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(71) Applicants: **BAYER AKTIENGESELLSCHAFT** [DE/DE]; Kaiser-Wilhelm-Allee 1, 51373 Leverkusen (DE). **THE BROAD INSTITUTE, INC.** [US/US]; 415 Main Street, Cambridge, Massachusetts 02142 (US).

(72) Inventors: **ELLERMANN, Manuel**; Linienstr. 103, 10115 Berlin (DE). **KOPITZ, Charlotte, Christine**; Ringstr. 33, 14612 Falkensee (DE). **LANGE, Martin**; Reiherallee 77a, 13503 Berlin (DE). **TERSTEEGEN, Adrian**; Rübezahlweg 8, 42111 Wuppertal (DE). **LIENAU, Philip**; Jahnstr. 13, 10967 Berlin (DE). **LEWIS, Timothy, A.**; c/o The Broad Institute, Inc 415 Main Street, Cambridge, MA 02142 (US). **GREULICH, Heidi**; c/o The Broad Institute, Inc 415 Main Street, Cambridge, MA 02142 (US). **WU, Xiaoyun**; c/o The Broad Institute, Inc, Cambridge, MA 02142 (US).

(74) Agent: **BIP PATENTS**; Alfred-Nobel-Str. 10, 40789 Monheim am Rhein NRW (DE).

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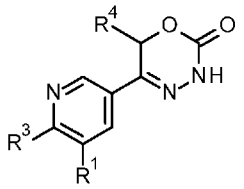
(54) Title: PYRIDYL SUBSTITUTED DIHYDROOXADIAZINONES



(I)

(57) Abstract: The present invention includes name compounds of general formula (I) : in which R^1, R^3 and R^4 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 diseases, as a sole agent or in combination with other active ingredients.

PYRIDYL SUBSTITUTED DIHYDROOXADIAZINONES

The present invention includes oxadiazinone compounds of general formula (I) as described and defined herein, a method of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions, combinations and the use of said compounds for the treatment or prophylaxis of diseases.

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 and/or PDE3B inhibitors which cause drug sensitivity have been found to stabilze the formation of a complex between PDE3A and/or PDE3B and SLFN12. PDE3A and/or PDE3B inhibitors which do not cause inhibition of tumor cell proliferation typically do not stabilize the PDE3A- and/or PDE3B–SLFN12 complex.

Some pyridyl substituted dihydooxydiazinone derivatives are known, especially in the context of treatment of cardiovascular diseases e.g. US4847251, US4489073, Journal of Heterocyclic Chemistry (1964), 1(4), 178-81; from EP0085227 some dihydrooxazinone compounds are known having cardiotonic or hypertensive activity.

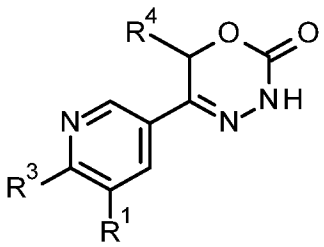
SUMMARY

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.

In particular, the compounds of the present invention have surprisingly been found to inhibit tumor cell proliferation with IC_{50} 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 IC_{50} values for enzymatic PDE3A and/or PDE3B inhibition may be > 10 times higher than IC_{50} 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 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- and/or PDE3B-SLFN12 complex, methods for their preparation, pharmaceutical composition and the use thereof and methods of 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 formula (I):



,

formula (I)

wherein

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

R^3 is

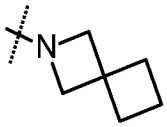
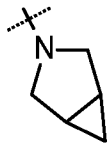
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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

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

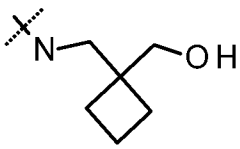
a  group, a  group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, is excluded,

a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group,

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

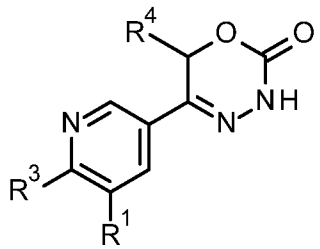
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 furter aspect, the present invention includes compounds of general formula (I):



formula (I)

wherein

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

R^3 is

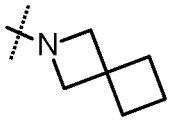
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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

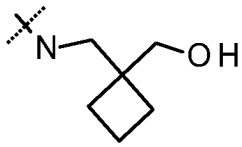
a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a  group, a group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group,

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 for use in the prophylaxis and treatment of hyperproliferative diseases, particularly cancer.

