(chloroacetyl)-3-(trifluoromethyl)benzohydrazide

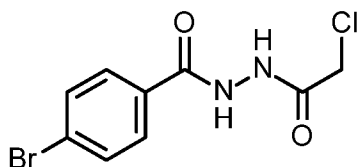


Chloroacetyl chloride (0.29ml, 3.63mmol) was added dropwise to an ice-cold solution of 4-bromo-3-(trifluoromethyl)benzohydrazide trifluoroacetate (1.20g, 3.02mmol, Intermediate 7) and Triethylamine (0.84ml, 6.04mmol) in Tetrahydrofuran (30ml). The reaction mixture was stirred for 1h at room temperature, then concentrated under vacuum. The residue was partitioned between dichloromethane and sat. NaHCO₃(aq), the phases were separated and the aqueous phase extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. The residue was dissolved in Methanol (10ml) and treated with 1M KOH(aq) for 30mins. The mixture was then diluted with water and extracted with dichloromethane. The organic extracts were dried over sodium sulfate and evaporated under vacuum. The reaction mixture was diluted with water (40ml) and extracted with DCM (3 x 50ml) and the combined organic extracts dried over sodium sulfate and evaporated under vacuum. The residue was purified by Biotage Isolera™ chromatography (silica gel, 50g kp-Sil, eluting with heptanes-EtOAc, 1:0 to 0:1) to afford 398mg (36% yield, 97% purity) of the title compound as a white solid.

LCMS (Method 3) 97% @ Rt = 0.98min, MS (ESI^{neg}): m/z = 357/359 (M+H)⁺. ¹H NMR (250 MHz, Chloroform-d) δ 4.21 (s, 2H), 7.80 - 7.87 (m, 2H), 8.15 (s, 1H), 8.91 (s, 1H), 9.15 (s, 1H). More product material was obtained from the aqueous phase by further extraction with chloroform/isopropanol; purification carried out as above to afford 417mg (38% yield) of the title compound as a white solid. Analytical data was consistent with above first crop. Total yield 73%

Intermediate 16

4-bromo-N'-(chloroacetyl)benzohydrazide



To a stirring suspension of 4-bromobenzohydrazide (2.60 g, 12.1 mmol) in 50 ml ethyl acetate was added chloroacetyl chloride (1.2 ml, 15 mmol) in 10 ml ethyl acetate dropwise

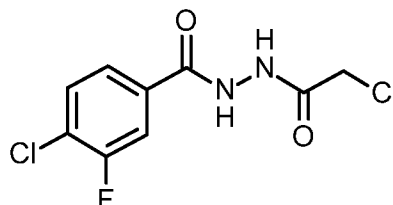
at 60°C under argon. The resulting mixture was stirred for 30 min maintaining that temperature. The mixture was allowed to cool to room temperature, the precipitate was collected by filtration, washed with ethyl acetate and dried in vacuo to give a white solid (2.69 g, 99 % purity, 76 % yield).

- 5 LC-MS (Method 3): $R_t = 0.78$ min; MS (ESIpos): $m/z = 291$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (0.93), 2.522 (0.59), 4.202 (16.00), 4.226 (0.50), 7.714 (0.59), 7.720 (4.68), 7.725 (1.62), 7.736 (2.27), 7.742 (8.21), 7.747 (1.23), 7.795 (1.29), 7.801 (8.60), 7.806 (2.24), 7.818 (1.72), 7.823 (4.69), 7.828 (0.57), 10.405 (3.08), 10.408 (3.08), 10.628 (3.09), 10.631 (3.01).

10 **Intermediate 17**

4-chloro-N'-(chloroacetyl)-3-fluorobenzohydrazide



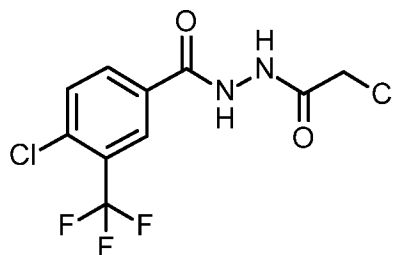
Synthesized in analogy to Intermediate 16 from Intermediate 9.

LC-MS (Method 3): $R_t = 0.80$ min; MS (ESIpos): $m/z = 265$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (0.82), 2.523 (0.58), 4.210 (16.00), 7.734 (0.92), 7.738 (0.81), 7.754 (3.52), 7.759 (4.16), 7.763 (3.10), 7.779 (2.65), 7.799 (0.95), 7.845 (1.60), 7.848 (1.66), 7.870 (1.90), 7.874 (1.77), 10.466 (2.63), 10.724 (2.61).

Intermediate 18

4-chloro-N'-(chloroacetyl)-3-(trifluoromethyl)benzohydrazide



20

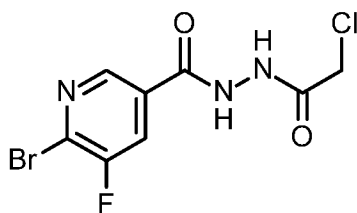
Synthesized in analogy to Intermediate 16 from Intermediate 10.

LC-MS (Method 3): $R_t = 0.96$ min; MS (ESIpos): $m/z = 315$ $[M+H]^+$

^1H -NMR (400 MHz, DMSO- d_6) δ [ppm]: 1.986 (0.47), 2.518 (1.47), 2.522 (0.94), 4.222 (16.00), 7.910 (2.42), 7.931 (2.84), 8.156 (1.69), 8.161 (1.75), 8.177 (1.42), 8.182 (1.50), 8.310 (3.10), 8.314 (2.95).

Intermediate 19

- 5 6-bromo-N'-(chloroacetyl)-5-fluoropyridine-3-carbohydrazide



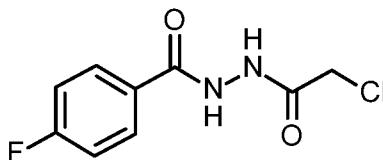
Synthesized in analogy to Intermediate 15 from Intermediate 11.

^1H NMR (500 MHz, DMSO- d_6) δ 10.92 (s, 1H), 10.56 (s, 1H), 8.75 - 8.69 (m, 1H), 8.22 (dd, J = 8.6, 1.8 Hz, 1H), 4.22 (s, 2H).

- 10 LC-MS (Method 3): R_t = 0.80 min; MS (ESIpos): m/z = 312 $[\text{M}+\text{H}]^+$

Intermediate 20

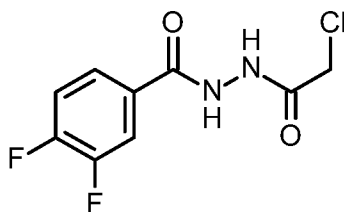
N'-(chloroacetyl)-4-fluorobenzohydrazide



Synthesized in analogy to Intermediate 16 from 4-fluorobenzohydrazide.

- 15 **Intermediate 21**

N'-(chloroacetyl)-3,4-difluorobenzohydrazide

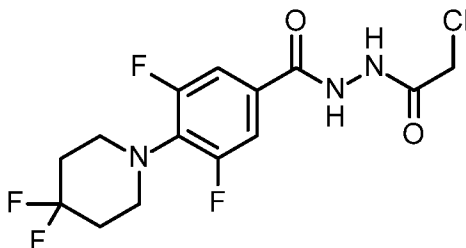


Synthesized in analogy to Intermediate 15 from Intermediate 8.

LC-MS (Method 3): R_t = 0.79 min; the product did not ionise by LCMS

Intermediate 22

N'-(chloroacetyl)-4-(4,4-difluoropiperidin-1-yl)-3,5-difluorobenzohydrazide

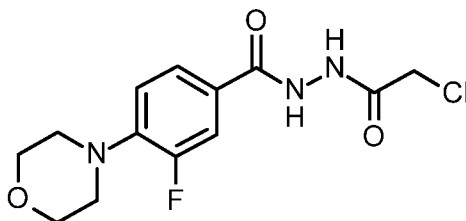


Synthesized in analogy to Intermediate 15 from Intermediate 12.

- 5 ^1H NMR (500 MHz, DMSO- d_6) δ 10.63 - 10.50 (m, 1H), 10.45 - 10.34 (m, 1H), 7.67 - 7.47 (m, 3H), 4.27 - 4.14 (m, 2H), 2.24 - 1.96 (m, 6H). LCMS (Method 3) R_t =1.05 mins, MS (ESIPos): m/z = 367.9 (M+H) $^+$

Intermediate 23

N'-(chloroacetyl)-3-fluoro-4-(morpholin-4-yl)benzohydrazide

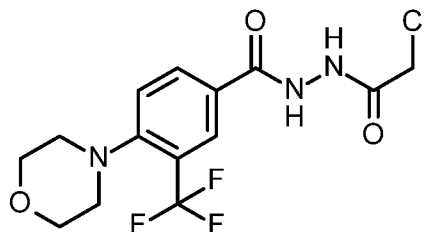


10

Synthesized in analogy to Intermediate 15 from Intermediate 13.

LC-MS (Method 3): R_t = 0.96 min; MS (ESIpos): m/z = 315 [M+H] $^+$ **Intermediate 24**

N'-(chloroacetyl)-4-(morpholin-4-yl)-3-(trifluoromethyl)benzohydrazide



15

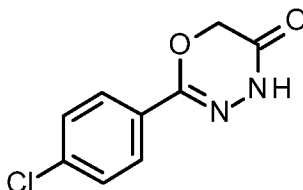
Synthesized in analogy to Intermediate 15 from Intermediate 14.

LCMS (Method 3) 100% @ R_t = 0.98 min, MS (ESIpos): m/z = 366 (M+H) $^+$. ^1H NMR (250 MHz, Chloroform- d) δ 2.94 - 3.08 (m, 4H), 3.79 - 3.90 (m, 4H), 4.20 (s, 2H), 7.33 (d,

J = 8.4 Hz, 1H), 7.97 (dd, J = 8.5, 2.1 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 9.02 (s, 1H), 9.26 (s, 1H)

Intermediate 25

2-(4-chlorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one



5

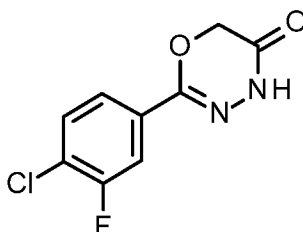
4-chloro-N'-(chloroacetyl)benzohydrazide (synthesized according to Moger et al., Journal of the Brazilian Chemical Society, 25(1), 104-111; 2014, 2.8 g, 11.3 mmol) was dissolved in dry DMF (80 ml). Sodium bicarbonate (1.14 g, 13.6 mmol) was added and the mixture was stirred at 60 °C overnight. Water and saturated ammonium chloride solution was added and the precipitate was collected. The filter cake was washed with water and dried to yield the desired product (1.4g, 56% yield).

10

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 11.10 (br s, 1H), 7.82-7.74 (m, 2H), 7.67-7.48 (m, 2H), 4.78 (s, 2H)

Intermediate 26

15 2-(4-chloro-3-fluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Intermediate 25 from Intermediate 17.

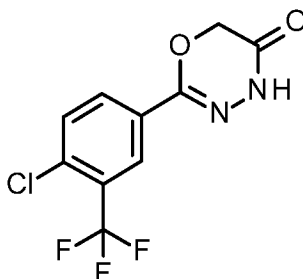
LC-MS (Method 3): R_t = 1.01 min; MS (ESIneg): m/z = 227 [M-H]⁻

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.171 (0.69), 1.986 (1.31), 2.522 (0.95), 4.210 (0.98), 4.797 (16.00), 4.923 (0.59), 7.597 (1.42), 7.602 (1.58), 7.619 (2.26), 7.623 (2.60), 7.655 (2.41), 7.659 (2.06), 7.674 (2.89), 7.680 (2.60), 7.685 (2.32), 7.693 (3.22), 7.714 (1.71), 7.754 (0.48), 7.762 (0.77), 7.778 (0.47), 7.799 (0.54), 11.174 (3.55).

20

Intermediate 27

2-[4-chloro-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



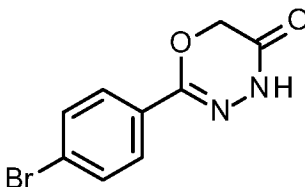
Synthesized in analogy to Intermediate 25 from Intermediate 18.

5 LC-MS (Method 1): $R_t = 1.14$ min; MS (ESI^{neg}): $m/z = 277$ [M-H]⁻

¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 2.518 (0.75), 2.523 (0.49), 3.359 (0.43), 4.827 (16.00), 7.827 (2.23), 7.848 (2.77), 8.012 (1.53), 8.017 (1.69), 8.033 (1.17), 8.038 (1.41), 8.079 (3.13), 8.084 (2.67), 11.219 (3.05).

Intermediate 28

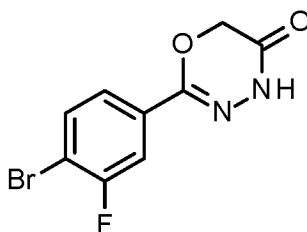
10 2-(4-bromophenyl)-4H-1,3,4-oxadiazin-5(6H)-one



To a stirring solution of 4-bromo-N'-(chloroacetyl)benzohydrazide (2.69 g, 9.23 mmol, Intermediate 16) in DMF (20 mL) was added sodium bicarbonate and the resulting mixture was stirred at 60°C for 48 h. The mixture was poured into 100 ml aq. sat. NH₄Cl-
15 solution and stirred for 30 min. The resulting precipitate was collected by filtration, washed with water and dried in vacuo at 50°C to give an offwhite solid. The mixture was purified by column chromatography (Biotage Isolera; hexane/ethyl acetate) to give the title compound as an offwhite solid (590 mg, 97% purity, 24% yield).

LC-MS (Method 1): $R_t = 1.01$ min; MS (ESI^{pos}): $m/z = 255$ [M+H]⁺20 **Intermediate 29**

2-(4-bromo-3-fluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one



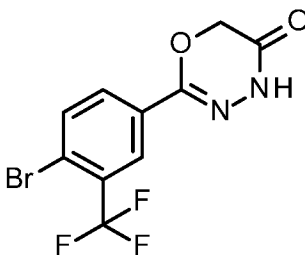
Synthesized in analogy to Intermediate 25

LC-MS (Method 1): $R_t = 1.03$ min; MS (ESIpos): $m/z = 273$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.522 (0.59), 4.795 (16.00), 7.525 (1.61), 7.530 (1.73), 7.546 (1.87), 7.550 (2.05), 7.607 (2.28), 7.612 (2.09), 7.631 (2.29), 7.636 (2.11), 7.792 (2.27), 7.809 (2.52), 7.813 (2.28), 7.831 (1.89), 11.173 (3.25).

Intermediate 30

2-[4-bromo-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

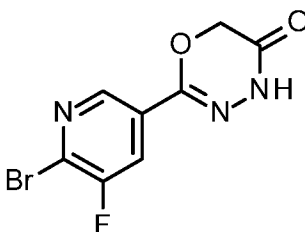


10 A mixture of 4-bromo-N'-(chloroacetyl)-3-(trifluoromethyl)benzohydrazide (417mg, 1.16mmol, Intermediate 15) and Sodium hydrogen carbonate (487mg, 5.80mmol) in N,N-Dimethylformamide (10ml) was heated at 100°C for 1h. The mixture was cooled to room temperature and concentrated under vacuum. The residue was triturated with water/sat. $\text{NH}_4\text{Cl(aq)}$ to afford 309mg (82% yield) of the title compound as a tan solid.

15 LCMS (Method 3) 100% @ $R_t = 1.09$ min, MS (ESIpos): $m/z =$ no molecular ion $^1\text{H NMR}$ (250 MHz, Chloroform- d) δ 4.81 (s, 2H), 7.69 - 7.91 (m, 2H), 8.15 (s, 1H), 8.26 (s, 1H).

Intermediate 31

2-(6-bromo-5-fluoropyridin-3-yl)-4H-1,3,4-oxadiazin-5(6H)-one



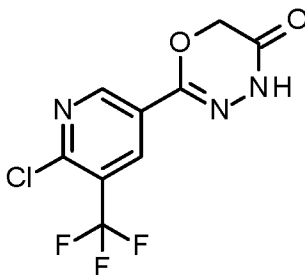
6-bromo-N'-(chloroacetyl)-5-fluoropyridine-3-carbohydrazide (2.2 g, 7.1 mmol, Intermediate 19) was dissolved in DMF (8 mL) and sodium hydrogen carbonate (3.0 g, 35.4 mmol) was added. The resulting mixture was heated at 100 °C for 3 hours and crude NMR showed conversion to the desired product. The mixture was cooled to RT and washed with 1M aq. HCl (50 mL), brine (2 x 50 mL), dried (Na₂SO₄), filtered and concentrated at reduced pressure. The product precipitated as a solid and was filtered and collected and dried giving the desired product (1.0 g, 51% yield) as a pale brown solid. The filtrate was collected and organics separated, dried (Na₂SO₄), filtered and concentrated at reduced pressure. The residue was slurried in DCM and the solids were separated (washed with TBME) dried giving further product (200 mg, 50% purity, 5% yield) as a brown solid.

¹H NMR (250 MHz, DMSO-d₆) δ 11.28 (s, 1H), 8.60 (d, J = 1.9 Hz, 1H), 8.06 (dd, J = 8.8, 1.9 Hz, 1H), 4.83 (s, 2H)

LC-MS (Method 3): R_t = 0.94 min; MS (ESIpos): m/z = 276 [M+H]⁺

15 Intermediate 32

2-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one

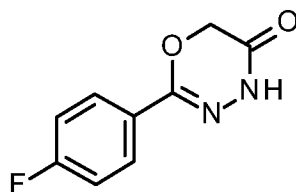


Synthesized in analogy to Intermediate 31.

¹H NMR (400 MHz, DMSO-d₆) δ 11.32 (s, 1H), 8.98 (d, 1H), 8.39 (d, 1H), 4.85 (s, 2H).

20 Intermediate 33

2-(4-fluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one

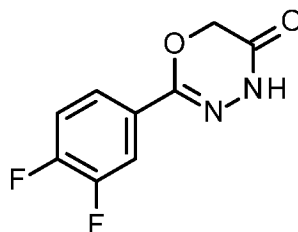


Synthesized in analogy to Intermediate 28 from Intermediate 20. The reaction temperature was 100 °C.

LC-MS (Method 1): $R_t = 0.86$ min; MS (ESIpos): $m/z = 195$ $[M+H]^+$

Intermediate 34

- 5 2-(3,4-difluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one



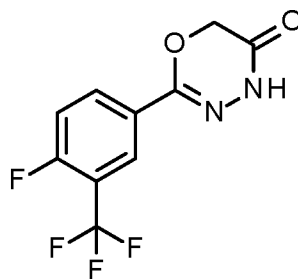
Synthesized in analogy to Intermediate 28 from Intermediate 21. The reaction temperature was 100 °C.

1H NMR (250 MHz, DMSO- d_6) δ 11.11 (s, 1H), 7.77 - 7.44 (m, 3H), 4.79 (s, 2H).

- 10 LCMS (Method 3) $R_t=0.98$ mins, the product did not ionise by LCMS.

Intermediate 35

- 2-[4-fluoro-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

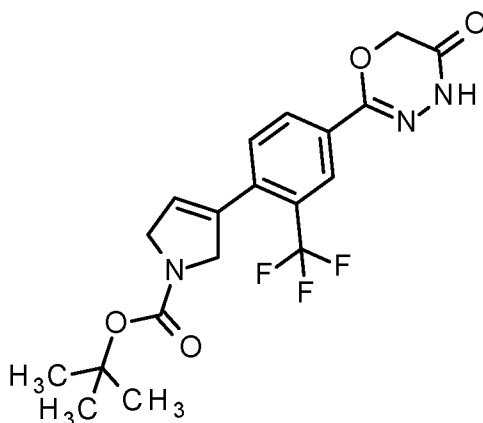


Synthesized in analogy to Intermediate 28.

- 15 1H NMR (400 MHz, DMSO- d_6) δ 11.16 (s, 1H), 8.1 (m, 1H), 8.02 (d, 1H), 7.62 (t, 1H), 4.82 (s, 2H).

Intermediate 36

tert-butyl 3-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]-2,5-dihydro-1H-pyrrole-1-carboxylate



Synthesized in analogy to Example 70 from Intermediate 28 and tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate

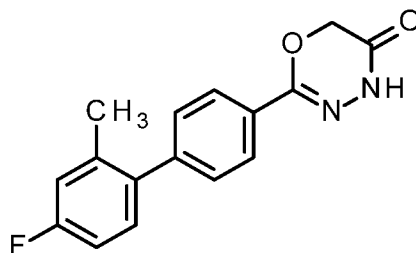
¹H NMR (250 MHz, Chloroform-d) δ = 1.52 (d, J = 3.4 Hz, 9H), 4.27 - 4.52 (m, 4H), 4.84 (s, 2H), 5.86 (d, J = 9.3 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 8.19 (s, 1H), 8.26 (s, 1H).

10

EXPERIMENTAL SECTION – EXAMPLES

Example 1

2-(4'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one



15 2-(4-chlorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one (Intermediate 25, 59.8 mg, 284 μ mol), (4-fluoro-2-methylphenyl)boronic acid (65.6 mg, 426 μ mol), potassium carbonate (78.5 mg, 568 μ mol), and XPhos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 6.70 mg, 8.52 μ mol) were combined in a microwave vial. Dioxane (1.3 ml) and water (430 μ l) were added and the vial was purged with argon for 5 minutes. XPhos Pd G2 (Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-

20

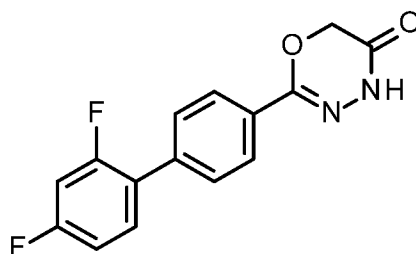
biphenyl)]palladium(II), 8.12 mg, 17.0 μ mol) was added under argon. The vial was sealed and the mixture was stirred at 80 °C over night. The mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic extracts were dried and concentrated. Preparative HPLC yields the desired product (35.7 mg, 95 % purity, 42 %
 5 yield)

LC-MS (Method 1): R_t = 1.23 min; MS (ESIpos): m/z = 285 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 11.09 (s, 1H), 7.85-7.80 (m, 2H), 7.47-7.38 (m, 2H), 7.26 (dd, 1H), 7.19 (dd, 1H), 7.10 (td, 1H), 4.80 (s, 2H), 2.24 (s, 3H)

Example 2

10 2-(2',4'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one



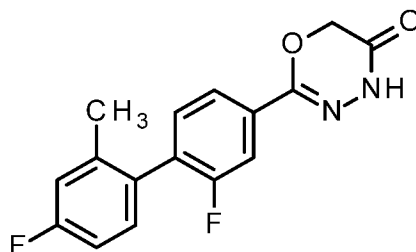
Synthesized in analogy to Example 1 from Intermediate 25 and 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

LC-MS (Method 1): R_t = 1.18 min; MS (ESIpos): m/z = 289 $[M+H]^+$

15 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ [ppm]: 2.518 (1.65), 2.523 (1.05), 4.805 (16.00), 7.202 (0.68), 7.206 (0.72), 7.208 (0.73), 7.222 (1.41), 7.228 (1.40), 7.244 (0.74), 7.248 (0.78), 7.250 (0.76), 7.375 (1.08), 7.381 (1.00), 7.398 (1.19), 7.404 (1.59), 7.409 (1.11), 7.426 (1.04), 7.433 (1.01), 7.611 (1.69), 7.615 (3.13), 7.619 (3.50), 7.628 (1.59), 7.636 (4.58), 7.640 (3.61), 7.650 (1.89), 7.656 (1.07), 7.672 (0.91), 7.852 (1.20), 7.856 (7.19), 7.861
 20 (2.11), 7.874 (2.01), 7.878 (5.69), 7.883 (0.81), 11.108 (4.63).

Example 3

2-(2,4'-difluoro-2'-methyl[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one



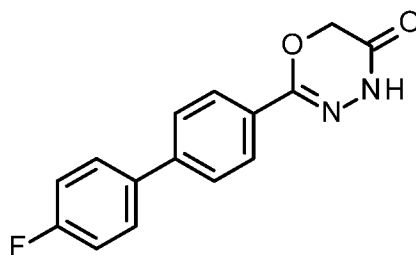
Synthesized in analogy to Example 1 from Intermediate 26 and (4-fluoro-2-methylphenyl)boronic acid

LC-MS (Method 1): $R_t = 1.24$ min; MS (ESI^{neg}): $m/z = 301$ $[M-H]^-$

¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 2.074 (0.40), 2.138 (12.92), 2.518 (1.79), 2.522 (1.13), 4.814 (16.00), 7.103 (0.64), 7.110 (0.75), 7.124 (1.46), 7.130 (1.70), 7.146 (0.97), 7.151 (0.96), 7.206 (1.53), 7.213 (1.38), 7.231 (1.56), 7.238 (1.39), 7.252 (1.85), 7.266 (1.97), 7.272 (1.56), 7.287 (1.39), 7.395 (1.87), 7.414 (3.65), 7.434 (2.02), 7.572 (2.05), 7.576 (2.21), 7.599 (2.00), 7.603 (2.17), 7.664 (2.96), 7.669 (2.75), 7.685 (2.54), 7.689 (2.27), 11.163 (4.89).

10 **Example 4**

2-(4'-fluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one



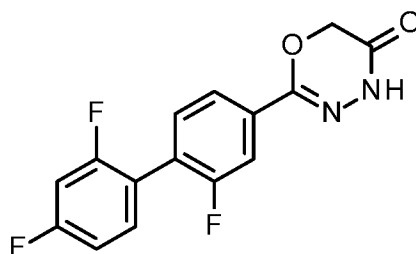
Synthesized in analogy to Example 1 from Intermediate 25 and (4-fluorophenyl)boronic acid

15 LC-MS (Method 1): $R_t = 1.17$ min; MS (ESI^{pos}): $m/z = 271$ $[M+H]^+$

¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 2.074 (0.68), 2.522 (0.98), 4.799 (16.00), 7.296 (3.02), 7.301 (1.09), 7.317 (6.31), 7.335 (1.15), 7.339 (3.32), 7.747 (4.99), 7.755 (3.83), 7.763 (3.38), 7.768 (10.55), 7.778 (3.78), 7.786 (1.45), 7.791 (3.06), 7.835 (7.92), 7.857 (4.87), 11.091 (4.51).

20 **Example 5**

2-(2,2',4'-trifluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one



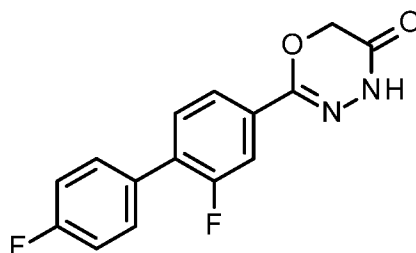
Synthesized in analogy to Example 1 from Intermediate 26 and (2,4-difluorophenyl)boronic acid

LC-MS (Method 1): $R_t = 1.19$ min; MS (ESI^{neg}): $m/z = 305$ [M-H]⁻

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.083 (0.40), 2.327 (0.54), 2.332 (0.40), 2.522 (2.09), 2.669 (0.54), 2.673 (0.40), 4.819 (16.00), 7.228 (0.79), 7.233 (0.84), 7.249 (1.65), 7.254 (1.71), 7.270 (0.91), 7.275 (0.94), 7.406 (1.08), 7.412 (1.05), 7.432 (1.54), 7.436 (1.51), 7.456 (1.08), 7.462 (1.03), 7.543 (2.38), 7.563 (4.39), 7.582 (3.57), 7.602 (2.99), 7.605 (2.66), 7.629 (2.18), 7.633 (2.38), 7.696 (3.19), 7.700 (2.81), 7.717 (2.36), 7.720 (2.20), 11.181 (4.76).

10 **Example 6**

2-(2,4'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one



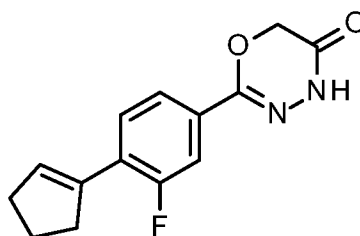
Synthesized in analogy to Example 1 from Intermediate 26 and 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

15 LC-MS (Method 1): $R_t = 1.19$ min; MS (ESI^{neg}): $m/z = 287$ [M-H]⁻

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.083 (0.45), 2.518 (1.37), 2.523 (0.85), 4.813 (16.00), 7.322 (3.16), 7.327 (0.96), 7.339 (1.16), 7.344 (6.57), 7.350 (1.18), 7.361 (1.06), 7.367 (3.34), 7.580 (1.98), 7.583 (2.11), 7.609 (1.94), 7.613 (2.28), 7.616 (1.68), 7.626 (1.78), 7.629 (2.11), 7.636 (3.77), 7.643 (2.57), 7.648 (2.39), 7.652 (1.96), 7.656 (3.25), 7.661 (1.91), 7.666 (1.58), 7.672 (4.21), 7.677 (3.82), 7.693 (1.56), 7.697 (1.68), 11.165 (3.72).

Example 7

2-[4-(cyclopent-1-en-1-yl)-3-fluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one



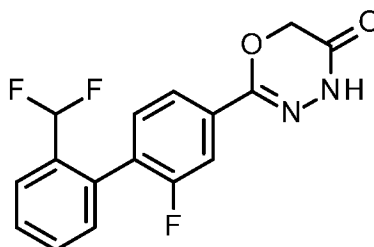
Synthesized in analogy to Example 1 from Intermediate 26 and cyclopent-1-en-1-ylboronic acid

LC-MS (Method 1): $R_t = 1.29$ min; MS (ESIpos): $m/z = 261$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 1.889 (0.58), 1.908 (1.80), 1.927 (2.65), 1.946 (2.04), 1.965 (0.72), 2.518 (2.18), 2.522 (1.94), 2.534 (1.70), 2.539 (1.70), 2.552 (1.01), 2.558 (0.99), 2.698 (1.05), 2.703 (1.15), 2.718 (1.80), 2.736 (1.04), 2.741 (0.92), 4.783 (16.00), 6.443 (1.85), 6.448 (1.86), 7.461 (2.45), 7.466 (2.21), 7.480 (2.97), 7.494 (2.07), 7.499 (3.45), 7.562 (3.20), 7.566 (2.63), 7.582 (1.92), 7.587 (1.92), 11.119 (4.21).

10 **Example 8**

2-[2'-(difluoromethyl)-2-fluoro[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



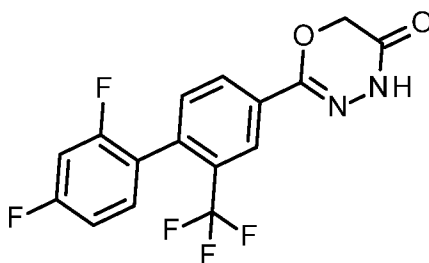
Synthesized in analogy to Example 1 from Intermediate 26 and 2-[2-(difluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

- 15 LC-MS (Method 1): $R_t = 1.17$ min; MS (ESI_{neg}): $m/z = 319$ $[M-H]^-$

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 2.079 (3.22), 2.323 (0.43), 2.665 (0.46), 4.820 (16.00), 6.635 (1.68), 6.772 (3.31), 6.908 (1.58), 7.396 (2.10), 7.414 (2.63), 7.429 (2.20), 7.449 (3.85), 7.468 (2.27), 7.594 (3.01), 7.621 (3.75), 7.641 (5.09), 7.656 (2.96), 7.679 (3.39), 7.682 (3.69), 7.703 (3.02), 7.750 (2.79), 7.766 (2.28), 11.181 (5.32).

20 **Example 9**

2-[2',4'-difluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



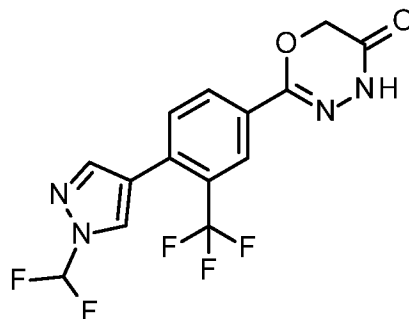
Synthesized in analogy to Example 1 from Intermediate 26 and 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

LC-MS (Method 1): $R_t = 1.27$ min; MS (ESIpos): $m/z = 357$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 2.074 (3.38), 2.518 (2.61), 2.523 (1.76), 4.855 (16.00), 7.187 (0.67), 7.192 (0.71), 7.194 (0.70), 7.209 (1.47), 7.214 (1.51), 7.216 (1.47), 7.230 (0.80), 7.235 (0.86), 7.237 (0.81), 7.387 (1.01), 7.393 (1.02), 7.402 (0.85), 7.411 (1.75), 7.418 (2.49), 7.423 (1.67), 7.441 (1.95), 7.461 (0.63), 7.561 (2.59), 7.581 (2.76), 8.083 (1.76), 8.086 (1.96), 8.104 (1.54), 8.107 (1.88), 8.135 (3.89), 8.139 (3.37), 11.228 (5.12).
- 10

Example 10

2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



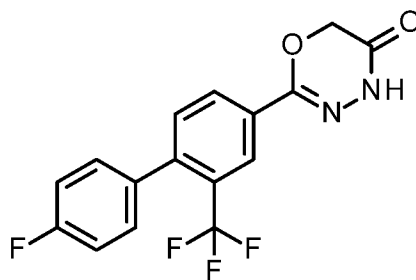
- 15 Synthesized in analogy to Example 1 from Intermediate 26 and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

LC-MS (Method 1): $R_t = 1.07$ min; MS (ESI_{neg}): $m/z = 359$ $[M-H]^-$

- $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (4.13), 2.518 (1.53), 2.523 (0.93), 4.847 (16.00), 7.693 (2.73), 7.714 (3.01), 7.750 (1.86), 7.897 (3.88), 7.995 (5.55), 8.045 (3.51), 8.049 (2.34), 8.066 (1.72), 8.070 (1.91), 8.118 (4.08), 8.121 (3.60), 8.498 (6.10), 11.208 (5.61).
- 20

Example 11

2-[4'-fluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



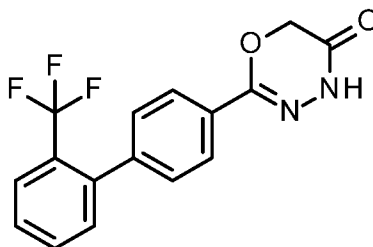
Synthesized in analogy to Example 1 from Intermediate 26 and 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

5 LC-MS (Method 1): $R_t = 1.27$ min; MS (ESI^{neg}): $m/z = 337$ [M-H]⁻

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.083 (4.18), 2.518 (1.06), 2.523 (0.70), 4.850 (16.00), 7.285 (2.44), 7.290 (0.91), 7.301 (1.30), 7.307 (6.26), 7.313 (1.22), 7.324 (1.14), 7.329 (4.03), 7.336 (0.51), 7.374 (2.68), 7.388 (3.05), 7.395 (2.10), 7.409 (1.58), 7.516 (2.57), 7.536 (2.72), 8.049 (1.72), 8.052 (1.86), 8.069 (1.52), 8.073 (1.76), 8.111 (3.77),
10 8.115 (3.22), 11.212 (4.65).

Example 12

2-[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



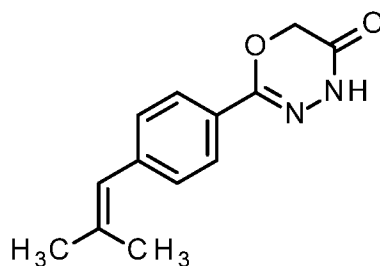
15 Synthesized in analogy to Example 1 from Intermediate 25 and [2-(trifluoromethyl)phenyl]boronic acid

LC-MS (Method 1): $R_t = 1.24$ min; MS (ESI^{pos}): $m/z = 321$ [M+H]⁺

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.518 (1.09), 2.523 (0.78), 4.808 (16.00), 7.397 (4.16), 7.417 (5.26), 7.440 (2.02), 7.624 (0.75), 7.643 (1.77), 7.663 (1.22), 7.727 (1.23), 7.746 (1.88), 7.763 (0.74), 7.823 (1.02), 7.827 (6.87), 7.832 (2.00), 7.844 (3.72), 7.849
20 (7.55), 7.853 (1.03), 7.865 (1.77), 11.106 (4.61).

Example 13

2-[4-(2-methylprop-1-en-1-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



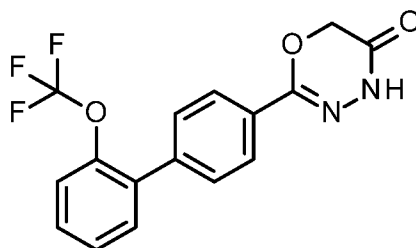
Synthesized in analogy to Example 1 from Intermediate 25 and 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane

LC-MS ((Method 1): R_t = 1.18 min; MS (ESIpos): m/z = 231 [M+H]⁺

- 5 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.854 (11.32), 1.857 (11.17), 1.895 (9.66), 1.897 (9.71), 2.518 (1.30), 2.523 (0.91), 4.760 (16.00), 6.296 (2.25), 7.298 (4.41), 7.319 (4.85), 7.711 (5.84), 7.715 (1.78), 7.727 (1.68), 7.732 (5.06), 11.031 (3.87).

Example 14

2-[2'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



10

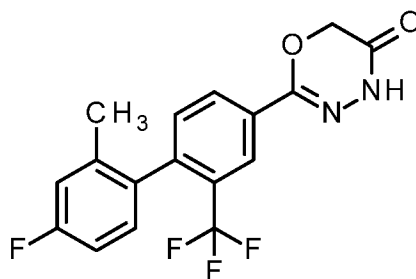
Synthesized in analogy to Example 1 from Intermediate 25 and [2-(trifluoromethoxy)phenyl]boronic acid

LC-MS (Method 1): R_t = 1.27 min; MS (ESIpos): m/z = 337 [M+H]⁺

- 15 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.326 (0.43), 2.522 (1.42), 2.669 (0.44), 4.807 (16.00), 7.147 (0.52), 7.373 (0.53), 7.464 (0.65), 7.485 (0.51), 7.498 (1.11), 7.505 (1.33), 7.519 (4.50), 7.536 (5.17), 7.543 (4.40), 7.556 (7.10), 7.561 (4.29), 7.572 (5.15), 7.577 (8.76), 7.587 (1.60), 7.593 (1.14), 7.861 (7.15), 7.882 (5.86), 8.096 (0.46), 8.115 (0.43), 11.110 (5.26).

Example 15

- 20 2-[4'-fluoro-2'-methyl-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



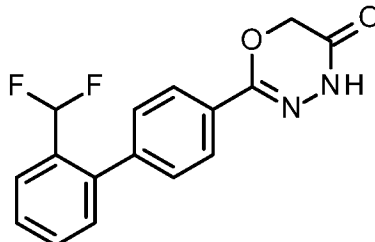
Synthesized in analogy to Example 1 from Intermediate 26 and (4-fluoro-2-methylphenyl)boronic acid

LC-MS (Method 1): $R_t = 1.33$ min; MS (ESIpos): $m/z = 353$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.975 (16.00), 2.522 (0.91), 4.850 (13.56), 7.063 (0.57), 7.069 (0.65), 7.084 (1.45), 7.091 (1.67), 7.106 (0.97), 7.112 (1.08), 7.145 (1.51), 7.160 (1.69), 7.184 (1.91), 7.191 (1.48), 7.210 (1.55), 7.217 (1.41), 7.432 (2.52), 7.452 (2.66), 8.052 (1.76), 8.056 (1.88), 8.076 (1.79), 8.125 (3.68), 8.129 (3.36), 11.209 (4.88).

Example 16

- 10 2-[2'-(difluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



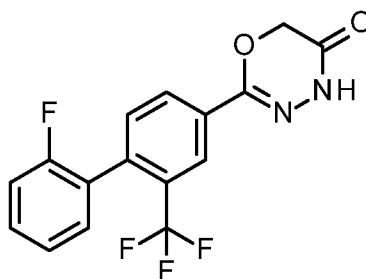
Synthesized in analogy to Example 1 from Intermediate 25 and 2-[2-(difluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

LC-MS (Method 1): $R_t = 1.18$ min; MS (ESIpos): $m/z = 303$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.985 (0.66), 2.518 (0.53), 4.811 (16.00), 6.684 (1.50), 6.821 (3.13), 6.957 (1.33), 7.403 (1.70), 7.422 (2.04), 7.441 (5.71), 7.446 (2.08), 7.458 (2.15), 7.462 (6.30), 7.569 (0.63), 7.573 (0.68), 7.588 (1.92), 7.591 (1.84), 7.606 (1.80), 7.610 (1.56), 7.623 (1.52), 7.641 (1.71), 7.657 (0.62), 7.749 (2.11), 7.767 (1.68), 7.856 (1.15), 7.861 (6.75), 7.866 (2.28), 7.878 (2.10), 7.882 (6.22), 7.887 (1.02), 11.122 (5.08).
- 20

Example 17

2-[2'-fluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



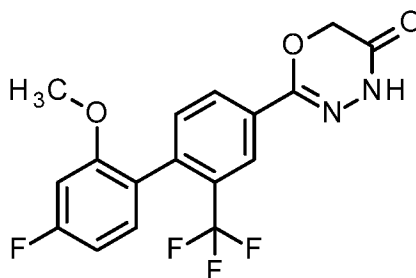
Synthesized in analogy to Example 1 from Intermediate 26 and (2-fluorophenyl)boronic acid

LC-MS (Method 1): $R_t = 1.24$ min; MS (ESIpos): $m/z = 339$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 2.074 (4.28), 2.518 (1.64), 2.522 (1.09), 4.856 (16.00), 7.147 (0.48), 7.281 (0.91), 7.284 (1.01), 7.300 (2.26), 7.303 (2.70), 7.309 (1.43), 7.318 (1.83), 7.320 (2.48), 7.333 (2.89), 7.336 (2.38), 7.355 (3.13), 7.372 (1.02), 7.375 (0.87), 7.464 (0.59), 7.484 (0.42), 7.495 (0.68), 7.500 (0.70), 7.508 (0.83), 7.512 (1.22), 7.515 (1.09), 7.521 (0.82), 7.526 (0.87), 7.533 (1.22), 7.538 (0.66), 7.552 (2.94), 7.573 (2.67), 8.080 (1.71), 8.083 (1.89), 8.099 (1.58), 8.103 (1.83), 8.115 (0.41), 8.135 (3.77), 8.140 (3.24), 11.225 (4.86).
- 10

Example 18

2-[4'-fluoro-2'-methoxy-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



15

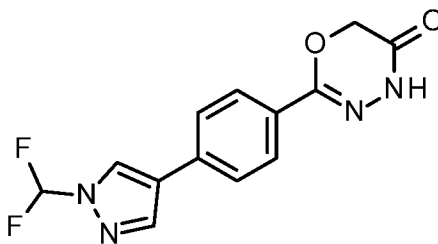
Synthesized in analogy to Example 1 from Intermediate 26 and (4-fluoro-2-methoxyphenyl)boronic acid

LC-MS (Method 1): $R_t = 1.27$ min; MS (ESIpos): $m/z = 369$ $[M+H]^+$

- 20 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 2.074 (2.33), 2.518 (1.18), 2.522 (0.75), 3.333 (12.31), 4.840 (16.00), 6.823 (1.07), 6.830 (1.24), 6.845 (2.19), 6.851 (2.49), 6.866 (1.21), 6.872 (1.28), 7.018 (2.00), 7.023 (2.00), 7.046 (2.07), 7.052 (1.95), 7.151 (1.63), 7.168 (1.95), 7.189 (1.41), 7.372 (0.42), 7.412 (2.68), 7.433 (2.81), 7.464 (0.50), 8.013 (1.77), 8.016 (1.89), 8.033 (1.57), 8.037 (1.83), 8.073 (3.93), 8.078 (3.42), 11.193 (5.10).

Example 19

2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



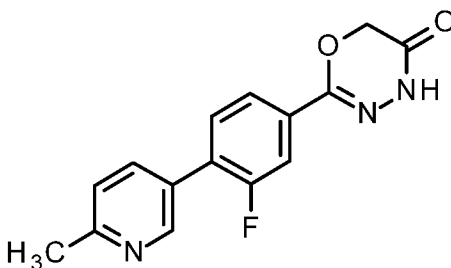
Synthesized in analogy to Example 1 from Intermediate 25 and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

LC-MS (Method 1): $R_t = 0.87$ min; MS (ESIpos): $m/z = 293$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 4.786 (12.56), 7.704 (1.43), 7.773 (0.76), 7.781 (0.57), 7.799 (16.00), 7.821 (0.83), 7.851 (3.00), 7.999 (1.28), 8.349 (5.95), 8.822 (5.86), 11.068 (4.64).

Example 20

2-[3-fluoro-4-(6-methylpyridin-3-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



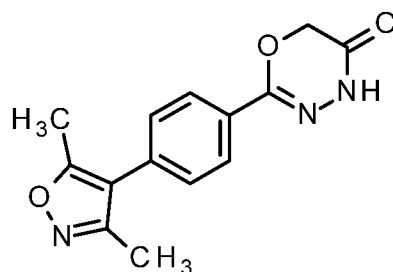
Synthesized in analogy to Example 1 from Intermediate 26 and (6-methylpyridin-3-yl)boronic acid (1.20 g, 8.75 mmol)

LC-MS (Method 1): $R_t = 0.66$ min; MS (ESIpos): $m/z = 286$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.083 (1.58), 2.518 (1.94), 2.529 (16.00), 2.539 (0.88), 4.819 (14.67), 7.384 (2.51), 7.403 (2.70), 7.603 (1.79), 7.606 (1.88), 7.634 (2.31), 7.669 (0.52), 7.689 (2.68), 7.696 (2.23), 7.702 (4.76), 7.704 (4.56), 7.719 (0.41), 7.895 (1.09), 7.899 (1.43), 7.904 (1.13), 7.915 (1.01), 7.920 (1.36), 7.925 (0.98), 8.660 (2.55), 11.174 (4.76).

Example 21

2-[4-(3,5-dimethyl-1,2-oxazol-4-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



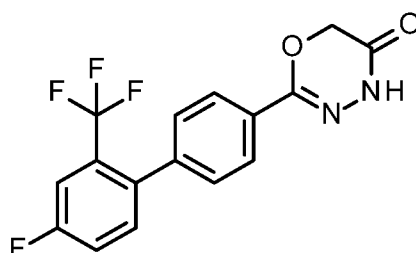
Synthesized in analogy to Example 1 from Intermediate 25 and (3,5-dimethyl-1,2-oxazol-4-yl)boronic acid

LC-MS (Method 1): $R_t = 0.93$ min; MS (ESIpos): $m/z = 272$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.245 (15.51), 2.425 (16.00), 2.518 (0.44), 4.795 (10.26), 7.472 (0.57), 7.476 (3.59), 7.481 (1.21), 7.493 (1.28), 7.498 (3.91), 7.503 (0.63), 7.835 (0.65), 7.840 (4.19), 7.845 (1.24), 7.857 (1.24), 7.862 (3.69), 7.866 (0.53), 11.097 (2.80).

Example 22

- 10 2-[4'-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



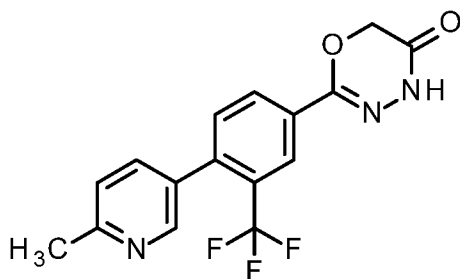
Synthesized in analogy to Example 1 from Intermediate 25 and [4-fluoro-2-(trifluoromethyl)phenyl]boronic acid

LC-MS (Method 1): $R_t = 1.21$ min; MS (ESIpos): $m/z = 339$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.522 (1.04), 4.807 (16.00), 7.391 (4.99), 7.412 (5.24), 7.479 (1.26), 7.493 (1.39), 7.500 (1.82), 7.514 (1.66), 7.604 (0.97), 7.610 (1.11), 7.625 (1.66), 7.631 (1.78), 7.646 (0.72), 7.652 (0.76), 7.751 (1.96), 7.757 (1.87), 7.774 (2.00), 7.781 (1.83), 7.825 (6.96), 7.846 (5.98), 11.110 (5.53).

Example 23

- 20 2-[4-(6-methylpyridin-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



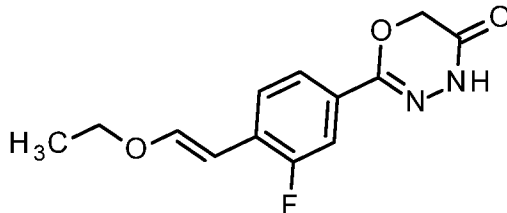
Synthesized in analogy to Example 1 from Intermediate 26 and (6-methylpyridin-3-yl)boronic acid

LC-MS (Method 2): $R_t = 1.00$ min; MS (ESIpos): $m/z = 336$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.074 (1.72), 2.518 (0.84), 2.523 (0.75), 2.539 (16.00), 4.855 (14.66), 7.357 (2.41), 7.377 (2.70), 7.551 (2.30), 7.571 (2.44), 7.666 (1.36), 7.672 (1.37), 7.686 (1.19), 7.692 (1.21), 8.074 (1.51), 8.078 (1.63), 8.095 (1.29), 8.098 (1.56), 8.133 (3.35), 8.138 (2.91), 8.399 (2.29), 8.405 (2.28), 11.219 (0.63).