DETAILED DESCRIPTION

DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

Structures drawn include all permissible rotations about bonds.

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

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

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

The term “comprising” when used in the specification includes “consisting of” but does not have to be 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 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 “C_1-C_6-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-, 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-, group, or an isomer thereof. More particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-alkyl-"), *e.g.,* a methyl-, ethyl-, *n*-propyl-, *iso*-propyl-, *n*-butyl-, *iso*-butyl-, *sec*-butyl- or a *tert*-butyl- group, 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl-"), *e.g.,* a methyl-, ethyl-, *n*-propyl- or a *iso*-propyl group, or 1 or 2 carbon atoms ("C_1-C_2-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 "C_1-C_6-alkylene" moiety. All names as mentioned above then will bear an "ene" added to the end, thus *e.g.*, a "pentyl" becomes a bivalent "pentylene" group. In addition, the term "C_1-C_6-heteroalkyl" refers to a C_1-C_6-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 "C_1-C_6-hydroxyalkyl" means a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-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.

The term "C_1-C_6-haloalkyl" means a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-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 C_1-C_6-haloalkyl group is, 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 "C_1-C_6-alkoxy" means a linear or branched, saturated, monovalent group of formula (C_1-C_6-alkyl)-O-, in which the term "C_1-C_6-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 "C_1-C_6-haloalkoxy" means a linear or branched, saturated, monovalent C_1-C_6-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, with a halogen atom. Particularly, said halogen atom

is a fluorine atom. Said C_1-C_6-haloalkoxy group is, for example, a fluoromethoxy-, difluoromethoxy-, trifluoromethoxy-, 2,2,2-trifluoroethoxy- or a pentafluoroethoxy group.

The term "C_2-C_6-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 ("C_2-C_3-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-, (*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-, (*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-, (*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-, (*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. 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 "C_1-C_6-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 "C_3-C_6-cycloalkyl-" means a saturated monocyclic or bicyclic hydrocarbon ring which contains 3, 4, 5, or 6, carbon atoms ("C_3-C_6-cycloalkyl-"). Said C_3-C_6-cycloalkyl-group may be, for example, a monocyclic hydrocarbon ring, such as, for example, a cyclopropyl-, cyclobutyl-, cyclopentyl-, or a cyclohexyl- ring,. Particularly, said hydrocarbon ring is monocyclic and contains 4, 5, or 6 carbon atoms ("C_4-C_6-cycloalkyl-"), such as, for example, a cyclopropyl-, cyclobutyl-, 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 "C_4-C_6-cycloalkenyl" means a monovalent, mono- or bicyclic hydrocarbon ring which contains 4, 5, or 6, carbon atoms and one double bond. Particularly, said ring contains 5 or 6 carbon atoms ("C_5-C_6-cycloalkenyl"). Said C_4-C_6-cycloalkenyl group is for example, a monocyclic hydrocarbon ring, such as , for example, a cyclobutenyl-, cyclopentenyl-, or a cyclohexenyl- group,

The term "4- to 6-membered heterocycloalkyl" means a monocyclic, saturated or partially unsaturated heterocycle with 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 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 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.

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 C_1-C_3-alkyl group, aC_1-C_3-haloalkyl group, a C_1-C_3-alkoxy group, a C_1-C_3-thioalkyl group, a C_1-C_3-haloalkoxy group, a C_1-C_3-halothioalkyl group, a C_3-C_5-cycloalkyl group, particularly a halogen atom, a C_1-C_3-alkyl group, a C_1-C_3-haloalkyl group, a C_1-C_3-alkoxy group, and a C_1-C_3-haloalkoxy group.