Example 24

- 10 2-{4-[(E)-2-ethoxyethenyl]-3-fluorophenyl}-4H-1,3,4-oxadiazin-5(6H)-one



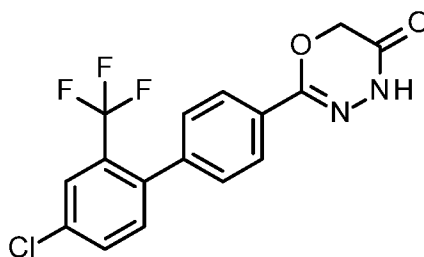
Synthesized in analogy to Example 1 from Intermediate 26 and 2-[(E)-2-ethoxyethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

LC-MS (Method 1): $R_t = 1.12$ min; MS (ESIpos): $m/z = 265$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.246 (6.02), 1.264 (13.39), 1.281 (5.92), 2.075 (0.80), 2.518 (0.93), 2.523 (0.69), 3.925 (1.62), 3.943 (5.45), 3.961 (5.33), 3.978 (1.56), 4.760 (16.00), 5.836 (3.00), 5.869 (3.18), 7.393 (3.96), 7.397 (2.41), 7.402 (2.32), 7.426 (4.74), 7.431 (2.31), 7.467 (1.84), 7.471 (1.49), 7.487 (2.69), 7.492 (2.57), 7.540 (1.96), 7.560 (2.80), 7.580 (1.21), 11.070 (4.87).

Example 25

- 20 2-[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



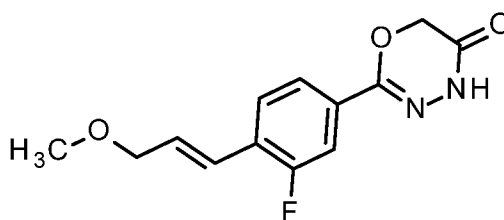
Synthesized in analogy to Example 1 from Intermediate 25 and [4-chloro-2-(trifluoromethyl)phenyl]boronic acid

LC-MS (Method 1): $R_t = 1.37$ min; MS (ESIpos): $m/z = 355$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.332 (0.78), 2.518 (4.08), 2.523 (2.86), 4.808 (16.00), 7.401 (4.27), 7.421 (4.64), 7.462 (2.51), 7.482 (2.77), 7.823 (1.79), 7.827 (2.77), 7.832 (7.17), 7.837 (2.25), 7.844 (1.70), 7.849 (3.62), 7.854 (6.13), 7.858 (0.94), 7.933 (3.64), 7.939 (3.36), 11.112 (5.25).

Example 26

- 10 2-{3-fluoro-4-[(1E)-3-methoxyprop-1-en-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



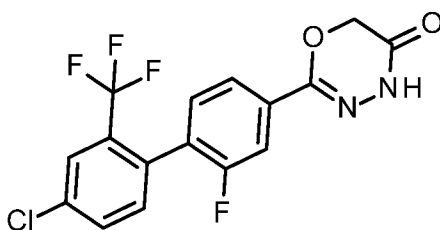
Synthesized in analogy to Example 1 from Intermediate 26 and 2-[(1E)-3-methoxyprop-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

LC-MS (Method 1): $R_t = 0.95$ min; MS (ESIpos): $m/z = 265$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (0.75), 2.523 (0.56), 3.330 (16.00), 4.081 (2.59), 4.085 (2.77), 4.094 (2.64), 4.098 (2.70), 4.782 (12.75), 6.511 (0.61), 6.525 (1.31), 6.538 (0.51), 6.552 (0.85), 6.565 (1.99), 6.578 (0.91), 6.698 (1.61), 6.739 (1.02), 7.460 (1.45), 7.464 (1.59), 7.490 (1.41), 7.494 (1.55), 7.555 (1.38), 7.559 (1.23), 7.576 (1.65), 7.580 (1.60), 7.709 (1.24), 7.729 (2.06), 7.749 (0.97), 11.128 (3.52).

Example 27

2-[4'-chloro-2'-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one



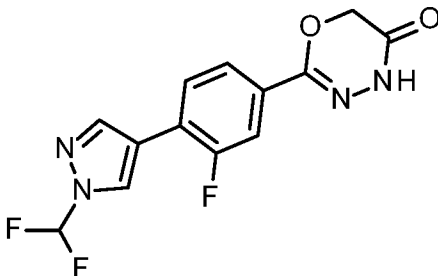
Synthesized in analogy to Example 1 from Intermediate 26 and [4-chloro-2-(trifluoromethyl)phenyl]boronic acid

LC-MS (Method 1): $R_t = 1.36$ min; MS (ESIpos): $m/z = 373$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.322 (0.71), 2.327 (0.95), 2.522 (3.70), 2.665 (0.71), 2.669 (0.97), 4.820 (16.00), 7.424 (1.44), 7.444 (2.96), 7.463 (1.71), 7.522 (2.78), 7.542 (3.11), 7.587 (2.26), 7.591 (2.46), 7.613 (2.23), 7.617 (2.49), 7.669 (3.17), 7.674 (2.77), 7.689 (2.59), 7.693 (2.39), 7.863 (1.94), 7.867 (2.04), 7.884 (1.68), 7.888 (1.84), 7.985 (4.03), 7.990 (3.74), 11.181 (5.86).

10 **Example 28**

2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]-3-fluorophenyl}-4H-1,3,4-oxadiazin-5(6H)-one



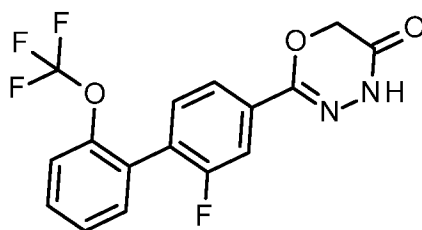
Synthesized in analogy to Example 1 from Intermediate 26 and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

- 15 LC-MS (Method 1): $R_t = 0.98$ min; MS (ESIpos): $m/z = 311$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.074 (0.62), 2.518 (1.58), 2.522 (0.99), 4.804 (16.00), 7.580 (2.04), 7.584 (2.34), 7.610 (1.90), 7.614 (2.41), 7.631 (2.88), 7.636 (2.12), 7.652 (2.87), 7.656 (2.54), 7.742 (1.72), 7.889 (3.62), 7.917 (1.99), 7.936 (3.36), 7.957 (1.65), 8.036 (1.49), 8.344 (4.51), 8.729 (3.75), 8.733 (3.58), 11.150 (5.32).

20 **Example 29**

2-[2-fluoro-2'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one

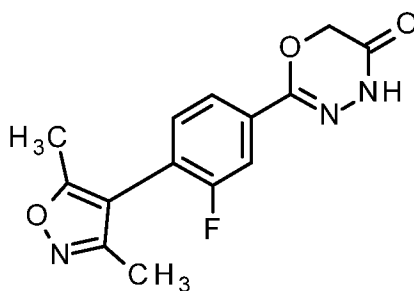


Synthesized in analogy to Example 1 from Intermediate 26 and [2-(trifluoromethoxy)phenyl]boronic acid

LC-MS (Method 1): $R_t = 1.27$ min; MS (ESIpos): $m/z = 355$ $[M+H]^+$

5 Example 30

2-[4-(3,5-dimethyl-1,2-oxazol-4-yl)-3-fluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one



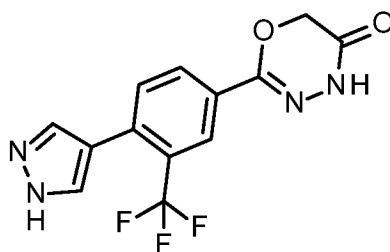
Synthesized in analogy to Example 1 from Intermediate 26 and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-oxazole

10 LC-MS (Method 1): $R_t = 0.92$ min; MS (ESIpos): $m/z = 290$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.159 (14.45), 2.160 (14.71), 2.327 (0.49), 2.332 (0.48), 2.345 (14.05), 2.347 (14.19), 2.518 (1.40), 2.523 (0.99), 2.669 (0.41), 4.812 (16.00), 7.523 (1.77), 7.542 (3.47), 7.562 (2.17), 7.615 (2.02), 7.619 (2.25), 7.642 (1.88), 7.647 (2.23), 7.680 (3.47), 7.684 (2.73), 7.700 (2.34), 7.704 (2.23), 11.178 (3.68).

15 Example 31

2-[4-(1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 1 from Intermediate 26 and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

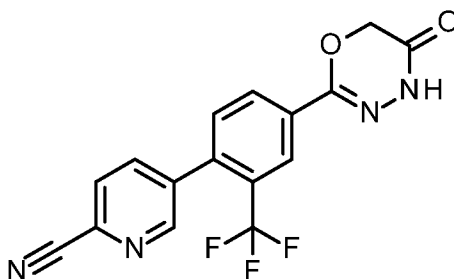
LC-MS (Method 1): $R_t = 0.79$ min; MS (ESIpos): $m/z = 311$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.074 (1.79), 2.518 (2.24), 2.523 (1.49), 2.539 (0.59), 4.834 (16.00), 7.655 (2.64), 7.676 (3.11), 7.695 (0.65), 7.993 (2.41), 7.997 (2.57), 8.013 (1.94), 8.017 (2.03), 8.083 (3.80), 8.087 (3.49), 11.171 (4.58).

Example 32

5-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]pyridine-2-carbonitrile

10



Synthesized in analogy to Example 1 from Intermediate 26 and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile

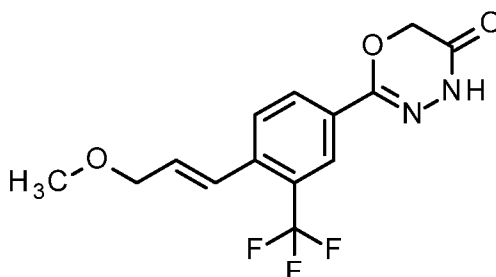
LC-MS (Method 1): $R_t = 1.00$ min; MS (ESIpos): $m/z = 347$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (1.47), 2.523 (1.10), 2.539 (3.06), 4.867 (16.00), 7.636 (2.49), 7.656 (2.71), 8.102 (1.31), 8.106 (1.31), 8.122 (2.57), 8.128 (3.60), 8.145 (1.36), 8.148 (1.82), 8.166 (3.75), 8.171 (3.04), 8.189 (4.43), 8.191 (4.60), 8.209 (2.62), 8.212 (2.94), 8.772 (2.68), 8.777 (2.66), 11.252 (5.30).

Example 33

2-{4-[(1E)-3-methoxyprop-1-en-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one

20



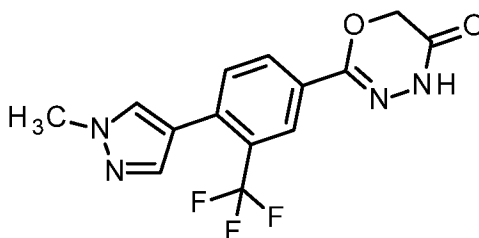
Synthesized in analogy to Example 1 from Intermediate 26 and 2-[(1E)-3-methoxyprop-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

LC-MS (Method 1): $R_t = 1.12$ min; MS (ESIpos): $m/z = 315$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.074 (0.54), 2.518 (0.54), 3.319 (16.00), 3.331 (6.15), 4.106 (1.52), 4.111 (1.62), 4.118 (1.62), 4.123 (1.55), 4.817 (7.00), 6.551 (0.53), 6.590 (0.70), 6.839 (0.44), 6.845 (0.45), 7.929 (0.51), 7.951 (1.37), 7.977 (1.19), 7.989 (1.42), 7.993 (2.05), 11.171 (2.09).

Example 34

2-[4-(1-methyl-1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



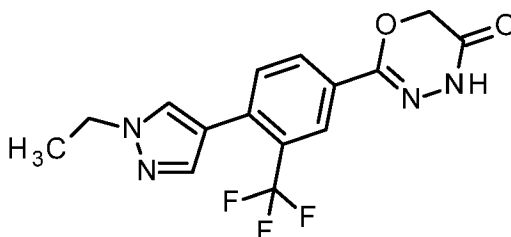
Synthesized in analogy to Example 1 from Intermediate 26 and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

LC-MS (Method 1): $R_t = 0.92$ min; MS (ESIpos): $m/z = 325$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.074 (0.63), 2.518 (0.71), 2.523 (0.44), 2.539 (0.41), 3.903 (16.00), 4.831 (10.45), 7.640 (3.31), 7.655 (1.85), 7.980 (3.12), 7.992 (1.20), 7.996 (1.23), 8.013 (1.00), 8.017 (1.10), 8.077 (2.39), 8.081 (2.17), 11.173 (3.34).

Example 35

2-[4-(1-ethyl-1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



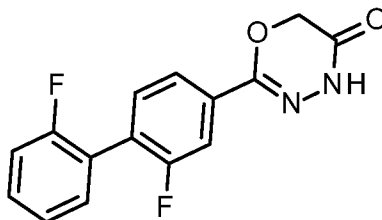
Synthesized in analogy to Example 1 from Intermediate 26 and (1-ethyl-1H-pyrazol-4-yl)boronic acid

LC-MS (Method 1): $R_t = 1.01$ min; MS (ESIpos): $m/z = 339$ $[M+H]^+$

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.386 (6.72), 1.404 (16.00), 1.422 (7.30), 2.074 (2.96), 2.518 (1.28), 2.523 (0.81), 4.169 (1.84), 4.187 (5.77), 4.205 (5.91), 4.223 (1.80), 4.825 (15.37), 7.650 (6.62), 7.670 (2.59), 7.989 (1.60), 7.994 (1.73), 8.010 (1.42), 8.015 (1.66), 8.024 (4.58), 8.077 (3.37), 8.081 (3.11).

5 **Example 36**

2-(2,2'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one



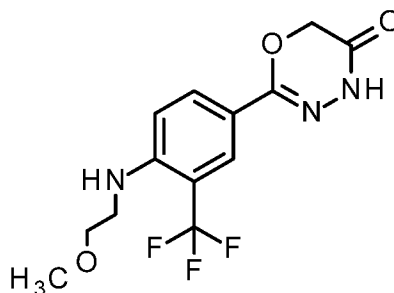
Synthesized in analogy to Example 1 from Intermediate 26 and (2-fluorophenyl)boronic acid

10 LC-MS (Method 1): R_t = 1.16 min; MS (ESIpos): m/z = 288 [M+H]⁺

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.237 (0.46), 2.331 (0.77), 2.518 (4.79), 2.522 (3.01), 2.673 (0.77), 3.565 (6.64), 3.623 (1.00), 4.821 (16.00), 7.179 (0.61), 7.326 (1.25), 7.329 (1.55), 7.336 (1.39), 7.339 (1.44), 7.347 (3.08), 7.357 (1.74), 7.360 (2.14), 7.364 (3.38), 7.383 (1.49), 7.483 (1.26), 7.497 (2.49), 7.502 (2.65), 7.511 (1.53), 7.516 (2.19),
 15 7.521 (2.05), 7.531 (1.33), 7.536 (1.39), 7.540 (0.78), 7.550 (1.85), 7.571 (3.01), 7.590 (1.92), 7.600 (2.26), 7.604 (2.38), 7.614 (0.43), 7.628 (2.12), 7.632 (2.44), 7.699 (3.11), 7.704 (2.90), 7.719 (2.31), 7.724 (2.19), 11.180 (4.08).

Example 37

2-{4-[(2-methoxyethyl)amino]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



20

To a stirred solution of 2-[4-fluoro-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (Intermediate 35, 100 mg, 381 μmol) in DMSO (0.62 mL) was added N,N-diisopropylethylamine (200 μl, 1.1 mmol), followed by 2-methoxyethan-1-amine (99 μl,

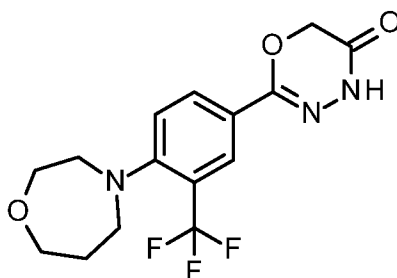
1.1 mmol). The resulting mixture was stirred at 120°C overnight. The reaction mixture was diluted with DMSO, filtered, and purified by mass triggered preparatory HPLC to yield the title compound (55mg, 99% purity, 45% yield).

LC-MS (Method 1): R_t = 1.03 min; MS (ESIpos): m/z = 318 $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.074 (0.75), 2.518 (0.73), 2.522 (0.45), 3.333 (13.61), 3.385 (0.85), 3.400 (2.86), 3.414 (3.48), 3.427 (1.52), 3.494 (3.63), 3.507 (5.95), 3.523 (1.84), 4.720 (16.00), 5.784 (0.79), 5.798 (1.55), 5.811 (0.78), 6.936 (2.38), 6.958 (2.51), 7.747 (2.68), 7.751 (4.38), 7.758 (2.36), 7.780 (1.68), 7.785 (1.30), 10.926 (5.09).

Example 38

- 10 2-[4-(1,4-oxazepan-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



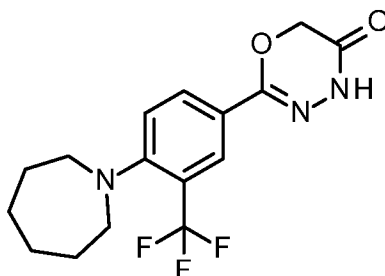
Synthesized in analogy to Example 37 from Intermediate 35 and 1,4-oxazepane

LC-MS (Method 1): R_t = 1.10 min; MS (ESIpos): m/z = 344 $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.871 (0.60), 1.886 (1.82), 1.900 (2.58), 1.915 (1.96), 1.930 (0.67), 2.074 (2.03), 2.518 (1.03), 2.523 (0.66), 2.606 (0.46), 3.157 (4.57), 3.171 (5.12), 3.180 (3.16), 3.186 (2.51), 3.677 (2.85), 3.684 (1.99), 3.689 (2.62), 3.693 (2.00), 3.700 (2.63), 3.772 (3.83), 3.787 (5.73), 3.802 (3.68), 4.787 (16.00), 4.803 (0.45), 4.820 (0.56), 7.547 (1.72), 7.569 (1.78), 7.946 (7.43), 7.965 (1.78), 7.970 (1.13), 11.094 (4.48).

20 Example 39

- 2-[4-(azepan-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



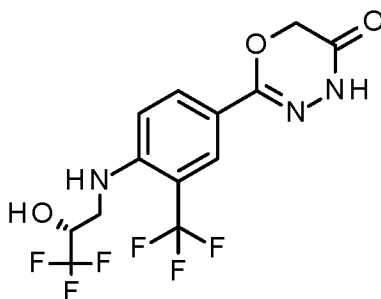
Synthesized in analogy to Example 37 from Intermediate 35 and azepane

LC-MS (Method 1): $R_t = 1.45$ min; MS (ESIpos): $m/z = 342$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.615 (2.84), 1.624 (4.00), 1.632 (3.80), 1.638 (3.17), 1.692 (2.90), 2.518 (0.74), 2.523 (0.48), 3.121 (4.65), 3.136 (5.86), 3.148 (3.93),
 5 4.777 (16.00), 7.465 (2.06), 7.473 (0.41), 7.480 (0.48), 7.488 (2.22), 7.911 (0.85), 7.919 (4.90), 7.924 (3.36), 7.934 (2.02), 7.939 (1.01), 11.072 (4.34).

Example 40

2-[4-[(2R)-3,3,3-trifluoro-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



10

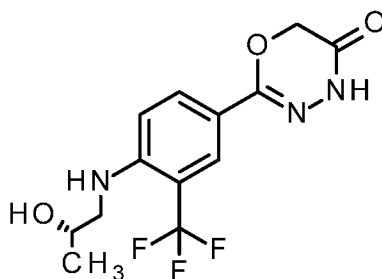
Synthesized in analogy to Example 37 from Intermediate 35 and (2R)-3-amino-1,1,1-trifluoropropan-2-ol hydrogen chloride

LC-MS (Method 1): $R_t = 0.99$ min; MS (ESIpos): $m/z = 372$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (2.19), 2.522 (1.36), 3.365 (0.46), 3.379 (0.53), 3.384 (0.53), 3.398 (1.05), 3.418 (0.78), 3.433 (0.62), 3.537 (0.64), 3.551 (0.94),
 15 3.563 (0.74), 3.572 (0.52), 3.584 (0.64), 3.597 (0.44), 4.241 (0.64), 4.251 (0.70), 4.258 (0.68), 4.269 (0.65), 4.729 (16.00), 5.878 (0.78), 5.891 (1.53), 5.905 (0.76), 6.621 (3.37), 6.637 (3.31), 6.980 (2.32), 7.002 (2.46), 7.767 (2.67), 7.772 (4.50), 7.779 (2.34), 7.801 (1.69), 7.806 (1.31), 10.941 (5.53).

20 Example 41

2-[4-[(2S)-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



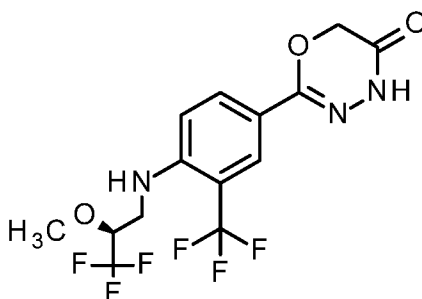
Synthesized in analogy to Example 37 from Intermediate 35 and (2S)-1-aminopropan-2-ol

LC-MS (Method 1): $R_t = 0.86$ min; MS (ESIpos): $m/z = 318$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.101 (10.29), 1.117 (10.65), 2.518 (1.61), 2.522 (0.98), 3.027 (0.50), 3.038 (0.57), 3.044 (0.60), 3.057 (0.99), 3.070 (0.78), 3.076 (0.83), 3.088 (0.72), 3.191 (0.69), 3.205 (1.06), 3.219 (0.88), 3.236 (0.75), 3.251 (0.50), 3.835 (0.79), 3.850 (1.02), 3.867 (0.74), 4.721 (16.00), 4.952 (4.32), 4.965 (4.05), 5.679 (0.80), 5.692 (1.34), 5.704 (0.77), 6.913 (2.18), 6.934 (2.29), 7.754 (6.13), 7.778 (1.69), 10.925 (5.08).
- 10

Example 42

2-[4-((2S)-3,3,3-trifluoro-2-methoxypropyl)amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



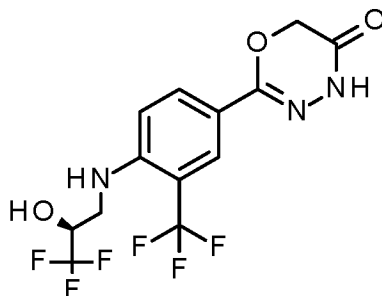
- 15 Synthesized in analogy to Example 37 from Intermediate 35 and (2S)-3,3,3-trifluoro-2-methoxypropan-1-amine

LC-MS (Method 1): $R_t = 1.16$ min; MS (ESIpos): $m/z = 386$ $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (1.44), 2.522 (0.90), 3.449 (16.00), 3.501 (0.47), 3.519 (0.86), 3.538 (0.97), 3.555 (0.62), 3.576 (0.65), 3.588 (1.04), 3.600 (0.75), 3.625 (0.52), 4.137 (0.51), 4.148 (0.65), 4.155 (0.76), 4.165 (0.81), 4.173 (0.55), 4.184 (0.48), 4.729 (13.44), 5.979 (0.65), 5.993 (1.25), 6.008 (0.64), 6.999 (1.95), 7.022 (2.04), 7.773 (2.33), 7.778 (3.53), 7.787 (1.79), 7.809 (1.37), 7.814 (1.09), 10.944 (4.41).
- 20

Example 43

2-[4-[[[(2S)-3,3,3-trifluoro-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



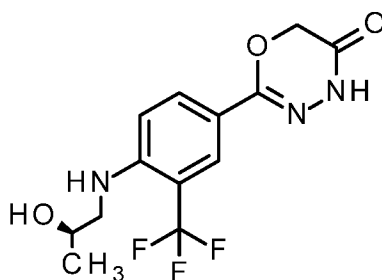
- 5 Synthesized in analogy to Example 37 from Intermediate 35 and (2S)-3-amino-1,1,1-trifluoropropan-2-ol hydrogen chloride

LC-MS (Method 1): R_t = 0.99 min; MS (ESIpos): m/z = 372 $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (1.52), 2.523 (0.97), 3.365 (0.50), 3.379 (0.55), 3.384 (0.55), 3.399 (1.08), 3.419 (0.80), 3.433 (0.63), 3.538 (0.66), 3.550 (0.96),
 10 3.563 (0.75), 3.572 (0.53), 3.584 (0.65), 3.598 (0.46), 4.241 (0.66), 4.251 (0.74), 4.258 (0.72), 4.269 (0.67), 4.729 (16.00), 5.877 (0.80), 5.891 (1.57), 5.905 (0.77), 6.619 (3.62), 6.636 (3.61), 6.980 (2.39), 7.002 (2.52), 7.768 (2.79), 7.772 (4.58), 7.779 (2.40), 7.801 (1.73), 7.806 (1.34), 10.941 (5.56).

Example 44

- 15 2-[4-[[[(2R)-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 37 from Intermediate 35 and (2R)-1-aminopropan-2-ol

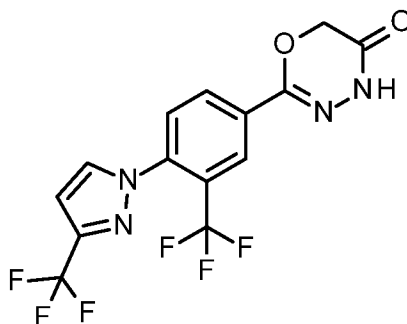
- 20 LC-MS (Method 1): R_t = 0.86 min; MS (ESIpos): m/z = 318 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.101 (10.38), 1.117 (10.74), 2.518 (1.74), 2.523 (1.07), 3.027 (0.51), 3.038 (0.57), 3.044 (0.60), 3.058 (0.99), 3.070 (0.78), 3.076 (0.83),

3.088 (0.73), 3.192 (0.70), 3.205 (1.06), 3.219 (0.88), 3.236 (0.74), 3.251 (0.51), 3.822 (0.40), 3.835 (0.80), 3.851 (1.03), 3.867 (0.75), 4.721 (16.00), 4.952 (4.36), 4.964 (4.42), 5.679 (0.80), 5.692 (1.33), 5.705 (0.77), 6.913 (2.19), 6.935 (2.30), 7.754 (6.13), 7.778 (1.69), 7.782 (1.25), 10.925 (5.28).