The term "heteroaryl" means a monovalent, monocyclic, bicyclic or tricyclic aromatic ring having 5, 6, 9 or 10 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, indolizinyl-, 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-, indolizinyl- 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 "C_1-C_6", as used throughout this text, *e.g.,* in the context of the definition of "C_1-C_6-alkyl-", "C_1-C_6-haloalkyl-", "C_1-C_6-alkoxy-" or "C_1-C_6-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 "C_1-C_6" is to be interpreted as disclosing any sub-range comprised therein, *e.g.* C_1-C_6, C_2-C_5, C_3-C_4, C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; particularly C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; more particularly C_1-C_4; in the case of "C_1-C_6-haloalkyl-" or "C_1-C_6-haloalkoxy-" even more particularly C_1-C_2.

Similarly, as used herein, the term "C_2-C_6", as used throughout this text, *e.g.,* in the context of the definitions of "C_2-C_6-alkenyl-" and "C_2-C_6-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 "C_2-C_6" is to be interpreted as disclosing any sub-range comprised therein, *e.g.,* C_2-C_6, C_3-C_5, C_3-C_4, C_2-C_3, C_2-C_4, C_2-C_5; particularly C_2-C_3.

Further, as used herein, the term "C_3-C_7", as used throughout this text, *e.g.,* in the context of the definition of "C_3-C_7-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 "C_3-C_7" is to be interpreted as disclosing any sub-range comprised therein, *e.g.,* C_3-C_6, C_4-C_5, C_3-C_5, C_3-C_4, C_4-C_6, C_5-C_7; particularly C_3-C_6.

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 descibed 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 tetrahydropyranoyl 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 tetrahydropyranoyl 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.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H

(deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and ^{131}I, respectively.

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

Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, particularly for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds (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 Patent 3966781). A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA. 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 P_{450}.

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

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

In order to distinguish different types of 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.* (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. 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 :

2H tautomer 1H tautomer

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

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

The present invention also 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.

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

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

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

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, or “mineral acid”, such as hydrochloric,

hydrobromic, hydroiodic, sulfuric, sulfamic, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as hydrochloric acid, hydrobromic acid, hydroiodic 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 acid, pamoic 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, methansulfonic acid, 2-naphthalenesulfonic acid, naphthalenedisulfonic acid, camphorsulfonic acid acid, citric acid, tartaric acid, stearic 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 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 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, 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.

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 alkyliodides;*e.g.* methyliodide, ethyliodide, propyliodide and butyliodide; dialkylsulfates such as dimethylsulfate, diethylsulfate, dibutylsulfate and diamylsulfates, long chain halides such as *e.g.* decylchloride, laurylchloride, myristylchloride and stearylchloride, decylbromide, laurylbromide, myristylbromide and stearylbromide, decyliodide, lauryliodide, myristyliodide and stearyliodide, aralkylhalides such as benzylchloride, benzylbromide, benzyliodide 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 inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the present invention are prepared by reacting the compounds of the present invention with the appropriate base via a variety of known methods.

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

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

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

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

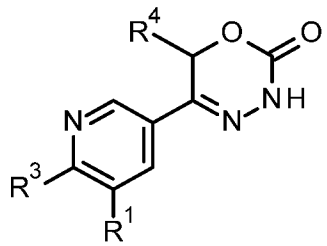
Solvates and hydrates of disclosed intermediates or example compounds, or salts thereof, which have been obtained, by the preparation and/or purification processes described herein, may be formed in any ratio.