5 **Example 45**

2-{3-(trifluoromethyl)-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



A mixture of 2-[4-fluoro-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (Intermediate 35, 100 mg, 0.36 mmol), 3-(trifluoromethyl)-1H-pyrazole (104 mg, 0.76 mmol) and cesium carbonate (249 mg, 0.76 mmol) in N,N-Dimethylacetamide (0.5 mL) was heated at 70°C for 1h. The reaction mixture was diluted with DMSO, filtered, and was purified by preparative-HPLC to afford 107 mg (73% yield, 99% purity) of the title compound as a white solid.

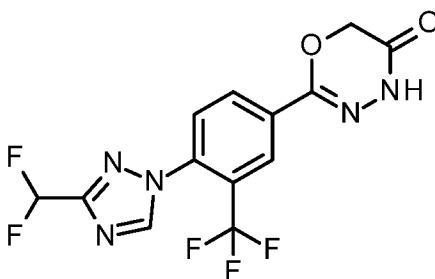
15

LC-MS (Method 1): R_t = 1.19 min; MS (ESIpos): m/z = 379 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.084 (2.32), 2.522 (1.08), 4.878 (16.00), 7.063 (3.69), 7.069 (3.71), 7.841 (2.68), 7.854 (0.59), 7.863 (3.00), 8.196 (4.97), 8.201 (3.88), 8.210 (2.56), 8.400 (2.88), 8.404 (2.82), 11.289 (5.56).

20 **Example 46**

2-{4-[3-(difluoromethyl)-1H-1,2,4-triazol-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



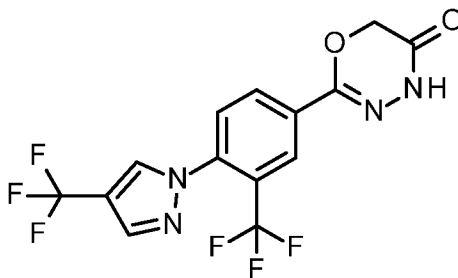
Synthesized in analogy to Example 45 from Intermediate 35 and 3-(difluoromethyl)-1H-1,2,4-triazole

LC-MS (Method 1): $R_t = 0.95$ min; MS (ESIpos): $m/z = 362$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.137 (0.62), 2.084 (16.00), 2.331 (0.68), 2.518 (3.57), 2.523 (2.27), 2.539 (3.03), 2.673 (0.68), 4.882 (5.62), 7.105 (0.76), 7.237 (1.61), 7.369 (0.66), 7.925 (0.77), 7.945 (0.88), 8.224 (3.12), 8.243 (0.79), 9.168 (2.00), 11.309 (2.00).

Example 47

- 10 2-{3-(trifluoromethyl)-4-[4-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



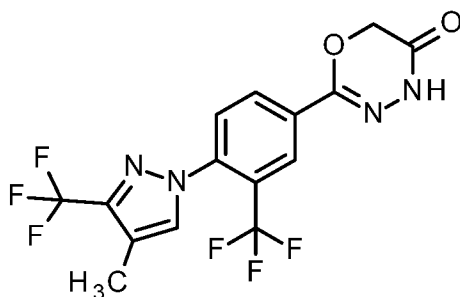
Synthesized in analogy to Example 45 from Intermediate 35 and 4-(trifluoromethyl)-1H-pyrazole

- 15 LC-MS (Method 1): $R_t = 1.18$ min; MS (ESIpos): $m/z = 379$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.083 (2.33), 2.326 (0.49), 2.522 (1.65), 2.669 (0.51), 4.875 (16.00), 7.833 (2.70), 7.845 (0.67), 7.856 (3.02), 8.184 (2.90), 8.192 (4.12), 8.197 (4.54), 8.201 (3.12), 8.272 (6.05), 8.890 (4.37), 11.287 (5.72).

Example 48

- 20 2-{4-[4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



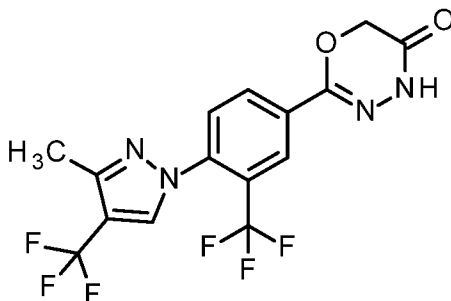
Synthesized in analogy to Example 45 from Intermediate 35 and 4-methyl-3-(trifluoromethyl)-1H-pyrazole

LC-MS (Method 1): $R_t = 1.26$ min; MS (ESIpos): $m/z = 393$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.083 (3.27), 2.195 (12.51), 2.326 (0.53), 2.522 (1.83), 2.539 (2.28), 2.665 (0.40), 2.668 (0.53), 4.871 (16.00), 7.799 (2.85), 7.811 (0.76), 7.821 (3.15), 8.173 (3.20), 8.181 (4.84), 8.186 (6.97), 8.190 (7.49), 11.280 (5.91).

Example 49

- 10 2-{4-[3-methyl-4-(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



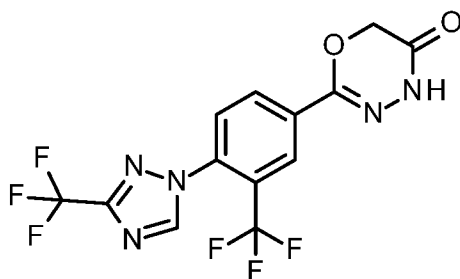
Synthesized in analogy to Example 45 from Intermediate 35 and 3-methyl-4-(trifluoromethyl)-1H-pyrazole

LC-MS (Method 1): $R_t = 1.24$ min; MS (ESIpos): $m/z = 393$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.137 (1.12), 2.084 (4.46), 2.115 (0.49), 2.322 (0.63), 2.327 (0.92), 2.343 (13.97), 2.518 (3.14), 2.522 (1.95), 2.664 (0.50), 2.669 (0.67), 2.673 (0.50), 4.869 (16.00), 7.795 (2.62), 7.803 (0.56), 7.809 (0.57), 7.818 (2.92), 8.158 (1.55), 8.162 (2.70), 8.172 (3.86), 8.177 (5.17), 8.720 (4.17), 11.276 (5.71).

Example 50

- 20 2-{3-(trifluoromethyl)-4-[3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



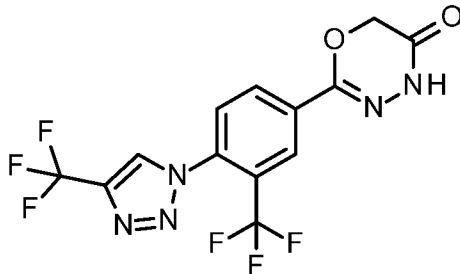
Synthesized in analogy to Example 45 from Intermediate 35 and 3-(trifluoromethyl)-1H-1,2,4-triazole

LC-MS (Method 1): $R_t = 1.11$ min; MS (ESI^{neg}): $m/z = 378$ $[M-H]^-$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.083 (9.99), 2.518 (1.80), 2.522 (1.12), 4.885 (16.00), 7.997 (2.64), 8.018 (3.13), 8.238 (4.36), 8.244 (2.86), 8.265 (1.85), 8.270 (1.42), 9.334 (4.56), 11.320 (5.33).

Example 51

- 2-{3-(trifluoromethyl)-4-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one
- 10

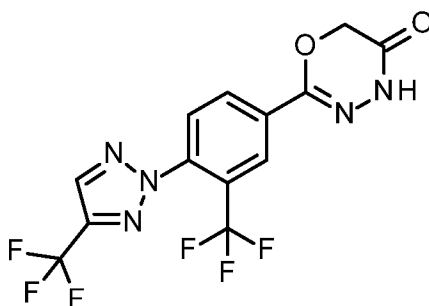


Synthesized in analogy to Example 45 from Intermediate 35 and 4-(trifluoromethyl)-2H-1,2,3-triazole. More polar isomer of two isomers (see also Example 52) isolated by preparative HPLC was assigned as the title compound.

- 15 LC-MS (Method 1): $R_t = 1.12$ min; MS (ESI^{pos}): $m/z = 380$ $[M+H]^+$

Example 52

2-{3-(trifluoromethyl)-4-[4-(trifluoromethyl)-2H-1,2,3-triazol-2-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



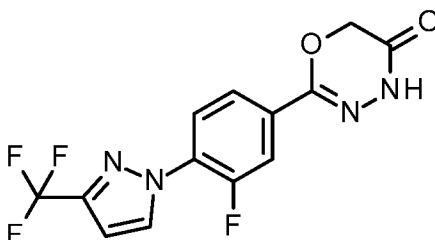
Synthesized in analogy to Example 45 from Intermediate 35 and 4-(trifluoromethyl)-2H-1,2,3-triazole. More polar isomer of two isomers (see also Example 51) isolated by preparative HPLC was assigned as the title compound.

- 5 LC-MS (Method 1): $R_t = 1.22$ min; MS (ESI^{neg}): $m/z = 378$ [M-H]⁻

NMR:

Example 53

2-{3-fluoro-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



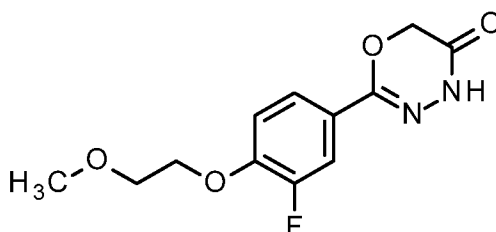
- 10 Synthesized in analogy to Example 45 from Intermediate 34 and 3-(trifluoromethyl)-1H-pyrazole

¹H NMR (250 MHz, DMSO-*d*₆) δ 4.83 (s, 2H), 7.09 (d, $J = 2.4$ Hz, 1H), 7.76 (s, 1H), 7.77 - 7.82 (m, 1H), 7.93 (t, $J = 8.2$ Hz, 1H), 8.50 (s, 1H), 11.20 (s, 1H).

LC-MS (Method 4): $R_t = 3.32$ min; MS (ESI^{pos}): $m/z = 329$ [M+H]⁺

- 15 **Example 54**

2-[3-fluoro-4-(2-methoxyethoxy)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



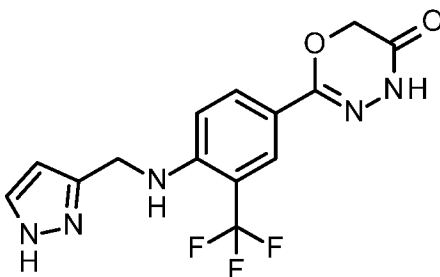
2-(3,4-difluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one (100mg, 0.47mmol, Intermediate 34) was added to a mixture of 2-methoxyethanol (63μl, 0.80mmol) and sodium hydride (60% wt, 94mg, 2.36mmol) in N,N-Dimethylformamide (5ml) and the mixture stirred at room temperature for 18h. The reaction was quenched with sat. NaHCO₃(aq), diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried over sodium sulfate and evaporated under vacuum. The residue was purified by Biotage Isolera™ chromatography (silica gel, eluting with heptanes-EtOAc, 1:0 to 0:1) to afford a crude material which was triturated with ethyl acetate/heptane. The solids were collected by filtration and dried under vacuum at 40°C to afford 22.5mg (17% yield, 97% purity) of the title compound as a white solid.

¹H NMR (250 MHz, Chloroform-d) δ 3.46 (s, 3H), 3.74 - 3.83 (m, 2H), 4.18 - 4.27 (m, 2H), 4.74 (s, 2H), 6.99 (t, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.54 - 7.60 (m, 1H), 8.13 (s, 1H).

LC-MS (Method 4): R_t = 2.21 min; MS (ESIpos): m/z = 269 [M+H]⁺

Example 55

2-[4-[(1H-pyrazol-3-yl)methyl]amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



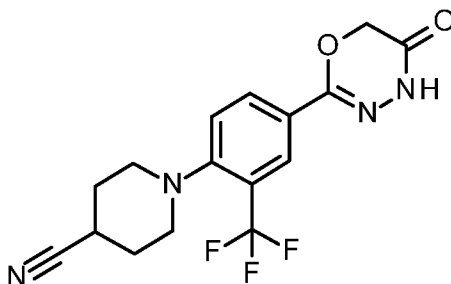
To a stirred solution of 2-[4-fluoro-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (100 mg, 381 μmol, Intermediate 35) in DMSO (0.63 mL) was added N,N-diisopropylethylamine (200 μl, 1.1 mmol), followed by 1-(1H-pyrazol-3-yl)methanamine (111 mg, 1.14 mmol) and the resulting mixture was stirred at 120°C overnight. Purification by preparative HPLC yielded the title compound as a white solid (30.4 mg, 98 % purity, 23 % yield).

LC-MS (Method 1): R_t = 0.88 min; MS (ESI_{neg}): m/z = 338 [M-H]⁻

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.518 (1.70), 2.522 (1.04), 4.436 (1.70), 4.705 (16.00), 6.109 (1.51), 6.504 (0.97), 6.891 (0.98), 6.913 (0.96), 7.643 (1.00), 7.699 (1.60), 7.704 (1.85), 7.721 (1.40), 7.726 (1.83), 7.750 (3.82), 7.755 (3.04), 10.912 (5.14), 12.651 (1.12).

Example 56

1-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]piperidine-4-carbonitrile

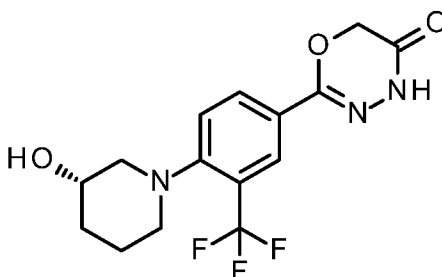


- 5 Synthesized in analogy to Example 55 from Intermediate 35 and piperidine-4-carbonitrile
LC-MS (Method 1): $R_t = 1.07$ min; MS (ESIpos): $m/z = 353$ $[M+H]^+$

1H -NMR (400 MHz, DMSO- d_6) δ [ppm]: 1.781 (0.46), 1.789 (0.58), 1.801 (0.98), 1.810 (1.35), 1.821 (1.25), 1.833 (1.64), 1.842 (1.37), 1.854 (0.85), 1.862 (0.70), 1.973 (1.19), 1.981 (1.46), 1.989 (1.34), 1.996 (1.25), 2.004 (0.98), 2.013 (1.05), 2.021 (0.89), 2.030 (0.51), 2.518 (1.17), 2.522 (0.69), 2.606 (0.95), 2.849 (0.83), 2.857 (0.99), 2.870 (1.02), 2.878 (2.05), 2.886 (1.47), 2.899 (1.52), 2.907 (1.22), 2.969 (1.26), 2.976 (1.61), 2.984 (1.54), 2.994 (1.65), 3.006 (0.96), 3.015 (1.04), 3.023 (0.82), 3.041 (0.59), 3.051 (0.83), 3.061 (1.02), 3.071 (0.80), 3.081 (0.53), 4.793 (16.00), 4.804 (0.97), 7.559 (2.44), 7.580 (2.60), 7.958 (3.22), 7.963 (4.44), 7.978 (2.19), 7.982 (1.37), 7.999 (1.74), 8.004 (1.39), 11.113 (5.44).

Example 57

2-{4-[(3S)-3-hydroxypiperidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one

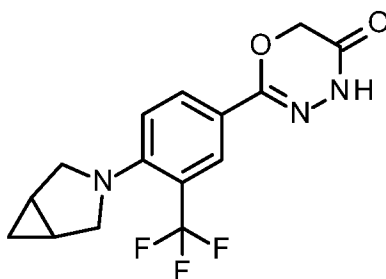


- 20 Synthesized in analogy to Example 55 from Intermediate 35 and (3S)-piperidin-3-ol
LC-MS (Method 1): $R_t = 0.99$ min; MS (ESI $_{neg}$): $m/z = 342$ $[M-H]^-$

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.190 (0.71), 1.201 (0.69), 1.217 (0.70), 1.227 (0.77), 1.535 (0.69), 1.565 (0.76), 1.709 (0.99), 1.734 (0.56), 1.743 (0.71), 1.910 (0.77), 1.919 (0.77), 1.941 (0.73), 2.074 (0.93), 2.461 (1.30), 2.522 (1.09), 2.619 (0.67), 2.642 (1.29), 2.647 (1.29), 2.669 (1.06), 2.914 (1.04), 2.943 (0.85), 3.079 (0.89), 3.089 (0.99),
 5 3.106 (0.89), 3.116 (0.85), 3.556 (0.47), 3.568 (0.73), 3.580 (0.93), 3.592 (0.91), 3.604 (0.67), 3.616 (0.43), 4.788 (16.00), 4.821 (3.62), 4.833 (3.50), 7.505 (2.48), 7.526 (2.70), 7.942 (2.90), 7.946 (5.04), 7.951 (3.05), 7.973 (1.90), 7.978 (1.42), 11.096 (5.19).

Example 58

2-[4-(3-azabicyclo[3.1.0]hexan-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-
 10 5(6H)-one



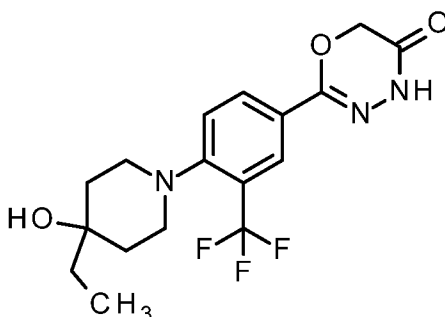
Synthesized in analogy to Example 55 from Intermediate 35 and 3-azabicyclo[3.1.0]hexane hydrogen chloride salt

LC-MS (Method 1): *R*_t = 1.28 min; MS (ESI^{neg}): *m/z* = 324 [M-H]⁻

15 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.353 (0.70), 0.362 (1.91), 0.372 (1.98), 0.383 (0.76), 0.552 (0.66), 0.563 (0.84), 0.571 (1.51), 0.582 (1.48), 0.590 (0.90), 0.601 (0.70), 1.614 (2.24), 1.623 (2.34), 1.627 (1.88), 1.629 (1.89), 1.633 (2.19), 2.074 (1.76), 2.518 (0.86), 2.522 (0.53), 3.304 (2.38), 3.468 (7.18), 3.491 (5.50), 4.752 (16.00), 7.170 (2.63), 7.193 (2.79), 7.794 (1.79), 7.800 (1.96), 7.816 (1.62), 7.822 (1.83), 7.885 (4.26), 7.890
 20 (3.78), 11.004 (4.62).

Example 59

2-[4-(4-ethyl-4-hydroxypiperidin-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-
 5(6H)-one



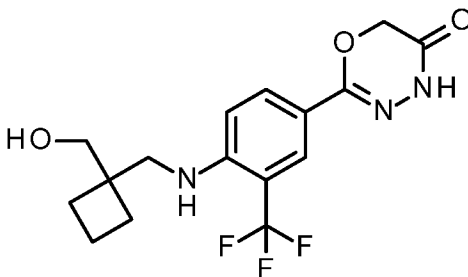
Synthesized in analogy to Example 55 from Intermediate 35 and 4-ethylpiperidin-4-ol

LC-MS (Method 1): $R_t = 1.14$ min; MS (ESIpos): $m/z = 372$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.842 (3.97), 0.861 (9.90), 0.880 (4.50), 1.405 (1.24), 1.423 (3.77), 1.442 (3.51), 1.460 (0.99), 1.538 (3.85), 1.548 (4.98), 1.555 (4.72), 1.565 (3.73), 2.074 (6.07), 2.518 (1.77), 2.523 (1.08), 2.808 (1.84), 2.827 (1.40), 2.836 (2.25), 3.030 (0.99), 3.047 (1.90), 3.064 (1.40), 3.076 (1.61), 3.093 (0.77), 4.102 (6.05), 4.785 (16.00), 4.820 (0.95), 7.528 (2.48), 7.550 (2.71), 7.936 (3.04), 7.942 (5.16), 7.947 (2.95), 7.969 (1.92), 7.974 (1.42), 11.087 (5.68).

10 **Example 60**

2-[4-({[1-(hydroxymethyl)cyclobutyl]methyl}amino)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



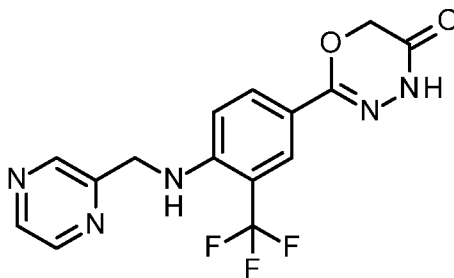
Synthesized in analogy to Example 55 from Intermediate 35 and [1-(aminomethyl)cyclobutyl]methanol

LC-MS (Method 1): $R_t = 1.08$ min; MS (ESI $_{\text{neg}}$): $m/z = 356$ $[M-H]^-$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.750 (1.58), 1.767 (4.93), 1.785 (3.64), 1.842 (0.66), 1.859 (1.21), 1.871 (1.08), 1.880 (1.04), 1.890 (0.79), 1.900 (0.57), 2.074 (0.70), 2.518 (0.91), 2.522 (0.56), 3.298 (3.18), 3.309 (3.16), 3.332 (16.00), 3.533 (3.69), 3.544 (3.72), 4.717 (11.44), 5.197 (1.16), 5.209 (2.82), 5.220 (1.15), 6.273 (1.25), 6.912 (1.77), 6.934 (1.86), 7.733 (2.28), 7.738 (3.09), 7.754 (1.48), 7.776 (1.25), 7.781 (1.03), 10.914 (3.84).

Example 61

2-[4-[[pyrazin-2-yl)methyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



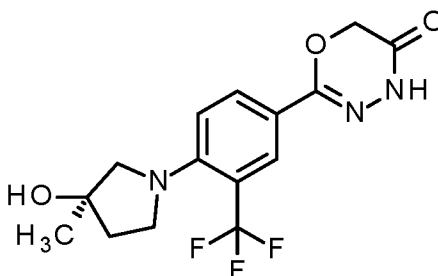
- 5 Synthesized in analogy to Example 55 from Intermediate 35 and 1-(pyrazin-2-yl)methanamine

LC-MS (Method 1): $R_t = 0.90$ min; MS (ESIpos): $m/z = 352$ $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (1.54), 2.522 (0.98), 4.664 (3.57), 4.679 (3.65), 4.707 (16.00), 6.801 (2.47), 6.823 (2.67), 6.834 (0.89), 6.848 (1.67), 6.862 (0.80),
 10 7.701 (1.49), 7.706 (1.64), 7.723 (1.38), 7.728 (1.59), 7.790 (3.65), 7.795 (3.30), 8.544 (3.69), 8.551 (4.37), 8.587 (3.94), 8.591 (4.79), 8.618 (3.63), 8.622 (3.30), 8.625 (3.51), 8.628 (2.75), 10.925 (5.38).

Example 62

- 2-[4-[(3R)-3-hydroxy-3-methylpyrrolidin-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 55 from Intermediate 35 and (3R)-3-methylpyrrolidin-3-ol

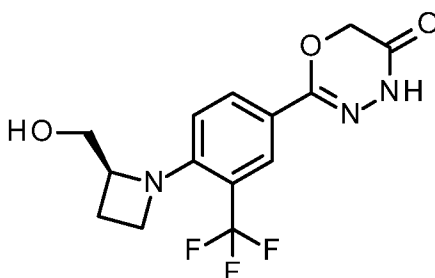
LC-MS (Method 1): $R_t = 0.97$ min; MS (ESIpos): $m/z = 344$ $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.335 (16.00), 1.845 (0.74), 1.869 (1.47), 1.878 (0.96), 1.888 (1.50), 1.896 (0.91), 3.209 (1.10), 3.234 (1.40), 3.349 (0.57), 3.366 (0.90), 3.388 (1.89), 3.413 (1.12), 3.646 (0.85), 3.665 (0.82), 4.735 (13.36), 4.844 (6.52), 6.984

(2.19), 7.007 (2.32), 7.736 (1.70), 7.742 (1.80), 7.759 (1.54), 7.765 (1.64), 7.881 (4.03), 7.887 (3.71), 10.945 (4.87).

Example 63

2-{4-[(2S)-2-(hydroxymethyl)azetidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



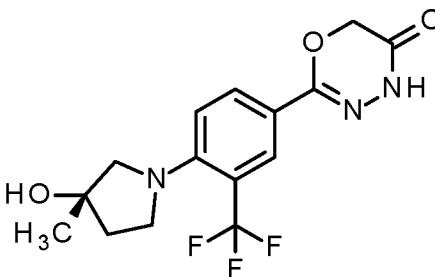
Synthesized in analogy to Example 55 from Intermediate 35 and [(2S)-azetidin-2-yl]methanol

LC-MS (Method 1): $R_t = 0.94$ min; MS (ESIpos): $m/z = 330$ $[M+H]^+$

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.073 (0.96), 2.113 (0.56), 2.119 (0.56), 2.123 (0.58), 2.130 (0.52), 2.139 (0.93), 2.145 (0.61), 2.152 (0.56), 2.156 (0.65), 2.162 (0.72), 2.289 (0.44), 2.299 (0.80), 2.311 (0.83), 2.321 (0.76), 2.333 (0.69), 2.337 (0.70), 3.594 (0.51), 3.610 (1.09), 3.623 (1.98), 3.628 (1.61), 3.635 (1.66), 3.640 (2.00), 3.652 (1.07), 3.669 (0.50), 3.839 (0.84), 3.858 (0.84), 4.139 (0.86), 4.153 (0.85), 4.431 (0.80), 4.446 (1.00), 4.452 (1.02), 4.467 (0.76), 4.729 (16.00), 4.962 (1.00), 4.976 (1.97), 4.989 (0.97), 6.956 (2.81), 6.978 (2.97), 7.719 (2.07), 7.724 (2.29), 7.742 (1.87), 7.747 (2.15), 7.806 (4.73), 7.811 (4.22), 10.945 (5.81).

Example 64

2-{4-[(3S)-3-hydroxy-3-methylpyrrolidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



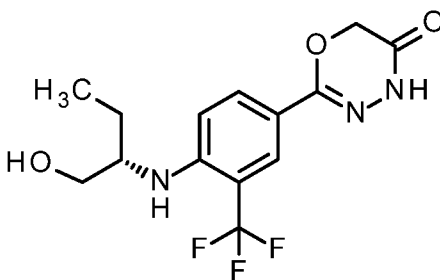
Synthesized in analogy to Example 55 from Intermediate 35 and (3S)-3-methylpyrrolidin-3-ol

LC-MS (Method 1): $R_t = 0.97$ min; MS (ESIpos): $m/z = 344$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.335 (16.00), 1.845 (0.76), 1.869 (1.50), 1.879 (0.98), 1.888 (1.51), 1.896 (0.92), 2.074 (0.41), 3.209 (1.11), 3.234 (1.42), 3.349 (0.62), 3.366 (0.92), 3.388 (1.93), 3.413 (1.13), 3.646 (0.86), 3.665 (0.83), 4.735 (13.22), 4.844 (5.94), 6.984 (2.21), 7.007 (2.34), 7.736 (1.69), 7.742 (1.80), 7.759 (1.54), 7.765 (1.64), 7.881 (3.98), 7.887 (3.67), 10.945 (4.80).

Example 65

2-[4-[(2S)-1-hydroxybutan-2-yl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



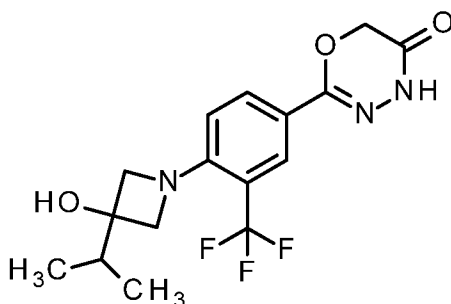
Synthesized in analogy to Example 55 from Intermediate 35 and (2S)-2-aminobutan-1-ol

LC-MS (Method 1): $R_t = 0.98$ min; MS (ESIpos): $m/z = 332$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.863 (4.31), 0.881 (10.52), 0.900 (4.65), 1.506 (0.59), 1.524 (0.91), 1.541 (0.86), 1.558 (0.58), 1.598 (0.58), 1.614 (0.79), 1.633 (0.90), 1.651 (0.53), 2.073 (2.67), 3.465 (0.85), 3.488 (1.92), 3.503 (1.25), 3.521 (1.37), 3.528 (1.38), 3.551 (0.82), 4.719 (16.00), 4.936 (0.49), 5.190 (1.19), 5.208 (1.16), 6.951 (1.85), 6.973 (1.85), 7.750 (7.46), 7.770 (1.75), 7.775 (1.20), 10.923 (5.44).

Example 66

2-{4-[3-hydroxy-3-(propan-2-yl)azetidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



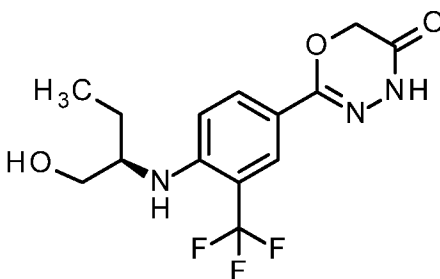
Synthesized in analogy to Example 55 from Intermediate 35 and 3-(propan-2-yl)azetidin-3-ol

LC-MS (Method 1): $R_t = 1.11$ min; MS (ESIpos): $m/z = 358$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.882 (15.37), 0.899 (16.00), 1.854 (1.03), 1.871 (1.35), 1.887 (0.95), 2.073 (1.32), 3.825 (2.19), 3.847 (2.64), 4.015 (2.84), 4.036 (2.25), 4.728 (13.57), 5.506 (5.36), 6.632 (2.30), 6.655 (2.41), 7.745 (1.66), 7.750 (1.83), 7.767 (1.48), 7.772 (1.77), 7.814 (3.72), 7.819 (3.17), 10.940 (4.97).

Example 67

- 10 2-[4-[(2R)-1-hydroxybutan-2-yl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

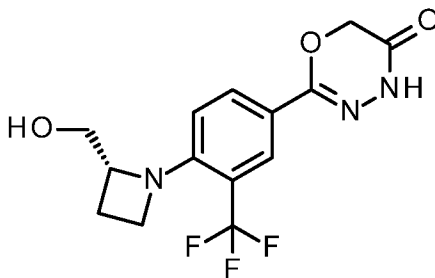


Synthesized in analogy to Example 55 from Intermediate 35 and (2R)-2-aminobutan-1-ol

- 15 LC-MS (Method 1): $R_t = 0.98$ min; MS (ESIpos): $m/z = 332$ $[M+H]^+$
- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.863 (4.26), 0.881 (10.61), 0.899 (4.64), 1.506 (0.57), 1.524 (0.89), 1.541 (0.84), 1.558 (0.56), 1.598 (0.57), 1.614 (0.77), 1.632 (0.89), 1.651 (0.52), 3.459 (0.66), 3.472 (1.11), 3.492 (1.76), 3.503 (1.26), 3.523 (1.48), 3.542 (0.78), 3.556 (0.63), 4.719 (16.00), 4.923 (0.82), 4.935 (1.62), 4.947 (0.86), 5.190 (1.17),
- 20 5.208 (1.13), 6.950 (1.81), 6.973 (1.81), 7.750 (7.32), 7.770 (1.72), 7.775 (1.18), 10.924 (5.19).

Example 68

2-{4-[(2R)-2-(hydroxymethyl)azetidin-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



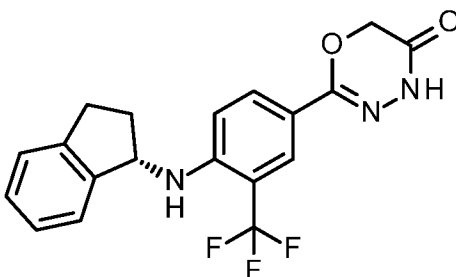
- 5 Synthesized in analogy to Example 55 from Intermediate 35 and [(2R)-azetidin-2-yl]methanol

LC-MS (Method 1): R_t = 0.94 min; MS (ESIpos): m/z = 330 $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.073 (0.77), 2.114 (0.56), 2.119 (0.57), 2.123 (0.59), 2.130 (0.52), 2.139 (0.94), 2.145 (0.62), 2.152 (0.57), 2.156 (0.66), 2.162 (0.72),
 10 2.289 (0.44), 2.299 (0.80), 2.311 (0.83), 2.321 (0.79), 2.326 (0.76), 2.333 (0.69), 2.337 (0.70), 2.518 (0.41), 3.594 (0.59), 3.609 (1.36), 3.623 (2.26), 3.628 (1.71), 3.635 (1.79), 3.640 (2.30), 3.653 (1.36), 3.669 (0.59), 3.839 (0.84), 3.859 (0.85), 4.139 (0.87), 4.153 (0.85), 4.432 (0.81), 4.446 (1.01), 4.453 (1.03), 4.467 (0.76), 4.729 (16.00), 4.962 (1.60), 4.975 (3.52), 4.989 (1.51), 6.956 (2.83), 6.979 (3.01), 7.719 (2.12), 7.724 (2.29), 7.742 (1.89), 7.747 (2.14), 7.806 (4.79), 7.811 (4.21), 10.945 (5.86).

Example 69

2-[4-[(1S)-2,3-dihydro-1H-inden-1-yl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



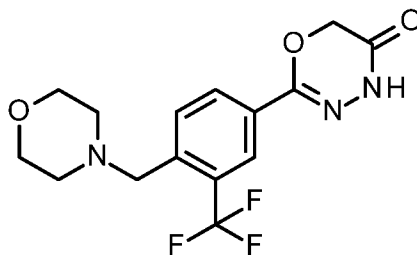
- 20 Synthesized in analogy to Example 55 from Intermediate 35 and (1S)-2,3-dihydro-1H-inden-1-amine

LC-MS (Method 1): R_t = 1.36 min; MS (ESIpos): m/z = 376 $[M+H]^+$

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.982 (0.95), 1.991 (0.49), 2.002 (0.99), 2.013 (1.02), 2.024 (0.49), 2.033 (1.04), 2.518 (1.71), 2.523 (1.23), 2.525 (0.84), 2.536 (0.50), 2.539 (0.68), 2.547 (0.78), 2.555 (0.87), 2.566 (0.92), 2.574 (0.70), 2.578 (0.77), 2.585 (0.76), 2.597 (0.43), 2.821 (0.41), 2.842 (0.69), 2.861 (1.04), 2.882 (1.35), 2.903 (0.65), 2.940 (0.90), 2.947 (0.98), 2.962 (1.00), 2.969 (0.93), 2.979 (0.55), 2.986 (0.52), 3.001 (0.48), 3.008 (0.40), 4.000 (1.02), 4.738 (16.00), 5.224 (0.48), 5.243 (1.38), 5.262 (1.40), 5.282 (0.49), 5.630 (1.67), 5.651 (1.50), 7.163 (1.91), 7.187 (2.38), 7.195 (4.10), 7.198 (4.64), 7.207 (5.50), 7.228 (0.66), 7.236 (1.14), 7.248 (1.02), 7.255 (1.78), 7.267 (1.75), 7.276 (1.11), 7.294 (3.06), 7.313 (1.38), 7.469 (0.42), 7.800 (7.63), 7.820 (1.83), 10.953 (5.33).

Example 70

2-{4-[(morpholin-4-yl)methyl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



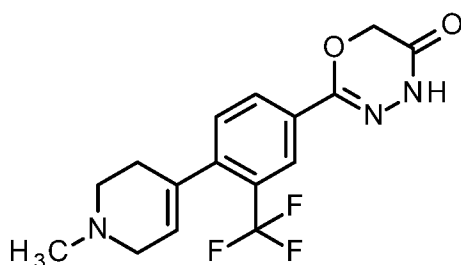
A nitrogen-sparged mixture of 2-[4-bromo-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (50mg, 0.16mmol, Intermediate 28), potassium trifluoro(morpholin-4-ylmethyl)borate (35mg, 0.17mmol), Potassium carbonate (1.2M aqueous, 0.39ml, 0.46mmol) and [1,1'-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (4mg, 0.006mmol) in 1,4-Dioxane (4ml) was heated at 100°C for 1h. The mixture was cooled to room temperature, diluted with sat. NaHCO₃(aq) and extracted with 3:1 chloroform/isopropanol. The organic extracts were dried over sodium sulfate and evaporated under vacuum. The residue was purified by Biotage Isolera™ chromatography (silica gel, eluting with dichloromethane-methanol, 1:0 to 9:1) to afford a crude material which was loaded to an SCX-2 cartridge. The cartridge was rinsed with dichloromethane and methanol, then eluted with 7N ammonia/methanol. The basic eluent was evaporated under vacuum and the residue triturated with EtOAc/heptane. The solids were collected by filtration to afford 19.6mg (37% yield) of the title compound as a pale yellow solid.

¹H NMR (500 MHz, DMSO-d₆) δ 2.36 - 2.43 (m, 4H), 3.54 - 3.62 (m, 4H), 4.81 (s, 2H), 7.89 (d, J = 8.2 Hz, 1H), 7.98 - 8.04 (m, 2H), 11.13 (s, 1H).

LC-MS (Method 4): R_t = 2.95 min; MS (ESIpos): m/z = 344 [M+H]⁺

Example 71

- 5 2-[4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



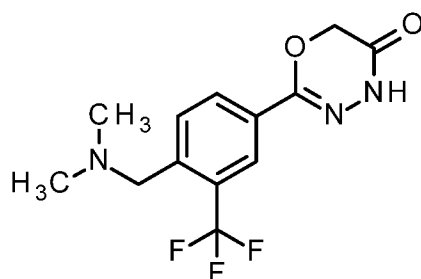
Synthesized in analogy to Example 70 from Intermediate 28 and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine

- 10 LC-MS (Method 4): R_t = 2.94 min; MS (ESIpos): m/z = 340 [M+H]⁺

¹H NMR (250 MHz, DMSO-d₆) δ 2.24 - 2.37 (m, 5H), 2.54 - 2.64 (m, 2H), 2.93 - 3.04 (m, 2H), 4.81 (s, 2H), 5.57 (s, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.90 - 8.04 (m, 2H), 11.14 (s, 1H).

Example 72

2-[4-[(dimethylamino)methyl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



15

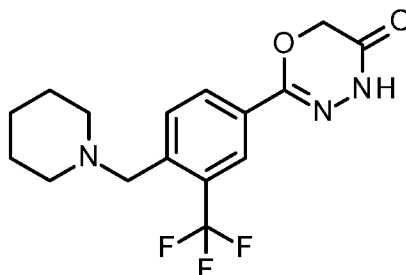
Synthesized in analogy to Example 70 from Intermediate 28 and potassium [(dimethylamino)methyl](trifluorido)borate

LC-MS (Method 1): R_t = 0.54 min; MS (ESIpos): m/z = 302 [M+H]⁺

- 20 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 2.187 (16.00), 2.518 (1.21), 2.523 (4.61), 4.813 (6.46), 7.854 (0.82), 7.875 (1.05), 7.990 (1.55), 8.011 (0.88), 8.032 (0.65), 8.195 (4.92), 11.151 (0.89).

Example 73

2-{4-[(piperidin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one



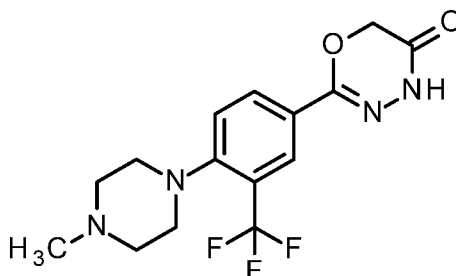
Synthesized in analogy to Example 70 from Intermediate 28 and potassium
5 trifluorido[(piperidin-1-yl)methyl]borate

LC-MS (Method 1): $R_t = 0.64$ min; MS (ESI^{neg}): $m/z = 340$ [M-H]⁻

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.403 (1.59), 1.415 (1.55), 1.488 (1.63), 1.501
(3.67), 1.514 (4.36), 1.527 (2.81), 1.542 (1.02), 2.084 (3.99), 2.323 (2.02), 2.327 (3.02),
2.331 (3.36), 2.336 (3.24), 2.344 (3.49), 2.518 (5.14), 2.522 (3.24), 2.659 (0.47), 2.664
10 (0.92), 2.669 (1.22), 2.673 (0.92), 2.678 (0.45), 2.727 (0.71), 2.888 (0.90), 2.982 (0.41),
2.997 (0.45), 3.592 (5.79), 4.547 (0.65), 4.811 (16.00), 4.875 (1.06), 5.758 (1.12), 7.874
(1.90), 7.894 (2.61), 7.981 (2.98), 7.986 (3.65), 8.008 (2.06), 8.028 (1.59), 8.165 (8.85),
11.144 (4.48).

Example 74

15 2-[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



A mixture of 2-[4-bromo-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (50mg,
0.15mmol, Intermediate 30) and 1-methylpiperazine (0.17mL, 1.55 mmol) in N,N-
Dimethylacetamide (1mL) was heated at 100°C for 48h, with addition of further 1-
20 methylpiperazine (0.24ml, 2.14mmol) after 24h. The reaction mixture was cooled to room
temperature, diluted with sat. NaHCO₃(aq) and extracted with 3:1
chloroform/isopropanol. The organic extracts were dried over sodium sulfate and
evaporated under vacuum. The residue was purified by Biotage Isolera™

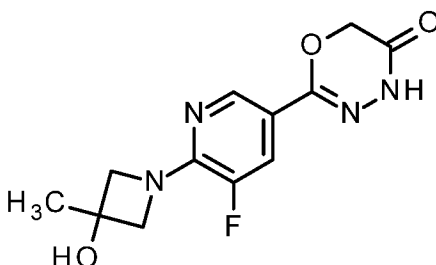
chromatography (silica gel, eluting with dichloromethane-methanol, 1:0 to 4:1) to afford a crude material which was triturated with ethyl acetate/heptane. The solids were collected by filtration, rinsed with heptane and dried under vacuum at 40°C to afford 15mg (25% yield, 91% purity) of the title compound as a pale pink solid

5 LC-MS (Method 4): $R_t = 1.25$ min; MS (ESIpos): $m/z = 343$ $[M+H]^+$

1H NMR (250 MHz, DMSO- d_6) δ 2.29 (s, 3H), 2.52 - 2.60 (m, 4H), 2.89 - 2.99 (m, 4H), 4.79 (s, 2H), 7.56 (d, $J = 8.2$ Hz, 1H), 7.91 - 8.02 (m, 2H), 11.09 (s, 1H).

Example 75

10 2-[5-fluoro-6-(3-hydroxy-3-methylazetidin-1-yl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one



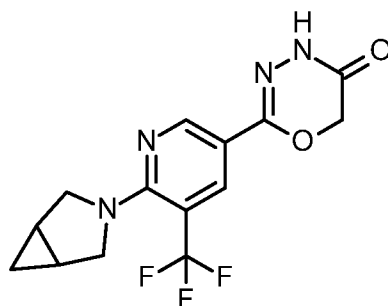
2-(6-bromo-5-fluoropyridin-3-yl)-4H-1,3,4-oxadiazin-5(6H)-one (Intermediate 31, 100 mg, 0.37 mmol) and 3-methylazetidin-3-ol hydrochloride (1:1) (45 mg, 0.37 mmol) were dissolved in DMSO (1.5 mL). Copper powder (23 mg, 0.37 mmol) and cesium acetate (210 mg, 1.1 mmol) were added. The resulting mixture was heated at 90 °C overnight giving a brown solution. Crude LCMS showed completed formation of the desired product. The mixture was diluted with water (20 mL) and the pH was adjusted to pH5 via addition of 1M aq. HCl. The mixture was extracted with EtOAc (2 x 30 mL) and the combined organics were washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated at reduced pressure. The residue was purified via prepHPLC to yield the title compound (34.0 mg, 95 % purity, 32 % yield).

LC-MS (Method 4): $R_t = 1.55$ min; MS (ESIpos): $m/z = 281$ $[M+H]^+$

1H NMR (500 MHz, DMSO- d_6) δ 10.98 (s, 1H), 8.24 (t, $J = 1.6$ Hz, 1H), 7.64 - 7.50 (m, 1H), 5.63 (s, 1H), 4.72 (s, 2H), 4.06 - 3.91 (m, 4H), 1.44 (s, 3H).

25 Example 76

2-[6-(3-azabicyclo[3.1.0]hexan-3-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one



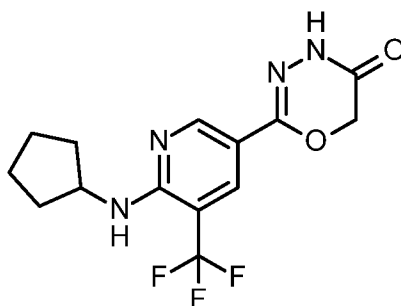
Synthesized in analogy to Example 37 from Intermediate 32 and 3-azabicyclo[3.1.0]hexane.

LC-MS (Method 1): $R_t = 1.22$ min; MS (ESI^{neg}): $m/z = 325$ [M-H]⁻

- 5 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.000 (0.73), 0.010 (1.89), 0.021 (1.96), 0.031 (0.79), 0.585 (0.55), 0.597 (0.73), 0.604 (1.26), 0.616 (1.28), 0.623 (0.78), 0.635 (0.61), 1.590 (1.30), 1.596 (2.20), 1.605 (2.30), 1.615 (2.14), 2.008 (0.56), 3.269 (7.92), 3.500 (1.97), 3.818 (5.55), 3.846 (4.66), 4.682 (16.00), 8.007 (3.90), 8.013 (4.10), 8.534 (3.52), 8.540 (3.46), 10.959 (4.93).

10 **Example 77**

2-[6-(cyclopentylamino)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one



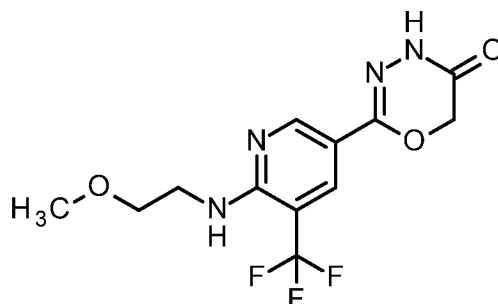
Synthesized in analogy to Example 37 from Intermediate 32 and cyclopentanamine.

LC-MS (Method 1): $R_t = 1.25$ min; MS (ESI^{neg}): $m/z = 327$ [M-H]⁻

- 15 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.512 (0.62), 1.517 (0.73), 1.523 (1.18), 1.537 (2.19), 1.542 (2.39), 1.544 (2.41), 1.548 (2.75), 1.559 (1.67), 1.574 (1.38), 1.587 (0.91), 1.593 (1.00), 1.606 (0.54), 1.655 (0.57), 1.668 (0.82), 1.676 (1.07), 1.687 (1.49), 1.691 (1.60), 1.696 (1.38), 1.702 (0.99), 1.901 (0.63), 1.907 (0.87), 1.912 (0.91), 1.919 (1.44), 1.922 (1.26), 1.938 (1.20), 1.949 (0.84), 1.967 (0.52), 2.074 (0.74), 2.518 (0.40), 4.490
20 (0.58), 4.508 (1.08), 4.526 (1.00), 4.544 (0.52), 4.739 (16.00), 6.401 (1.57), 6.419 (1.53), 7.941 (3.11), 7.946 (3.01), 8.599 (2.79), 8.604 (2.70), 10.997 (4.60).

Example 78

2-{6-[(2-methoxyethyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-4H-1,3,4-oxadiazin-5(6H)-one



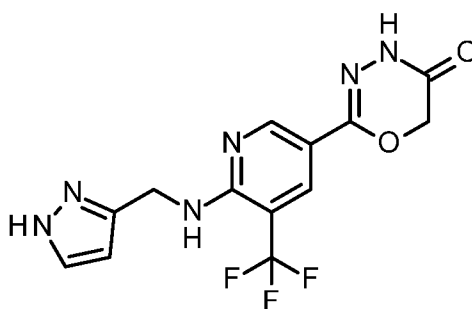
- 5 Synthesized in analogy to Example 37 from Intermediate 32 and 2-methoxyethan-1-amine.

LC-MS (Method 1): $R_t = 0.94$ min; MS (ESIpos): $m/z = 319$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (2.22), 2.523 (1.36), 3.253 (16.00), 3.463 (1.05), 3.478 (2.90), 3.493 (1.58), 3.609 (0.69), 3.623 (1.63), 3.638 (1.44), 3.653 (0.48),
 10 4.741 (7.03), 6.931 (0.41), 6.945 (0.81), 6.958 (0.41), 7.953 (1.52), 7.958 (1.53), 8.598 (1.42), 8.602 (1.38), 11.002 (2.27).

Example 79

2-[6-[(1H-pyrazol-3-yl)methyl]amino]-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one



15

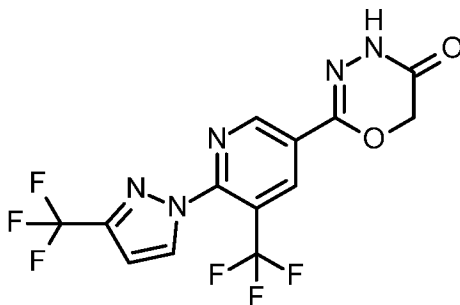
Synthesized in analogy to Example 37 from Intermediate 32 and 1-(1H-pyrazol-3-yl)methanamine.

LC-MS (Method 1): $R_t = 0.81$ min; MS (ESIpos): $m/z = 341$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.072 (0.51), 4.657 (4.24), 4.671 (4.24), 4.739 (16.00), 6.067 (2.65), 6.070 (2.63), 7.383 (0.56), 7.972 (3.64), 7.977 (3.66), 8.599 (3.21),
 20 8.604 (3.18), 11.004 (5.58), 12.571 (1.20).