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 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 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 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)

in which:

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

R^3 is

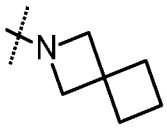
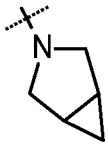
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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

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

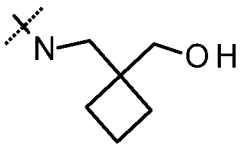
a  group, a  group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, is excluded,

a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

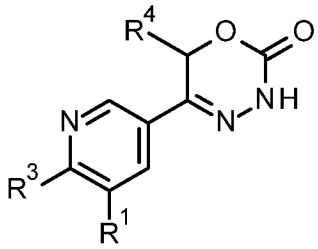
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 an embodiment of the first aspect the present invention includes compounds of general formula (I), *supra*,



formula (I)

in which:

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

R^3 is

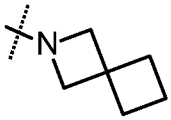
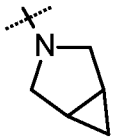
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group; with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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

a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

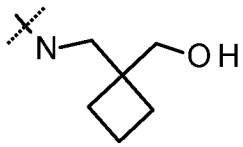
a  group, a  group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

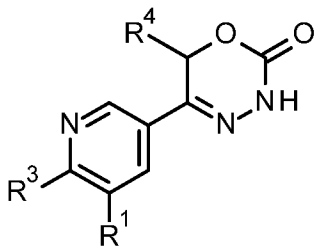
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 an embodiment of the first aspect the present invention includes compounds of general formula (I), *supra*,



formula (I)

in which:

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

R^3 is

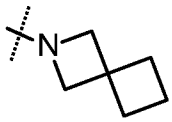
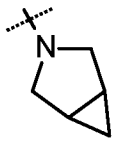
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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

a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

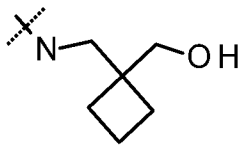
a  group, a  group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

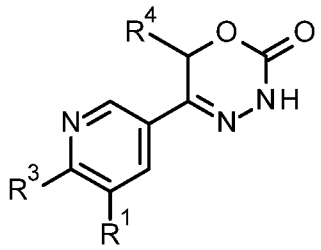
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 an embodiment of the first aspect the present invention includes compounds of general formula (I), *supra*,



formula (I)

in which:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

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,

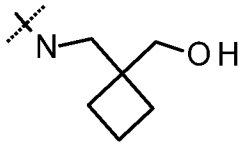
a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, an imidazolyl group is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

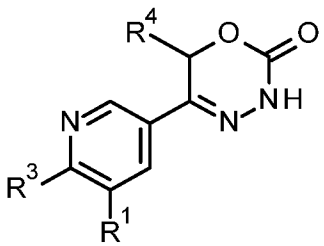
a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 an embodiment of the first aspect the present invention includes compounds of general formula (I), *supra*,



,

formula (I)

in which:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

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,

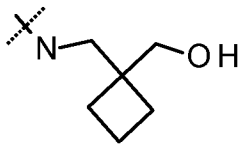
a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

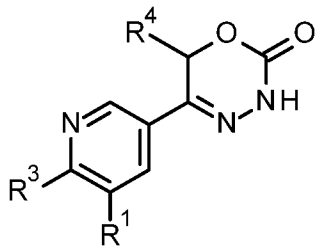
a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 an embodiment of the first aspect the present invention includes compounds of general formula (I), *supra*,



formula (I)

in which:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group;

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,

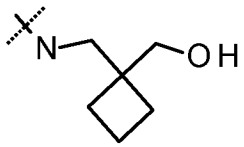
a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

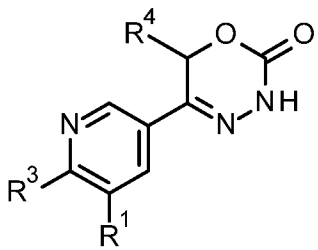
a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 an embodiment of the first aspect the present invention includes compounds of general formula (I), *supra*,



formula (I)

in which:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

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,

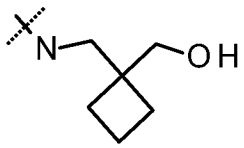
a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, R^3= an imidazolyl group is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

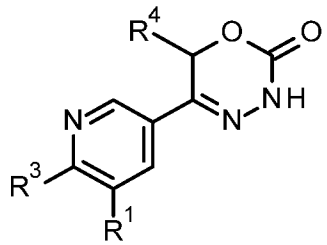
a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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 an embodiment of the first aspect the present invention includes compounds of general formula (I), *supra*,



formula (I)

in which:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group,

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,

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

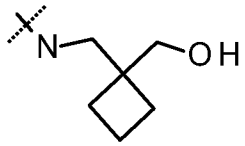
a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a

C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

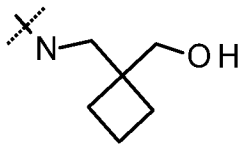
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice

with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

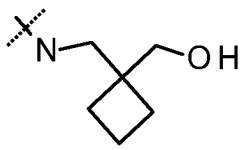
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group,

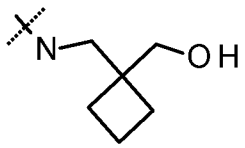
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a

hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

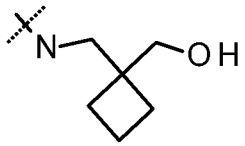
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

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,

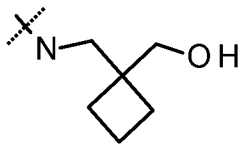
a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group;

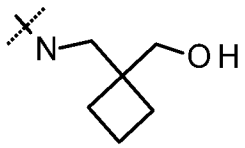
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

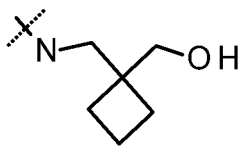
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl groupis excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group with the proviso that R^3 is not methyl if R^1 and R^4 are hydrogen;

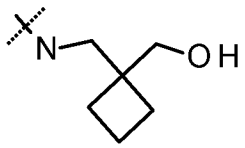
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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

a 5- to10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

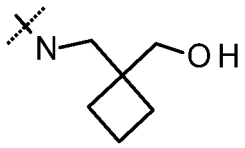
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

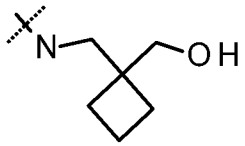
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

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,

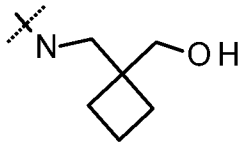
a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a

C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

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,

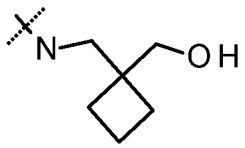
a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

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,

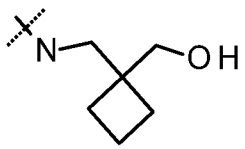
a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

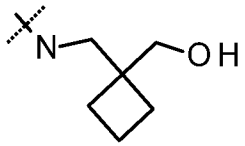
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

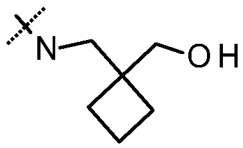
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group is excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

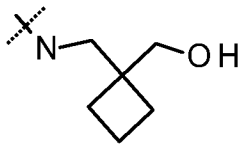
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

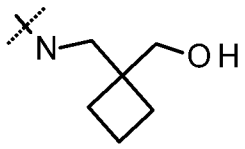
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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

a 5- to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

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, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, a hydroxy 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.

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

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

R^3 is a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, a hydroxy 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.

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

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

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, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, a hydroxy 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.

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

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

R^3 is a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, a hydroxy 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.

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

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

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, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, a hydroxy 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.

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

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

R^3 is a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, a hydroxy 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.

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

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

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, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, and a hydroxy 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:

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

R^3 is a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, and a hydroxy 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:

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

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, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, and a hydroxy 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:

R^1 is a trifluormethyl group;

R^2 is; a hydrogen atom

R^3 is a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, and a hydroxy 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 yet another embodiment of the first aspect, the present invention includes compounds of general formula (I), selected from

5-[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[(2-methoxyethyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(morpholin-4-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,,

5-{6-[ethyl(methyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(ethylamino)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one and

5-{6-[(2-hydroxy-2-methylpropyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-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 accordance with a further embodiment of the first aspect, the present invention includes compounds of general formula (I), selected from