Example 80

2-{5-(trifluoromethyl)-6-[3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl}-4H-1,3,4-oxadiazin-5(6H)-one



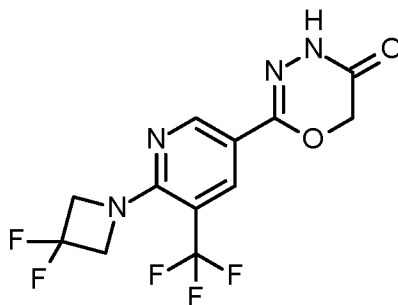
- 5 Synthesized in analogy to Example 37 from Intermediate 32 and 3-(trifluoromethyl)-1H-pyrazole.

LC-MS (Method 1): $R_t = 1.17$ min; MS (ESIpos): $m/z = 380$ $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.518 (1.45), 2.522 (0.91), 4.897 (16.00), 7.124 (3.56), 7.131 (3.61), 8.583 (4.06), 8.588 (4.10), 8.648 (2.57), 8.651 (2.74), 8.655 (2.69),
10 8.657 (2.49), 9.133 (3.61), 9.138 (3.48), 11.382 (5.35).

Example 81

2-[6-(3,3-difluoroazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one



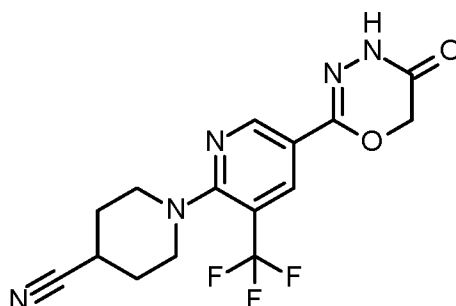
- 15 Synthesized in analogy to Example 37 from Intermediate 32 and 3,3-difluoroazetidine.

LC-MS (Method 1): $R_t = 1.10$ min; MS (ESIpos): $m/z = 337$ $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.073 (0.44), 4.565 (3.38), 4.596 (6.86), 4.627 (3.34), 4.776 (16.00), 8.113 (3.53), 8.118 (3.53), 8.704 (3.30), 8.709 (3.19), 11.081 (5.02).

Example 82

1-[5-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-3-(trifluoromethyl)pyridin-2-yl]piperidine-4-carbonitrile



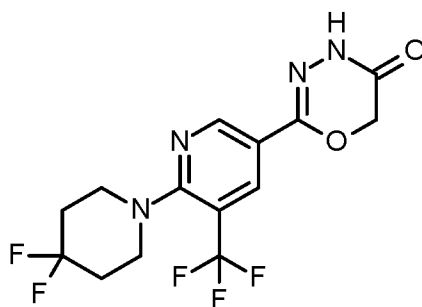
Synthesized in analogy to Example 37 from Intermediate 32 and piperidine-4-carbonitrile.

5 LC-MS (Method 1): $R_t = 1.03$ min; MS (ESIpos): $m/z = 354$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.765 (0.58), 1.774 (0.70), 1.787 (1.23), 1.796 (1.75), 1.808 (1.48), 1.820 (2.08), 1.829 (1.71), 1.842 (1.00), 1.850 (0.85), 1.961 (0.84), 1.969 (1.53), 1.978 (1.80), 1.985 (1.65), 1.993 (1.54), 2.002 (1.21), 2.010 (1.30), 2.018 (1.12), 2.027 (0.62), 2.073 (0.97), 3.107 (0.40), 3.117 (0.83), 3.128 (1.20), 3.138 (1.52),
 10 3.148 (1.15), 3.159 (0.75), 3.219 (1.19), 3.226 (1.38), 3.240 (1.36), 3.251 (2.05), 3.259 (1.71), 3.274 (1.69), 3.281 (1.44), 3.485 (1.37), 3.494 (1.73), 3.501 (1.67), 3.509 (1.53), 3.518 (1.30), 3.527 (1.31), 3.535 (1.38), 3.543 (1.04), 4.787 (16.00), 8.156 (4.54), 8.161 (4.70), 8.741 (3.74), 8.746 (3.64), 11.126 (5.86).

Example 83

15 2-[6-(4,4-difluoropiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 37 from Intermediate 32 and 4,4-difluoropiperidine.

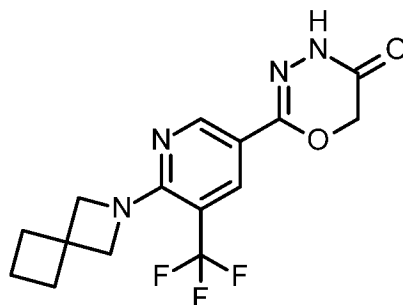
LC-MS (Method 1): $R_t = 1.20$ min; MS (ESIpos): $m/z = 365$ $[M+H]^+$

20 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 2.048 (0.86), 2.062 (1.25), 2.074 (2.98), 2.083 (1.93), 2.098 (2.43), 2.112 (1.91), 2.133 (1.25), 2.147 (0.88), 2.518 (0.62), 2.523 (0.41),

3.466 (3.61), 3.480 (4.62), 3.494 (3.50), 4.796 (16.00), 8.186 (4.25), 8.192 (4.35), 8.760 (3.15), 8.766 (3.03), 11.140 (5.13).

Example 84

2-[6-(2-azaspiro[3.3]heptan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one



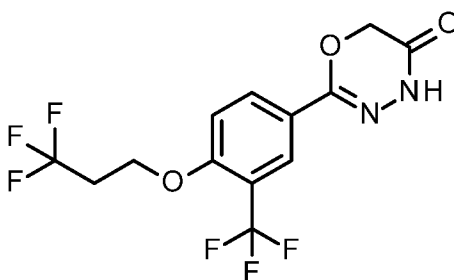
Synthesized in analogy to Example 37 from Intermediate 32 and 2-azaspiro[3.3]heptane.

LC-MS (Method 1): $R_t = 1.28$ min; MS (ESIpos): $m/z = 341$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 1.765 (0.54), 1.783 (1.57), 1.803 (2.93), 1.820 (1.97), 1.841 (0.74), 2.075 (1.64), 2.174 (5.77), 2.193 (8.54), 2.212 (4.80), 2.518 (0.93), 2.523 (0.63), 4.162 (12.52), 4.745 (16.00), 8.008 (3.57), 8.014 (3.61), 8.618 (3.45), 8.623 (3.35), 11.010 (5.22).

Example 85

2-[3-(trifluoromethyl)-4-(3,3,3-trifluoropropoxy)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



15

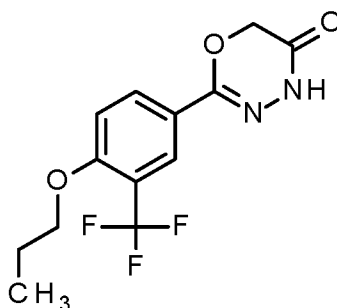
2-[4-bromo-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (45.0 mg, 139 μmol , Intermediate 30), 2-di(tert-butyl)phosphino-2',4',6'-triisopropyl-3-methoxy-6-methylbiphenyl (3.3 mg, 0.007 mmol, CAS No 1262046-34-3), [(2-Di-tert-butylphosphino-3-methoxy-6-methyl-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2-aminobiphenyl)]palladium(II) methanesulfonate (6 mg, 0.007 mmol), Cesium carbonate (64 mg, 0.2 mmol) were added to a 5 ml reaction vessel, the vessel was crimp sealed

20

and flushed with argon. Toluene (anhydrous, degassed, 0.9 ml) and 3,3,3-trifluoro-1-propanol (61 μ l, 0.7 mmol) were added and the mixture stirred at 80°C overnight. The mixture was filtered through a column of Isolute (2 g, 1 cm diameter), the Isolute was washed with a mixture of DCM:MeOH (9:1), and the filtrate concentrated under reduced pressure. Further purification was achieved using reverse phase HPLC chromatography yielding the title compound (22 mg, 44 %, 100% purity).

Example 86

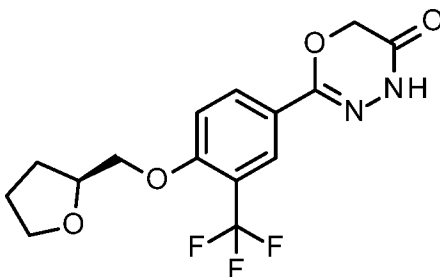
2-[4-propoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 85 from Intermediate 30 and 1-propanol.

Example 87

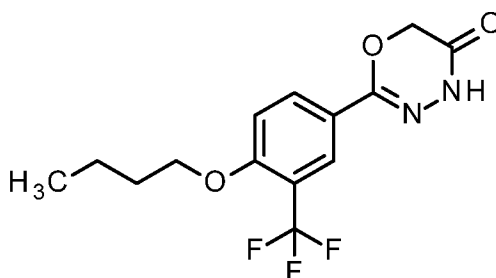
2-[4-[(2S)-oxolan-2-yl]methoxy]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 85 from Intermediate 30 and tetrahydrofurfuryl alcohol.

Example 88

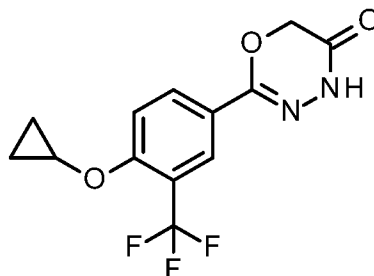
2-[4-butoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



5 Synthesized in analogy to Example 85 from Intermediate 30 and 1-butanol.

Example 89

2-[4-(cyclopropyloxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



10

Synthesized in analogy to Example 85 from Intermediate 30 and cyclopropanol.

LC-MS (Method 1): $R_t = 1.14$ min; MS (ESIpos): $m/z = 301$ $[M+H]^+$

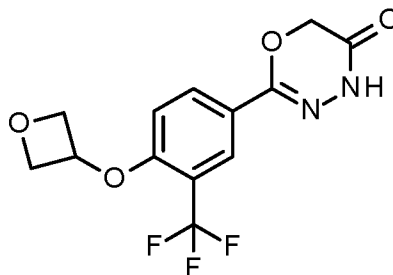
$^1\text{H-NMR}$ (400 MHz, ACETONITRILE- d_3) δ [ppm]: 0.725 (0.43), 0.727 (0.51), 0.732 (0.47), 0.734 (0.56), 0.739 (1.41), 0.743 (1.44), 0.746 (2.88), 0.749 (2.13), 0.752 (1.74), 0.756 (1.36), 0.760 (0.79), 0.765 (0.84), 0.767 (0.69), 0.808 (0.45), 0.849 (0.86), 0.851 (0.83), 0.860 (1.27), 0.864 (2.45), 0.866 (2.12), 0.869 (1.60), 0.875 (1.31), 0.879 (1.79), 0.881 (1.81), 0.884 (2.12), 0.897 (0.58), 0.899 (0.50), 1.268 (1.42), 2.101 (0.47), 2.107 (0.63), 2.114 (0.66), 2.149 (2.55), 3.960 (0.43), 3.967 (0.90), 3.975 (1.28), 3.982 (1.70), 3.990 (1.20), 3.998 (0.87), 4.005 (0.42), 4.708 (16.00), 7.533 (1.75), 7.554 (1.93), 7.985 (1.66), 7.990 (2.35), 8.005 (1.41), 8.009 (0.87), 8.025 (1.17), 8.031 (0.91), 9.055 (0.76).

15

20

Example 90

2-{4-[(oxetan-3-yl)oxy]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one

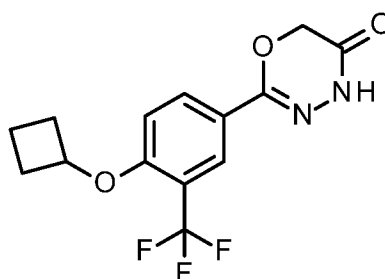


Synthesized in analogy to Example 85 from Intermediate 30 and oxetan-3-ol.

5

Example 91

2-[4-(cyclobutyloxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



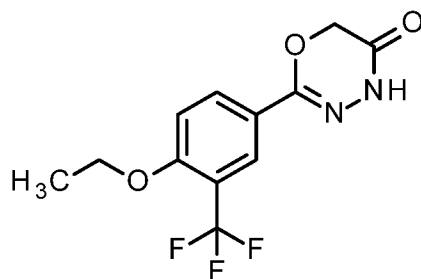
Synthesized in analogy to Example 85 from Intermediate 30 and cyclobutanol.

10 LC-MS (Method 1): $R_t = 1.25$ min; MS (ESIneg): $m/z = 313$ $[M-H]^-$

1H -NMR (400 MHz, ACETONITRILE- d_3) δ [ppm]: 1.129 (0.50), 1.707 (0.64), 1.709 (0.53), 1.734 (0.88), 1.756 (0.46), 1.759 (0.50), 1.768 (0.53), 1.846 (0.63), 1.871 (0.61), 1.964 (0.50), 2.084 (0.43), 2.090 (0.50), 2.095 (0.48), 2.101 (1.00), 2.107 (1.80), 2.115 (1.54), 2.127 (2.72), 2.144 (16.00), 2.181 (0.68), 2.450 (0.46), 2.457 (0.66), 2.464 (0.49), 2.467 (0.60), 2.471 (0.64), 2.474 (1.02), 2.477 (0.83), 2.481 (1.07), 2.488 (0.96), 2.494 (1.03), 2.498 (0.81), 2.501 (0.97), 2.505 (0.61), 2.508 (0.48), 2.518 (0.59), 4.698 (14.13), 4.834 (0.77), 4.852 (1.12), 4.870 (0.76), 7.020 (1.54), 7.042 (1.60), 7.932 (0.88), 7.937 (1.05), 7.954 (0.79), 7.959 (1.04), 7.991 (1.96), 7.996 (1.55), 9.039 (0.72).

Example 92

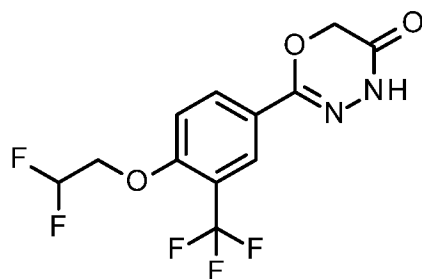
20 2-[4-ethoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 85 from Intermediate 30 and ethanol.

5 **Example 93**

2-[4-(2,2-difluoroethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



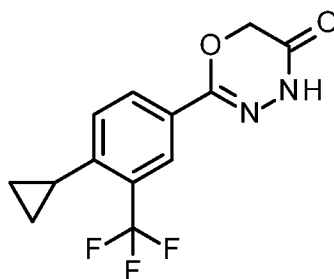
Synthesized in analogy to Example 85 from Intermediate 30 and 2,2-difluoroethanol.

LC-MS (Method 1): $R_t = 1.05$ min; MS (ESIpos): $m/z = 325$ $[M+H]^+$

- 10 $^1\text{H-NMR}$ (400 MHz, ACETONITRILE- d_3) δ [ppm]: 1.268 (1.11), 2.145 (2.88), 4.369 (1.57), 4.378 (1.60), 4.403 (3.17), 4.412 (3.13), 4.438 (1.56), 4.447 (1.49), 4.715 (16.00), 6.068 (0.44), 6.077 (0.94), 6.086 (0.45), 6.204 (0.92), 6.213 (1.80), 6.222 (0.90), 6.340 (0.44), 6.349 (0.91), 6.358 (0.43), 7.203 (1.59), 7.224 (1.68), 8.008 (0.95), 8.013 (1.39), 8.035 (4.71), 9.075 (0.89).

15 **Example 94**

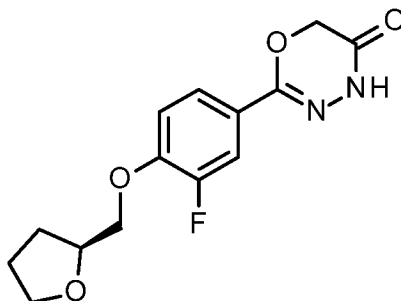
2-[4-cyclopropyl-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



2-[4-bromo-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (50.0 mg, 155 μ mol, Intermediate 30) and di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I) (13 mg, 0.015 mmol) were sealed in a vessel and were flushed with argon. Toluene (pre-flushed with argon) was added. The mixture was stirred at room temperature for 10 min, then Cyclopropylzinc bromide solution in THF (930 μ l, 0.5M, 460 μ mol) was added. The mixture was stirred at room temperature for 1h. The vessel was opened and the mixture was filtered through a 2g silica column. The column was washed with DCM/MeOH (9:1) three times. The filtrate was concentrated and purified using preparative HPLC to yield the title compound (20.4 mg, 100 % purity, 46 % yield).

Example 95

2-(3-fluoro-4-[(2*S*)-oxolan-2-yl]methoxy}phenyl)-4H-1,3,4-oxadiazin-5(6H)-one



2-(4-bromo-3-fluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one (45.0 mg, 165 μ mol, Intermediate 29), 2-(di-*tert*-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl (8 mg, 0.016 mmol, CAS No 1160861-53-9), [(2-di-*tert*-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (14 mg, 0.016 mmol, CAS No 1536473-72-9), Cesium carbonate (75 mg, 0.23 mmol) were added to a 5 ml reaction vessel, the vessel was crimp sealed and flushed with argon. Toluene (anhydrous, degassed, 1 ml) and tetrahydrofurfuryl alcohol (160 μ l, 1.6 mmol) were added and the mixture stirred at 80°C overnight. The mixture was filtered through a column of Isolute (2 g, 1 cm diameter), the Isolute was washed with

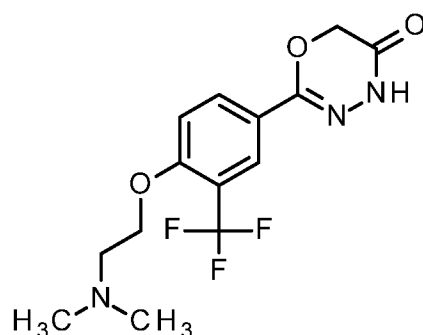
a mixture of DCM:MeOH (9:1) and the filtrate concentrated under reduced pressure. Further purification was achieved using reverse phase HPLC chromatography yielding the title compound (4.5 mg, 8 % yield).

LC-MS (Method 1): R_t = 0.90 min; MS (ESIpos): m/z = 295 $[M+H]^+$

5 1H -NMR (400 MHz, ACETONITRILE- d_3) δ [ppm]: 1.693 (0.67), 1.697 (0.43), 1.710 (0.45), 1.714 (0.82), 1.723 (0.78), 1.727 (0.50), 1.732 (0.51), 1.740 (0.50), 1.744 (0.95), 1.762 (0.59), 1.875 (0.69), 1.879 (0.62), 1.887 (0.42), 1.896 (0.96), 1.901 (0.77), 1.909 (0.69), 1.913 (1.06), 1.964 (1.21), 2.006 (0.62), 2.019 (0.50), 2.024 (0.67), 2.027 (0.53), 2.036 (0.86), 2.040 (0.48), 2.045 (0.56), 2.050 (0.50), 2.054 (0.62), 2.057 (0.69), 2.068 (0.53),
10 2.074 (0.48), 2.088 (0.43), 2.162 (1.37), 3.711 (0.65), 3.727 (0.79), 3.732 (1.14), 3.747 (1.27), 3.750 (1.14), 3.765 (0.93), 3.802 (1.02), 3.818 (1.70), 3.822 (0.79), 3.836 (1.09), 3.839 (1.08), 3.856 (0.63), 3.999 (0.97), 4.015 (1.17), 4.025 (2.01), 4.041 (2.45), 4.071 (2.02), 4.080 (2.35), 4.096 (0.99), 4.105 (1.06), 4.184 (0.43), 4.193 (0.41), 4.202 (1.01), 4.211 (0.95), 4.219 (0.94), 4.228 (0.82), 4.678 (16.00), 4.741 (0.51), 4.898 (0.48), 7.090
15 (1.46), 7.112 (2.67), 7.134 (1.46), 7.521 (1.60), 7.526 (2.09), 7.542 (0.74), 7.547 (2.34), 7.552 (2.72), 7.557 (1.86), 7.565 (1.42), 7.568 (1.21), 7.571 (0.78), 7.573 (0.92), 9.023 (0.99).

Example 96

2-{4-[2-(dimethylamino)ethoxy]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one

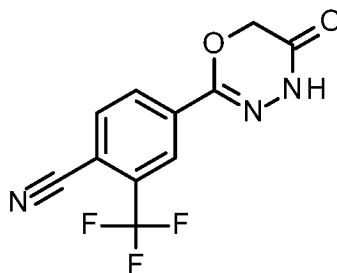


20

Synthesized in analogy to Example 85 from Intermediate 30 and N,N-dimethylethanolamine.

Example 97

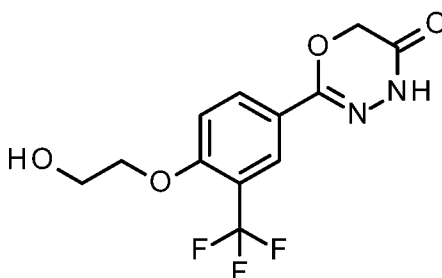
25 4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)benzonitrile



2-[4-bromo-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (50.0 mg, 155 μ mol, Intermediate 30), [Pd(cinnamyl)Cl]₂: (4.01 mg, 7.74 μ mol; CAS-RN:[12131-44-1]), 1,1'-bis(diphenylphosphanyl)ferrocene (4.29 mg, 7.74 μ mol; CAS-RN:[12150-46-8]), and
 5 zinc cyanide (21.8 mg, 186 μ mol) were added to a 5 ml reaction vessel, the vessel was crimp sealed and flushed with argon. N,N-dimethylacetamide (1.0 ml) and N,N-diisopropylethylamine (54 μ l, 310 μ mol) were added and the mixture stirred at 80°C overnight. The mixture was filtered through a column of Isolute (2 g, 1 cm diameter), the Isolute was washed with a mixture of DCM:MeOH (9:1) and the filtrate concentrated
 10 under reduced pressure. Further purification was achieved using reverse phase HPLC chromatography yielding the title compound (19.4 mg, 47 % yield, 100% purity).

Example 98

2-[4-(2-hydroxyethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

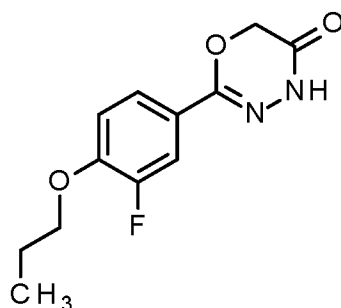


15

Synthesized in analogy to Example 85 from Intermediate 30 and ethylene glycol.

Example 99

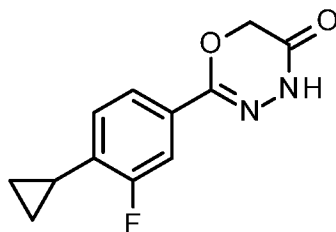
20 2-(3-fluoro-4-propoxyphenyl)-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 85 from Intermediate 29 and 1-propanol.

Example 100

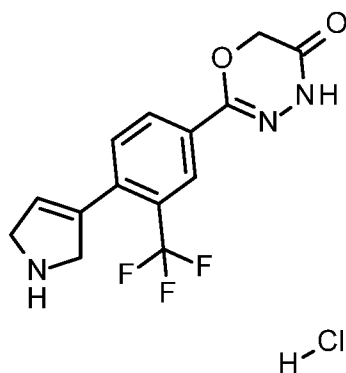
- 5 2-(4-cyclopropyl-3-fluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one



Synthesized in analogy to Example 94 from Intermediate 29.

Example 101

- 10 2-[4-(2,5-dihydro-1H-pyrrol-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one—hydrogen chloride (1/1)



- To a cooled solution of tert-butyl 3-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]-2,5-dihydro-1H-pyrrole-1-carboxylate (295 mg, 0.72 mmol, Intermediate 36) in anhydrous MeOH at 0 °C was added acetyl chloride (153 μL, 2.15

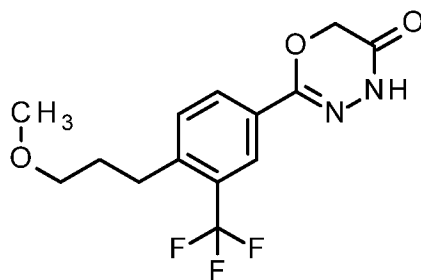
mmol) dropwise, with stirring continued for 1 h. After this time, further acetyl chloride (153 μ L, 2.15 mmol) was added dropwise, with stirring continued for 1 h. After this time, the reaction mixture was concentrated in vacuo, and azeotoped with further MeOH (twice). This material was triturated with Et₂O/EtOAc/MeOH (2:1:1), with the insoluble material isolated by suction filtration to afford the title compound (194 mg, 76%) as a pale pink solid.

¹H NMR (250 MHz, DMSO-d₆) δ = 4.04 - 4.34 (m, 4H), 4.85 (s, 2H), 6.05 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 7.7 Hz, 2H), 9.68 (s, 2H), 11.22 (s, 1H).

LC-MS (Method 4): R_t = 2.45 min; MS (ESIpos): m/z = 312 [M+H]⁺

10 Example 102

2-[4-(3-methoxypropyl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

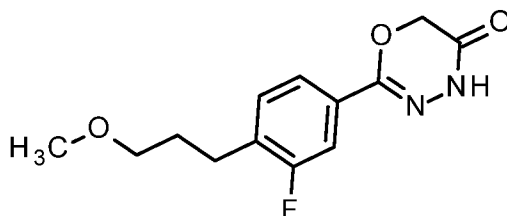


2-{4-[(1E)-3-methoxyprop-1-en-1-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one (41.0 mg, 130 μ mol) was suspended in ethanol (2.0 ml). Palladium on carbon (10 wt%, 8.33 mg, 7.83 μ mol) was added and the mixture was stirred under an atmosphere of hydrogen gas for 1h. The mixture was filtered, the solids were washed with ethanol and the combined washes were concentrated. Preparative HPLC yielded the title compound as a beige solid (25.0 mg, 100 % purity, 61 % yield).

LC-MS (Method 1): R_t = 1.13 min; MS (ESIpos): m/z = 317 [M+H]⁺

20 Example 103

2-[3-fluoro-4-(3-methoxypropyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

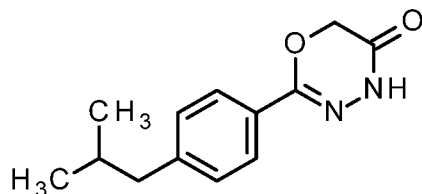


Synthesized in analogy to Example 102 from Example 26.

LC-MS (Method 1): $R_t = 1.01$ min; MS (ESIpos): $m/z = 267$ $[M+H]^+$

Example 104

2-[4-(2-methylpropyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



5 Synthesized in analogy to Example 102 from Example 13.

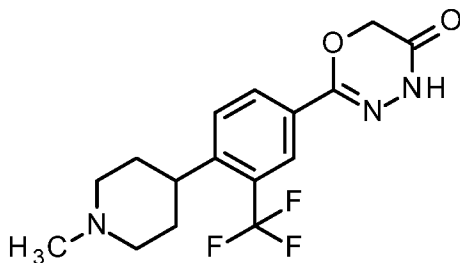
LC-MS (Method 1): $R_t = 1.24$ min; MS (ESIpos): $m/z = 233$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.845 (15.73), 0.862 (16.00), 1.232 (0.40), 1.829 (0.76), 1.845 (0.93), 1.862 (0.73), 2.476 (4.06), 2.518 (2.36), 2.522 (1.47), 4.752 (12.86), 7.229 (3.44), 7.250 (3.82), 7.667 (0.71), 7.671 (4.52), 7.676 (1.41), 7.688 (1.34), 7.692 (4.00), 11.006 (2.55).

10

Example 105

2-[4-(1-methylpiperidin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



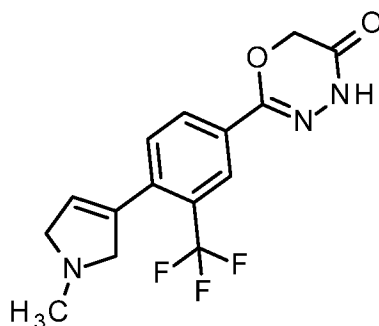
Synthesized in analogy to Example 102 from Example 71.

15 $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 1.58 - 1.67 (m, 2H), 1.71 - 1.84 (m, 2H), 1.88 - 1.98 (m, 2H), 2.20 (s, 3H), 2.70 - 2.81 (m, 1H), 2.85 - 2.92 (m, 2H), 4.80 (s, 2H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.93 - 8.03 (m, 2H), 11.12 (s, 1H).

LC-MS (Method 4): $R_t = 3.10$ min; MS (ESIpos): $m/z = 342$ $[M+H]^+$

Example 106

20 2-[4-(1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



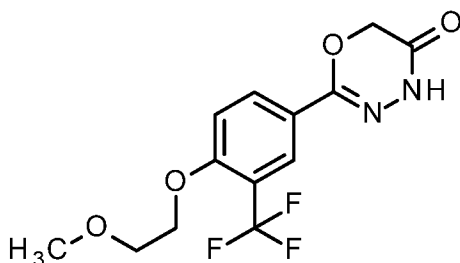
To a mixture of 2-[4-(2,5-dihydro-1H-pyrrol-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one hydrochloride (1:1) (194 mg, 0.56 mmol, Example 101), 36% formaldehyde solution in water (47 μ L, 0.56 mmol) and AcOH (37 μ L, 0.61 mmol) dissolved in DMF (1.4 mL) was added sodium triacetoxyborohydride (154 mg, 0.72 mmol) with the reaction stirred at r.t. for 16 h. After this time, the reaction mixture was partitioned between EtOAc and saturated aqueous sodium hydrogen carbonate solution. The organic layer was isolated, washed with saturated aqueous sodium chloride solution (thrice), dried (MgSO_4), filtered and concentrated in vacuo. The residual material was purified by Biotage IsoleraTM chromatography (silica gel, eluting with 10% MeOH in DCM:DCM, 0:1 to 1:0), with further purification of required by Biotage IsoleraTM chromatography (silica gel, eluting with [DCM:MeOH:AcOH:Water 90:18:3:2] :DCM (0:1 to 1:1 to 1:0), with the desired fractions combined and concentrated in vacuo. Residual AcOH was removed by passage through a SCX cartridge, with the desired material released upon elution with 7M methanolic ammonia solution. Removal of the solvent afforded the title compound (53 mg, 28%) as a colourless solid.

¹H NMR (500 MHz, DMSO- d_6) δ = 2.43 (s, 3H), 3.59 (dd, J = 4.1, 1.9 Hz, 2H), 3.65 - 3.73 (m, 2H), 4.83 (s, 2H), 5.91 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.99 (dd, J = 8.1, 1.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 11.17 (s, 1H).

LC-MS (Method 4): R_t = 2.50 min; MS (ESIpos): m/z = 326 $[\text{M}+\text{H}]^+$

Example 107

2-[4-(2-methoxyethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



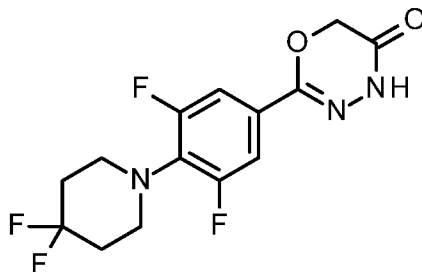
To a solution of 2-[4-hydroxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one (100 mg, 384 μ mol, which can be synthesized in analogy to Example 85 from Intermediate 20 and water) and 2-methoxyethan-1-ol (61 μ l, 770 μ mol) in tetrahydrofuran were added tri-n-butylphosphine and diisopropyl azodicarboxylate at 0 °C. The mixture was stirred under cooling for 5mins then at room temperature for 18h with addition of further Diisopropyl azodicarboxylate (151 μ l, 0.77mmol) after 45mins. The reaction mixture was diluted with ethyl acetate and washed with sat. NaHCO₃(aq) and brine. The organic phase was dried over sodium sulfate and evaporated under vacuum. The residue was purified by Biotage Isolera™ chromatography (silica gel, eluting with heptanes-EtOAc, 1:0 to 0:1) to afford a crude material which was triturated with ethyl acetate/heptane. The solids were collected by filtration and rinsed with heptane to afford 36.8mg (28% yield, 94% purity) of the title compound as an off-white solid.

¹H NMR (500 MHz, DMSO-d₆) δ 3.32 (s, 3H), 3.66 - 3.72 (m, 2H), 4.30 (dd, J = 5.3, 3.8 Hz, 2H), 4.78 (s, 2H), 7.37 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.98 (dd, J = 8.8, 2.2 Hz, 1H), 11.04 (s, 1H).

LC-MS (Method 4): R_t = 2.72 min; MS (ESIpos): m/z = 319 [M+H]⁺

Example 108

2-[4-(4,4-difluoropiperidin-1-yl)-3,5-difluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one



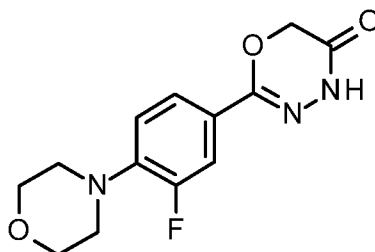
N'-(chloroacetyl)-4-(4,4-difluoropiperidin-1-yl)-3,5-difluorobenzohydrazide (380 mg, 1.0 mmol, Intermediate 22) was dissolved in DMF (5 mL) and NaHCO₃ (434 mg, 5.2 mmol) was added. The resulting mixture was heated at 100 °C in a sealed tube for 3 hours. The mixture was diluted with EtOAc (50 mL) and washed with 1M aq. HCl (2 x 30 mL) and brine (30 mL), dried (Na₂SO₄), filtered and concentrated at reduced pressure. The residue was purified via Biotage Isolera chromatography (using a gradient of eluents, 8:2 to 2:8 Heptane:EtOAc). The residue obtained with recrystallised (heptane/EtOAc) to give the desired product (34 mg, 10% yield) as yellow crystals.

¹H NMR (500 MHz, DMSO-d₆) δ 11.10 (s, 1H), 7.40 - 7.24 (m, 2H), 4.75 (s, 2H), 3.30 - 3.20 (m, 4H), 2.18 - 1.95 (m, 4H).

LC-MS (Method 4): $R_t = 3.32$ min; MS (ESIpos): $m/z = 332$ $[M+H]^+$

Example 109

2-[3-fluoro-4-(morpholin-4-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

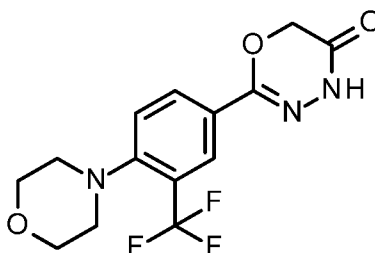


- 5 Synthesized in analogy to Example 108 from Intermediate 23.

LC-MS (Method 1): $R_t = 0.83$ min; MS (ESIpos): $m/z = 280$ $[M+H]^+$

Example 110

2-[4-(morpholin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one



- 10 Synthesized in analogy to Example 108 from Intermediate 24.

1H NMR (250 MHz, Chloroform- d) δ 2.91 - 3.05 (m, 4H), 3.78 - 3.90 (m, 4H), 4.79 (s, 2H), 7.32 (d, $J = 8.5$ Hz, 1H), 7.97 (dd, $J = 8.5, 2.1$ Hz, 1H), 8.10 (d, $J = 2.0$ Hz, 1H), 8.28 (s, 1H).

LC-MS (Method 4): $R_t = 2.86$ min; MS (ESIpos): $m/z = 330$ $[M+H]^+$

15

EXPERIMENTAL SECTION – BIOLOGICAL ASSAYS

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

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

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

- 10 The *in vitro* activity of the compounds of the present invention can be demonstrated in the following assays:

Assay 1

Cell proliferation measurement

- The antiproliferative activity of the compounds of the general formula (I) was examined in vitro in human cancer cells. For this purpose, the appropriate number of cells (Hela: 800; SK-MEL-3: 1000; IGR-37:800) were plated in 384-well plates with appropriate growth medium (; Hela: DMEM/Ham's F12 (Biochrom; # FG 4815 with stabile Glutamine), FCS 10% final (Biochrom; # S 0415); SK-MEL-3: McCoy's 5A (Biochrom; # F 1015), FCS 10% final (Biochrom; # S 0415), L-Alanyl-L-Glutamine final: 2mM, (Biochrom; # K 0302); IGR-37: DMEM; (Biochrom; # FG 0445, high glucose; with stable glutamine, FCS (final: 15%); (Biochrom; # S 0415)) and incubated at 37°C overnight. After 24 h, cells on one plate (0 h plate) were treated with 30 µl/cavity of CTG solution (Promega Cell Titer Glo (catalogue # G755B and G756B)) and incubated at room temperature for 10 min, and luminescence was measured by means of a VICTOR V (Perkin Elmer), in order to determine cell viability on commencement of treatment. The cells on the test plate were treated with the compounds of the general formula (I) as and incubated at 37°C for 72 h. The compounds were added to the cells by means of an HP D300 digital dispenser in a 10-step 2,5-fold dilution series generally starting at a maximum final drug concentration of 100nM . As control, the cells were treated with vehicle (DMSO at 0.3% final concentration). After 72 h, the cells were treated with 30 µl/cavity of CTG solution (Promega Cell Titer Glo (catalogue # G755B and G756B)) and incubated at room temperature for 10 min, and luminescence was measured by means of a VICTOR V (Perkin Elmer), in order to determine cell viability at the end of treatment. The percentage effect on cell growth and the IC50 derived therefrom were determined for each test

substance using the values from the 0 h plate (= maximum inhibition) and the DMSO control (= minimum inhibition). The IC₅₀ values were calculated using a 4-parameter fit.

Table 2: Anti-proliferation IC₅₀ values of several examples *in vitro* in different cell lines

Example	HeLa	SK-MEL-3	IGR-37
	IC ₅₀ [nM]	IC ₅₀ [nM]	IC ₅₀ [nM]
1	7	13	21
2	8	15	29
3	8	18	29
4	11	23	39
5	3	7	
6	4	10	
7	6	11	
8	6	12	17
9	38	58	
10	2	5	5
11	10	29	
12	14	28	
13	14	35	
14	14	38	
15	88	>100	
16	4	10	12
17	38	62	
18	58	>100	
19	65	>100	
20	2	6	10
21	5	14	
22	6	19	
23	10	31	
24	15	42	
25	15	46	
26	21	52	
27	25	62	
28	11	18	28
29	31	67	
30	4	8	

Example	HeLa	SK-MEL-3	IGR-37
31	5	10	
32	12	19	
33	2	4	4
34	6	12	
35	7	15	
36	8	20	
37	2	5	5
38	5	10	11
39	17	43	46
40	2	5	4
41	5	8	6
42	24		
43	2	4	4
44	9		
45	21	43	49
46	45		
47	39		
48	64		
49	65		
50	60	>100	>100
51	66	77	75
52	14	17	26
53	68	71	91
54	33	60	56
55	1	3	3
56	1	3	2
57	1	3	3
58	2	4	5
59	3	7	12
60	4	8	12
61	5	10	8
62	5	11	12
63	6	12	14
64	7	14	16
65	8	17	17
66	17	40	42
67	26	46	50
68	40	59	69

Example	HeLa	SK-MEL-3	IGR-37
69	54	>100	>100
70	22	62	58
71	47	>100	>100
72	19	42	40
73	58	>100	>100
74	5	11	12
75	39	>100	>100
76	8	18	19
77	9	20	24
78	15	30	33
79	16	31	29
80	26	50	42
81	37	58	77
82	38	63	69
83	50	69	89
84	5	12	16
85	1	2	1
86	1	2	3
87	1	2	2
88	2	4	5
89	1	3	2
90	1	3	2
91	2	6	3
92	2	6	5
93	3	6	4
94	8	23	22
95	28	53	52
96	38	57	61
97	42	63	64
98	6	12	10
99	9	16	28
100	>69	>100	>100
101	39	83	68
102	3	7	
103	49	>100	
104	79	>100	
105	62		
106	16	55	28

Example	HeLa	SK-MEL-3	IGR-37
107	1	2	2
108	10	19	
109	38	46	
110	3	8	

Thus one aspect of the invention is the use of the compounds of formula (I) for the treatment of cervical cancer.

Another aspect of the invention is the use of the compounds of formula (I) for the treatment of skin cancer, especially melanoma.

- 5 Yet another aspect of the invention is the use of compounds of formula (I), for the treatment of skin cancer, especially melanoma, and cervical cancer.

Another aspect are compounds of formula (I) which effectively inhibit tumor cell proliferation (e.g. in HeLa cells) with IC_{50} values of < 100 nM.

- 10 Yet another aspect of the invention is the use of compounds of formula (I), for the treatment of skin cancer, especially melanoma, and cervical cancer.

Another aspect are compounds of formula (I) which effectively inhibit tumor cell proliferation (e.g. in HeLa cells) with IC_{50} values of < 10 nM.

Assay 2

Cell proliferation measurement

- 15 The antiproliferative activity of the compounds of the general formula (I) is examined in vitro in human cancer cells. For this purpose, 500 cells, including HeLa cells, A2058 cells, DU145 cells, HMCB cells, IGR37 cells, NCIH1734 cells, OSRC2 cells, or 750 cells, including CAL51 cells, COLO741 cells, DBTRG05MG cells, DKMG cells, G292CLONEA141B1 cells, GB1 cells, HEL cells, HEL9217 cells, JHUEM1 cells, L3.3
- 20 cells, LI7 cells, TE4 cells, or 1000 cells, including 8505C cells, HUT78 cells, NCIH1563 cells, NCIH2122 cells, NCIH2172 cells, RVH421 cells, SKMEL3 cells, or 1500 cells, including C32 cells, HS578T cells, JHOM1 cells, NCIH196 cells, OVKATE cells, are plated in 384-well plates with appropriate growth medium and incubated at 37°C overnight. After 24 h, the cells on the test plate are treated with the compounds of the
- 25 general formula (I) and incubated at 37°C for 72 h. The compounds are added to the cells by means of an HP D300 digital dispenser in a 10 (or more) -step dilution series. As control, the cells are treated with vehicle (DMSO at 0.3% final concentration). After 72 h, the cells are treated with 20 μ l/well of 50% CTG solution in PBS (Promega Cell Titer Glo (catalogue # G755B and G756B)) and incubated at room temperature for 10 min, and
- 30 luminescence is measured by means of a VICTOR V (Perkin Elmer), in order to determine cell viability at the end of treatment. The percentage effect on cell growth and the IC_{50}

derived therefrom are determined for each test substance using the values from untreated wells (= percent viability). The IC₅₀ values are calculated using a 4-parameter fit.

Assay 3

Method for PDE3A enzyme inhibition

5 The commercially available 3H-cAMP Scintillation Proximity Assay (SPA, Perkin Elmer) system was used for enzyme inhibition studies. For the determination of the *in vitro* effect of example compounds on the PDE3A reactions 2 µl of the respective example compound solution in DMSO (serial dilutions) were placed in wells of microtiter plates (Isoplate-96/200W; Perkin Elmer). 50 µl of a dilution of PDE3A cell extract from Sf9 cells
10 overexpressing human full length PDE3A (SB Drug Discovery, UK) in buffer A (50 mM Tris/HCl pH 7.5, 8.3 mM MgCl₂, 1.7 mM EDTA, 0.2% BSA) was added. The dilution of the PDE3A cell extract was chosen such that the reaction kinetics was linear and less than 70% of the substrate was consumed (typical dilution 1:5000). The reaction was started by addition of 50 µl (0.025 µCi) of 1:2000 in buffer A w/o BSA diluted substrate
15 [8-3H] adenosine 3', 5'-cyclic phosphate (1 µCi/µl; Perkin Elmer). After incubation at room temperature for 60 min, the reaction was stopped by addition of 25 µl of a suspension containing 18 mg/ml yttrium scintillation proximity beads (Perkin Elmer) in water. The microtiter plates were sealed and measured in a Microbeta scintillation counter (PerkinElmer Wallac). IC₅₀ values were determined from sigmoidal curves by plotting
20 percentage PDE3A activity vs log compound concentration.

Assay 4

PDE3B enzyme inhibition

 The commercially available 3H-cAMP Scintillation Proximity Assay (SPA, Perkin Elmer) system was used for enzyme inhibition studies. For the determination of the *in vitro* effect of example compounds on the PDE3B reactions 2 µl of the respective example
25 compound solution in DMSO (serial dilutions) were placed in wells of microtiter plates (Isoplate-96/200W; Perkin Elmer). 50 µl of a dilution of PDE3B cell extract from Sf9 cells overexpressing human full length PDE3B (SB Drug Discovery, UK) in buffer A (50 mM Tris/HCl pH 7.5, 8.3 mM MgCl₂, 1.7 mM EDTA, 0.2% BSA) was added. The dilution of
30 the PDE3B cell extract was chosen such that the reaction kinetics was linear and less than 70% of the substrate was consumed (typical dilution 1:6000). The reaction was started by addition of 50 µl (0.025 µCi) of 1:2000 in buffer A w/o BSA diluted substrate [8-3H] adenosine 3', 5'-cyclic phosphate (1 µCi/µl; Perkin Elmer). After incubation at room temperature for 60 min, the reaction was stopped by addition of 25 µl of a suspension
35 containing 18 mg/ml yttrium scintillation proximity beads (Perkin Elmer) in water. The

microtiter plates were sealed and measured in a Microbeta scintillation counter (PerkinElmer Wallac). IC₅₀ values were determined from sigmoidal curves by plotting percentage PDE3B activity vs log compound concentration.

One aspect of the invention are compounds of formula (I) which effectively inhibit tumor cell proliferation with IC₅₀ values of < 100 nM in e.g. HeLa cells while IC₅₀ values for enzymatic PDE3A or PDE3B inhibition are often > 10 times higher than IC₅₀ values for tumor cell proliferation.

Another aspect of the invention are compounds of formula (I) which effectively inhibit tumor cell proliferation with IC₅₀ values of < 100 nM in e.g. HeLa cells while IC₅₀ values for enzymatic PDE3A or PDE3B inhibition are often > 30 times higher than IC₅₀ values for tumor cell proliferation.

Another aspect of the invention are compounds of formula (I) which effectively inhibit tumor cell proliferation with IC₅₀ values of < 10 nM in e.g. HeLa cells while IC₅₀ values for enzymatic PDE3A or PDE3B inhibition are often > 30 times higher than IC₅₀ values for tumor cell proliferation.

Table 3 Inhibition of PDE3A and PDE3B

Example	PDE3A IC ₅₀ [nM]	PDE3B IC ₅₀ [nM]
1	250	400
2	166	225
3	340	525
4	320	640
5	194	158
6	238	287
7	260	380
8	263	238
9	700	820
10	130	188
11	>860	>901
12	730	480
13	>1000	>1000
14	290	330
15	>1000	>1000
16	332	301
17	>1000	>1000

18	>1000	>1000
19	>1000	>1000
20	153	150
21	200	100
22	>877	780
23	485	585
24	>1000	>1000
25	>1000	>1000
26	>1000	>1000
27	>1000	>1000
28	195	215
29	480	270
30	46	45
31	71	110
32	230	350
33	150	290
34	90	180
35	56	110
36	130	190
37	220	290
38	140	150
39	760	860
40	250	280
41	220	260
42	770	870
43	245	350
44	330	650
45	>1000	>1000
46	>1000	>1000
47	>1000	>1000
48	>1000	>1000
49	>1000	>1000
50	>1000	>1000
51	>1000	>1000

52	>1000	>1000
53	>1000	>1000
54	>913	950
55	103	240
56	67	59
57	100	100
58	140	200
59	115	185
60	105	255
61	225	380
62	290	280
63	350	360
64	530	540
65	620	690
66	210	260
67	510	520
68	730	820
69	970	>1000
70	>1000	>1000
71	>1000	>1000
72	>1000	>1000
73	>1000	>1000
74	645	810
75	>1000	>1000
76	320	280
77	590	380
78	565	855
79	745	>1000
80	>1000	>1000
81	>1000	>1000
82	980	>1000
83	>1000	>1000
84	730	560
85	100	91

86	78	100
87	150	210
88	230	310
89	29	38
90	78	77
91	62	79
92	93	100
93	79	135
94	390	290
95	970	920
96	>1000	>1000
97	>1000	>1000
98	88	150
99	240	320
100	>1000	>1000
101	>1000	>1000
102	380	310
103	>1000	>1000
104	>1000	>1000
105	>1000	>1000
106	590	740
107	220	250
108	400	290
109	690	990
110	89	91

Assay 5

Validation of PDE3A modulator-induced PDE3A protein interactions using immunoprecipitation and immunoblotting

- 5 HeLa cells can be transfected with ORF overexpression constructs expressing V5-tagged SLFN12, or V5-tagged GFP. ORF expression constructs can be obtained from the TRC (clone IDs: TRCN0000468231, TRCN0000476272, ccsbBroad304_99997). At 72 hours post transfection, cells can be treated with 10 μ M DNMDP or trequinsin for 4 hours followed by lysis using the ModRipa lysis buffer and

immunoprecipitation of PDE3A. For each condition, 2 mg total protein lysate can be incubated with 1 µg of anti-PDE3A antibody at 4° C overnight, after which 7.5 µl each of Protein A- and Protein G- Dynabeads (Life Technologies 10001D and 10003D) can be added and incubated for another 1 hour. Beads can be washed and bound proteins can be eluted with 30 µl of LDS PAGE gel loading buffer. Input (~60 µg total protein lysate) and IP products can be resolved on 4-12% Tris-Glycine PAGE gels and can be immunoblotted with an anti-V5 antibody (Life Technologies R96205, 1:5000), the Bethyl anti-PDE3A antibody (1:1000), and secondary antibodies from LiCOR Biosciences (Cat.# 926-32210 and 926068021, each at 1:10,000). Blots can be washed and imaged using a LiCOR Odyssey infrared imager.

Assay 6

In vivo xenotransplantation models

The anti-tumor activities of Compounds of the invention can be examined in murine xenotransplantation models of human cancer. For this purpose, mice can be implanted subcutaneously with tumor cells. At a mean tumor size of 20-40 mm² animals can be randomized into treatment and control groups (at least n=10 animals/group) and treatment can be started with vehicle only or respective Compound. The oral application volume can be 10 ml/kg. In the case of twice daily treatments, the time interval between two applications per day can be 6-7h. The tumor size and the body weight can be determined at least weekly. The tumor area can be detected by means of an electronic caliper [length (mm) x width (mm)]. The experiment can be ended when the study reaches the pre-determined ethical endpoint based on German and European animal welfare regulations. In vivo anti-tumor efficacy can be presented as T/C ratio at study end (Treatment/Control; mean tumor weight of treatment group / mean tumor weight of control group). A compound having a T/C below 0.5 is defined as active (i.e., effective). Statistical analysis can be assessed using SigmaStat software. A one-way analysis of variance can be performed and differences to the control can be compared by a pair-wise comparison procedure (Dunn's method).

Assay 7

Effects on cardiovascular function in conscious telemetered rats

The measurement of cardiovascular parameters in small laboratory animals such as the rat by telemetry is an integral part of cardiac safety assessment. The telemetry technology provides precise measurements while avoiding stress artifacts inherent with

the use of physical or chemical restraint and is suitable to detect potential drug-induced alterations of cardiovascular parameters.

5 Conscious telemetered normotensive Wistar rats (n=4-6/group) are treated with single doses of a compound (three dose groups and a vehicle control group). Cardiovascular parameters such as arterial systolic and diastolic blood pressure, heart rate, left ventricular systolic and end diastolic pressure, left ventricular contractility, as well as body temperature and locomotor activity are continuously monitored before and over 24 hours after administration. For statistical analysis of cardiovascular parameters a mixed
10 model approach and a Dunnett's t-test procedure is used.

A compound of formula (I) not causing substantial effects on cardiovascular parameters is preferred.

15

Other Embodiments

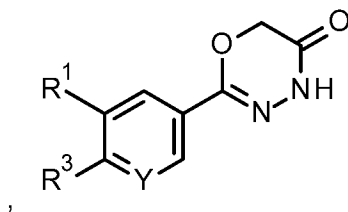
From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

20 The recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or subcombination) of listed elements. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

25

CLAIMS

1. A compound of formula (I)



formula (I)

5 wherein

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR² or N, where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group selected from

10 a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

15 a C₂-C₆-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group;

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

20 a C₁-C₃-alkoxy group,

an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group,

a C₃-C₆-cycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with

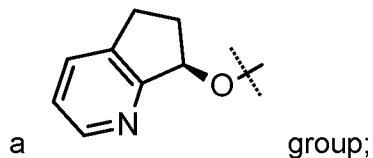
25 a C₁-C₃-alkyl group, and

a 5- to 6-membered heteroaryl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if

Y is N, R³ as an unsubstituted methyl group is excluded;

a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group;



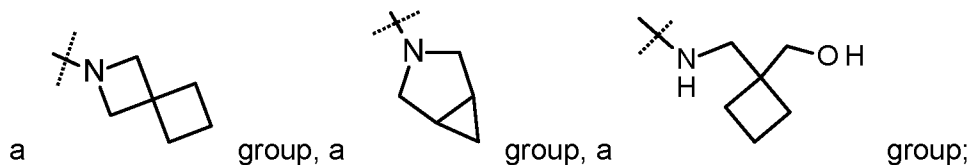
5 a 4- to 6-membered heterocycloalkoxy group,

a C₃-C₆-cycloalkyl group;

a C₅-C₆-cycloalkenyl group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group;

a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



15 a partially unsaturated 4 to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a cyano group, a halogen atom, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group;

and

a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

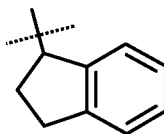
R⁶ is selected from

25 a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a 4- to 6-membered

heterocycloalkyl group, a C₁-C₃-alkoxy group, a hydroxy group, a C₁-C₃-haloalkyl group, and a C₃-C₆-cycloalkyl,

whereby said C₃-C₆-cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,

5



a C₅-C₆-cycloalkyl group, a group,

a 4- to 6-membered heterocycloalkyl group, and

a -C(O)-(C₁-C₆-alkyl) group;

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

10

2. The compound according to claim 1 of formula (I)

wherein

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

15 Y is CR² or N, where R² is a hydrogen atom, or a halogen atom;

R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group,

20 an amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group,

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

25 a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from

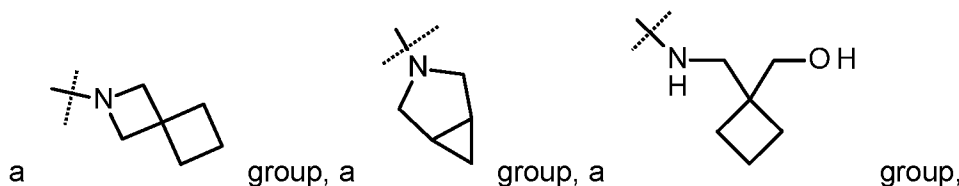
a C₁-C₃-haloalkyl group,

a hydroxy group,

a C₁-C₃-alkoxy group,

30 amino group which is optionally substituted once or twice with a C₁-C₃-alkyl group, and

- a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,
- with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded; a 4- to 6-membered cycloalkoxy group which is optionally substituted one or more times with a group independently selected from a halogen atom, and a C₁-C₃-haloalkyl group,
- a 4- to 6-membered heterocycloalkoxy group;
- a C₃-C₆-cycloalkyl group;
- a C₅-C₆-cycloalkenyl group,
- a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, C₁-C₃-alkoxy group, a C₁-C₃-haloalkoxy group and a C₁-C₃-haloalkyl group,
- a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group,



- a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group,
- a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a cyano group, a C₁-C₃-alkyl group, a C₁-C₃-haloalkyl group, and
- a NR⁵R⁶ group,
- R⁵ is a hydrogen atom;
- R⁶ is selected from
- a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,
- whereby said cycloalkyl group is optionally substituted with a C₁-C₃-hydroxyalkyl group,
- a C₅-C₆-cycloalkyl group,
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

3. The compound according to claim 1, wherein:

R¹ is a hydrogen atom, a halogen atom, a C₁-C₃-alkyl group, or a C₁-C₃-haloalkyl group;

Y is CR² or N where R² is a hydrogen atom, or a halogen atom;

5 R³ is selected from

a C₁-C₆-alkyl group which is optionally substituted with a group independently selected from

a C₁-C₃-alkoxy group, and

10 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group;

a C₂-C₄-alkenyl group, which is optionally substituted with a C₁-C₃-alkoxy group,

a C₁-C₆-alkoxy group which is optionally substituted with a group independently selected from

15 C₁-C₃-haloalkyl group,

a hydroxy group,

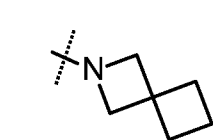
a C₁-C₃-alkoxy group, and

a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

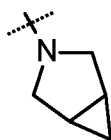
20 with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded; a 4- to 6-membered heterocycloalkoxy group;

a phenyl group which is substituted one or more times with a group independently selected from halogen atom, and a C₁-C₃-haloalkyl group;

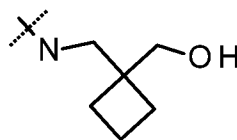
25 a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, and a cyano group;



group, a



group, a



group;

30 a partially unsaturated 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group and a C₁-C₃-haloalkyl group;

a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, a halogen atom, and a C₁-C₃-haloalkyl group; and

a NR⁵R⁶ group;

5 R⁵ is a hydrogen atom;

R⁶ is selected from

a C₁-C₃-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

4. The compound according to claim 1

wherein

15 R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, or a trifluoromethyl group;

Y is C-R² or N and R² is a hydrogen atom, a fluorine atom, or a chlorine atom;

R³ is selected from

20 a C₁-C₄-alkyl group which is optionally substituted with a group independently selected from

a methoxy group, and

a 4- to 6-membered heterocycloalkyl group, which itself is optionally substituted with a C₁-C₃-alkyl group;

25 a C₁-C₄-alkoxy group which is optionally substituted with a group independently selected from

a C₁-C₃-haloalkyl group,

a hydroxy group,

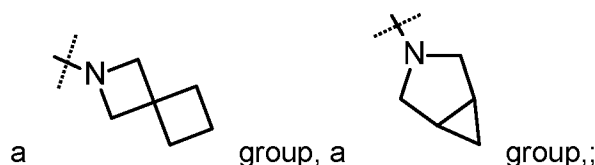
a C₁-C₃-alkoxy group, and

30 a 4- to 6-membered heterocycloalkyl group which itself can be substituted with a C₁-C₃-alkyl group,

with the provisos that R³ as an unsubstituted methoxy group is excluded and if Y is N, R³ as an unsubstituted methyl group is excluded; a phenyl group which is

substituted one or more times with a group independently selected from halogen atom, C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

- 5 a 4- to 7-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a halogen atom, a hydroxy group, a C₁-C₃-alkyl group, a C₁-C₃-hydroxyalkyl group and a cyano group;



a 5- to 10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from a C₁-C₃-alkyl group, and a C₁-C₃-haloalkyl group;

- 10 and

a NR⁵R⁶ group,

R⁵ is a hydrogen atom;

R⁶ is selected from

- 15 a C₁-C₄-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C₁-C₃-alkoxy group, a hydroxy group, and a C₁-C₃-haloalkyl group,

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

- 20 5. The compound according to claim 1,

R¹ is a hydrogen atom, a fluorine atom, or a trifluoromethyl group;

Y is C-R² or N and R² is a hydrogen atom, or a fluorine atom,;

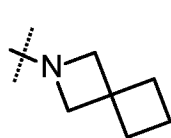
with the proviso that both, R¹ and R², may not be a hydrogen atom at the same time;

- 25 R³ is selected from a -(CH₂)-CH(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group, a -CH₂-(morpholin-4-yl) group, -CH₂-piperidin-1-yl, a -CH₂-N(CH₃)₂ group, a -CH=C(CH₃)₂ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group, a cyclopropyl group, a cyclopent-1-en-1-yl group,

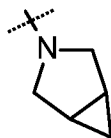
a -O-CH₂-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CF₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-OH group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-(CH₂)₂-N(CH₃)₃ group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-CH₂-(oxolan-2-yl) group, a -O-(oxetan-3-yl) group, a -O-CH₂-tetrahydrofuran-2-yl group,

a 4-fluoro-phenyl group, a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-trifluoromethoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 4-fluoro-2-trifluoromethylphenyl group, a 4-chloro-2-trifluoromethylphenyl group, a 3-methyl-4-trifluoromethylphenyl group, a 4-methyl-3-trifluoromethylphenyl group, a 2,4-difluoro-phenyl group, a 4-fluoro-2-methyl-phenyl group, a 3-fluoro-4-methyl-phenyl group,

an azepan-4-yl group, a 1,4-oxazepan-4-yl group, a piperidin-1-yl group, a 1-methyl-piperidin-4-yl group, a 3-hydroxy-piperidin-1-yl group, a 4-cyano-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a 4-methyl-piperazin-1-yl group, a piperazin-1-yl group, a morpholin-4-yl group, a 3-hydroxy-2-(propan-2-yl)azetidin-1-yl group, a 2-hydroxymethylazetidin-1-yl group, a 3,3-difluoroazetidin-1-yl group, 3-hydroxy-3-methylazetidin-1-yl, a



group, a

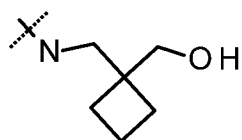


group, a pyrrolidin-1-yl group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group,

a 1-methyl-1,2,3,6-tetrahydropyridin-4-yl group, a 2,5-dihydro-1H-pyrrol-3-yl group, a 1-methyl-2,5-dihydro-1H-pyrrol-3-yl group;

a pyridin-4-yl group, a 6-methyl-pyridin-3-yl group, a 6-cyanopyridin-3-yl group, a piperazin-2-yl group, a pyrazol-4-yl group, a 1-methylpyrazol-4-yl group, a 1-ethylpyrazol-4-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethylpyrazol-1-yl group, a 3-methyl-3-trifluoromethyl-pyrazol-1-yl group, a 4-trifluoromethyl-pyrazol-1-yl group, a 3,5-dimethyl-1,2-oxazol-4-yl group, a 4-trifluoromethyl-1H-1,2,3-triazol-2-yl group, a 4-trifluoromethyl-2H-1,2,3-triazol-1-yl group, a 3-difluoromethyl-2H-1,2,4-triazol-1-yl group, a 3-difluoromethyl-1H-1,2,4-triazol-1-yl group, a 4-methyl-3-trifluoromethyl-1H-pyrazol-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CF₃ group, a -NH-CH(CH₂CH₃)-CH₂-OH group, a



group, a -NH-cyclopentyl group,

5 a -NH-CH₂-(pyrazol-3-yl) group, a -NH-CH₂-pyrazin-2-yl group, a -NH-2,3-dihydro-1H-inden-1-yl group and

a cyano group,

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

10 6. The compound according to claim 1,

wherein

R¹ is a hydrogen atom, a fluorine atom or a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom, or a fluorine atom,

15 R³ is selected from a -CH₂-(morpholin-4-yl) group, a CH₂-N(CH₃)₂ group, a -(CH₂)₃-O-CH₃ group,

a -CH=CH-CH(CH₃)CH₃ group, a -CH=CH-O-CH₂-CH₃ group, a -CH=CH-CH₂-O-CH₃ group,

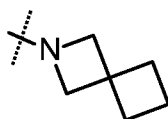
a cyclopropyl group,

a cyclopentenyl group,

20 a 3,4-didehydro-1-methyl-pyrrolidin group,

a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-CH₂-CH₃ group, a -O-CH₂-CHF₂ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-tetrahydropyran-2-yl group, a -O-cyclopropyl group, a -O-cyclobutyl group, a -O-(oxetan-3-yl) group,

25 a 2-fluoro-phenyl group, a 2-trifluoromethylphenyl group, a 2-difluoromethylphenyl group, a 4-fluoro-2-trifluoromethyl-phenyl group, a 2,4-difluorophenyl group, a 4-chloro-2-trifluoromethylphenyl group,



2-hydroxymethylazetidin-1-yl, a group, a 3-azabicyclo[3.1.0]hexan-3-yl group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-cyano-piperidin group, 3-hydroxypiperidin-1-yl, 4-hydroxy-4-ethyl-piperidin-1-yl, 4,4-difluoropiperidin-1-yl, a 4-methyl-piperazin-1-yl group, a azepan-1-yl group,

- 5 a 3-trifluoromethyl-pyrazol-1-yl group, a 1-difluoromethylpyrazol-4-yl group, a 3-trifluoromethyl-1,2,5-triazol-2-yl group, a 2-methylpyridin-5-yl group,
- a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, a -NH-CH₂-CH(OH)CH₃ group, a -NH-CH₂-CH(OCH₃)CH₃ group, a -NH-CH(CH₂OH)CH₂-CH₃ group, a -NH-cyclopentyl group, a -NH-CH₂-C(-CH₂-CH₂-CH₂)-CH₂-OH group, a -NH-CH₂-(3-pyrazolyl) group and a -NH-CH₂-pyrazin-2-yl group,
- 10

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

7. The compound according to claim 1,

15 wherein

R¹ is a hydrogen atom or a trifluoromethyl group,

Y is C-R² and R² is a hydrogen atom

R³ is selected from a -(CH₂)₃-OCH₃ group, a -CH=CH-CH₂-O-CH₃ group, a -O-(CH₂)₂-CH₃ group, a -O-(CH₂)₃CH₃ group, a -O-(CH₂)₂-CF₃ group, a -O-(CH₂)₂-O-CH₃ group, a -O-CH₂-(tetrahydropyranyl) group,

20

a 4-fluoro-2-trifluoromethyl-phenyl group,

a 4-methyl-piperazin-1-yl group,

a -NH-(CH₂)₂-O-CH₃ group, a -NH-CH₂-CH(OH)CF₃ group, and a -NH-CH₂-pyrazol-3-yl group

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

8. The compound according to claim 1 to 7 selected from

2-(4'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,

2-(2',4'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-(2,4'-difluoro-2'-methyl[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-(4'-fluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-(2,2',4'-trifluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-(2,4'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(cyclopent-1-en-1-yl)-3-fluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2'-(difluoromethyl)-2-fluoro[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2',4'-difluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]-3-(trifluoromethyl)phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-fluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(2-methylprop-1-en-1-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-fluoro-2'-methyl-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2'-(difluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2'-fluoro-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-fluoro-2'-methoxy-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-fluoro-4-(6-methylpyridin-3-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(3,5-dimethyl-1,2-oxazol-4-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(6-methylpyridin-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[(E)-2-ethoxyethenyl]-3-fluorophenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{3-fluoro-4-[(1E)-3-methoxyprop-1-en-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4'-chloro-2-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-{4-[1-(difluoromethyl)-1H-pyrazol-4-yl]-3-fluorophenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[2-fluoro-2'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(3,5-dimethyl-1,2-oxazol-4-yl)-3-fluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one,

2-[4-(1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
5-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]pyridine-2-carbonitrile,
2-[4-[(1E)-3-methoxyprop-1-en-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1-methyl-1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1-ethyl-1H-pyrazol-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-(2,2'-difluoro[1,1'-biphenyl]-4-yl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2-methoxyethyl)amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1,4-oxazepan-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(azepan-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2R)-3,3,3-trifluoro-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-3,3,3-trifluoro-2-methoxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2R)-2-hydroxypropyl]amino]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-(trifluoromethyl)-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[3-(difluoromethyl)-1H-1,2,4-triazol-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-(trifluoromethyl)-4-[4-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[3-methyl-4-(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-(trifluoromethyl)-4-[3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl]phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-(trifluoromethyl)-4-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-(trifluoromethyl)-4-[4-(trifluoromethyl)-2H-1,2,3-triazol-2-yl]phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,

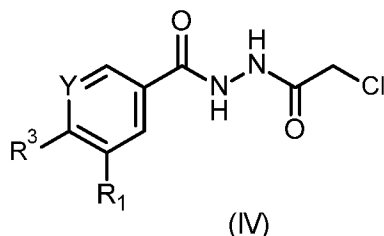
2-{3-fluoro-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4H-1,3,4-oxadiazin-5(6H)-one,
2-[3-fluoro-4-(2-methoxyethoxy)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-{{(1H-pyrazol-3-yl)methyl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
1-[4-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-2-(trifluoromethyl)phenyl]piperidine-4-carbonitrile,
2-[4-[(3S)-3-hydroxypiperidin-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(3-azabicyclo[3.1.0]hexan-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(4-ethyl-4-hydroxypiperidin-1-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-{{[1-(hydroxymethyl)cyclobutyl]methyl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-{{(pyrazin-2-yl)methyl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(3R)-3-hydroxy-3-methylpyrrolidin-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2S)-2-(hydroxymethyl)azetidin-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(3S)-3-hydroxy-3-methylpyrrolidin-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-{{(2S)-1-hydroxybutan-2-yl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[3-hydroxy-3-(propan-2-yl)azetidin-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-{{(2R)-1-hydroxybutan-2-yl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(2R)-2-(hydroxymethyl)azetidin-1-yl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-{{(1S)-2,3-dihydro-1H-inden-1-yl}amino}-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(morpholin-4-yl)methyl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(dimethylamino)methyl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(piperidin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
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2-[6-(3-azabicyclo[3.1.0]hexan-3-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-(cyclopentylamino)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-[(2-methoxyethyl)amino]-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-[(1H-pyrazol-3-yl)methyl]amino]-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[5-(trifluoromethyl)-6-[3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-(3,3-difluoroazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
1-[5-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-3-(trifluoromethyl)pyridin-2-yl]piperidine-4-carbonitrile,
2-[6-(4,4-difluoropiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[6-(2-azaspiro[3.3]heptan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]-4H-1,3,4-oxadiazin-5(6H)-one,
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2-[4-[(2S)-oxolan-2-yl]methoxy]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-butoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(cyclopropyloxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-[(oxetan-3-yl)oxy]-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
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2-[4-ethoxy-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(2,2-difluoroethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-cyclopropyl-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
2-(3-fluoro-4-[(2S)-oxolan-2-yl]methoxy)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
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2-(3-fluoro-4-propoxyphenyl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-(4-cyclopropyl-3-fluorophenyl)-4H-1,3,4-oxadiazin-5(6H)-one,
2-[4-(2,5-dihydro-1H-pyrrol-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one—hydrogen chloride (1/1),
2-[4-(3-methoxypropyl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,

2-[3-fluoro-4-(3-methoxypropyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(2-methylpropyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(1-methylpiperidin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(2-methoxyethoxy)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[4-(4,4-difluoropiperidin-1-yl)-3,5-difluorophenyl]-4H-1,3,4-oxadiazin-5(6H)-one,
 2-[3-fluoro-4-(morpholin-4-yl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one, and
 2-[4-(morpholin-4-yl)-3-(trifluoromethyl)phenyl]-4H-1,3,4-oxadiazin-5(6H)-one

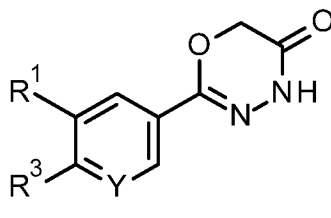
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

9. A method of preparing a compound of general formula (I) according to any one of
 5 claims 1 to 8, said method comprising the step of allowing an intermediate compound of general formula (IV) :



in which R¹, R³, and Y are as defined for the compound of general formula (I) according to any of the claims 1-8,

- 10 to react in
 with sodium bicarbonate, in DMF, at a temperature range of about 50 °C – 100 °C,
 thereby giving a compound of general formula (I)



- 15 in which R¹, Y, and R³ are as defined according to anyone of claims 1-8.

10. A pharmaceutical composition comprising a compound of general formula (I) according to any one of claims 1 to 8 and one or more pharmaceutically acceptable excipients.

5

11. A pharmaceutical combination comprising:

- one or more first active ingredients, in particular compounds of general formula (I) according to any one of claims 1 to 8, and
- one or more further active ingredients, in particular anti-cancer agents.

10

12. Use of a compound of general formula (I) according to any one of claims 1-8 for the preparation of a pharmaceutical composition according to claim 10 or 11.

13. Use of a compound of general formula (I) according to any one of claims 1 to 8 for the treatment or prophylaxis of a disease.

15

14. Use of a compound of general formula (I) according to any one of claims 1 to 8 for the preparation of a medicament for the treatment or prophylaxis of a disease.

15. Use according to claim 13 or 14, wherein the disease is a hyperproliferative disease.

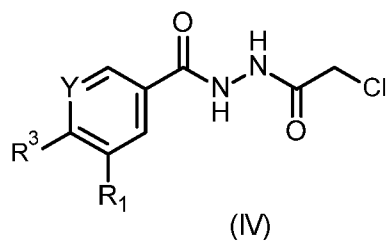
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16. Use according to claim 15, wherein the hyperproliferative disease is a cancer disease.

17. Use according to claim 16, wherein the cancer disease is cervix cancer or melanoma.

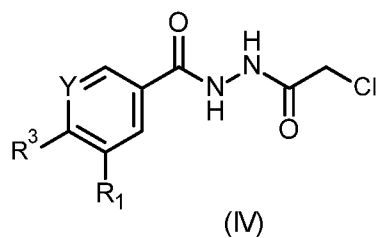
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18. A compound of general formula (IV):



in which R^1 , Y and R^3 are as defined for the compound of general formula (I) according to any of the claims 1-8.

- 5 19. Use of intermediate compound Use of a compound of general formula (IV)



in which R^1 , Y and R^3 are as defined for the compound of general formula (I) according to any one of claims 1 to 8,

for the preparation of a compound of general formula (I) according to any one of claims

- 10 1 to 8.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/052295

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D211/36 A61K31/5395 C07D273/04 C07D295/14 C07D413/10
C07D413/12 A61P35/00

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 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANDUVINAHALLI DEVANNA GURUPADASWAMY ET AL: "Synthesis of Pyrimidones and Evaluation of Their Xanthine Oxidase Inhibitory and Antioxidant Activities : X0 Inhibitory and Antioxidant Activities of Pyrimidone Analogs", ARCHIV DER PHARMAZIE, vol. 346, no. 11, 20 September 2013 (2013-09-20), pages 805-811, XP055678001, Weinheim ISSN: 0365-6233, DOI: 10.1002/ardp.201300240 example 3e ----- -/--	18

☒ 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

23 March 2020

Date of mailing of the international search report

02/04/2020

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Authorized officer

Fazzi, Raffaella

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/052295

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/139966 A1 (OSLO UNIVERSITY HOSPITAL HF [NO]; HOLSWORTH DAN [US] ET AL.) 9 December 2010 (2010-12-09) page 91; example 15 -----	18
X	CAO S ET AL: "Syntheses and insecticidal activity of new 2-(5-(trifluoromethyl)pyridyloxymethyl)-1,3,4-oxadiazoles", JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER, NL, vol. 117, no. 1, 28 September 2002 (2002-09-28), pages 63-66, XP004382392, ISSN: 0022-1139, DOI: 10.1016/S0022-1139(02)00172-0 page 64 -----	18
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Information on patent family members

International application No

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