6-methyl-5-[6-(piperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3-hydroxypiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[(dimethylamino)methyl]-5-(trifluoromethyl)pyridin-3-yl}-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-isobutyl-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3-methoxypropyl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3-fluoro-4-methylphenyl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(4-chlorophenyl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(cyclopent-1-en-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(4-ethyl-4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-{6-[(pyrazin-2-ylmethyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(4,4-difluoropiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3,3-dimethylbutoxy)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[6-propoxy-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3-fluoro-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[6-(morpholin-4-ylmethyl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[3-(trifluoromethyl)[2,4'-bipyridin]-5-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-({[1-(hydroxymethyl)cyclobutyl]methyl}amino)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3-azabicyclo[3.1.0]hexan-3-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(2-hydroxypropoxy)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(2-hydroxy-2-methylpropoxy)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-{6-[(1H-pyrazol-3-ylmethyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[1-(difluoromethyl)-1H-pyrazol-4-yl]-5-(trifluoromethyl)pyridin-3-yl}-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-{5-(trifluoromethyl)-6-[3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[2'-amino-3-(trifluoromethyl)[2,4'-bipyridin]-5-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[4-fluoro-2-(trifluoromethyl)phenyl]pyridin-3-yl}-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(4-fluoro-2-methylphenyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(4-fluorophenyl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[6-(1H-pyrazol-3-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(3-hydroxy-3-methylpyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[(E)-2-ethoxyvinyl]-5-(trifluoromethyl)pyridin-3-yl}-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[(1E)-3-methoxyprop-1-en-1-yl]-5-(trifluoromethyl)pyridin-3-yl}-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[6-(2-methylprop-1-en-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-butoxy-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-{5-(trifluoromethyl)-6-[4-(trifluoromethyl)-2H-1,2,3-triazol-2-yl]pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[6-(morpholin-4-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-{6-[(3,3,3-trifluoro-2-hydroxypropyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[5'-chloro-3-(trifluoromethyl)[2,2'-bipyridin]-5-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[5-(trifluoromethyl)-6-(3,3,3-trifluoropropoxy)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(2-azaspiro[3.3]heptan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[(2-methoxyethyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

6-methyl-5-[6-(tetrahydrofuran-2-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(cyclobutylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(2-methoxyethoxy)-5-(trifluoromethyl)pyridin-3-yl]-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one and

6-methyl-5-[6-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-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:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice 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.

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, a C_1-C_3-haloalkyl group;

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 is hydrogen;

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, a C_1-C_3-haloalkyl group;

R^3 is a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-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:

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

R^3 is a C_5-C_6-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:

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

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 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, a C_1-C_3-haloalkyl group;

R^3 is a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and 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.

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

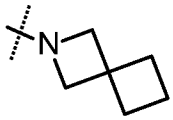
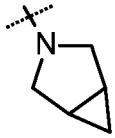
R^1 is a hydrogen atom, a halogen atom, a C_1-C_3-alkyl group, a C_1-C_3-haloalkyl group;

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, and 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.

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, a C_1-C_3-haloalkyl group;

R^3 is a  group or 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 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, a C_1-C_3-haloalkyl group;

R^3 is a 5- to 10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl 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:

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

R^3 is 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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl 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:

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

R^3 is a NR^5R^6 group,

R^5 is a hydrogen atom or a C_1-C_3-alkyl group; and

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5 to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a

hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

R^1 is a trifluoromethyl group

R^3 is a phenyl group which is substituted one or more times with a group selected from halogen atom, a C_1-C_3-alkyl group, a C_1-C_3-haloalkyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a phenyl group which is substituted one or more times with a group selected from fluorine atom, a chlorine atom, a methyl group, a trifluoromethyl group and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a C_1-C_6-alkyl group, or a C_1-C_3-alkyl group which is optionally subtituted one or more times with a group selected from a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and a NR^5R^6 group, and

R^4 is a methyl group;

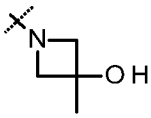
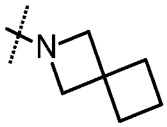
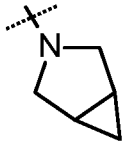
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^1 is a trifluoromethyl group

R^3 is

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

a  group, a  group, or a  group, and

R^4 is a methyl group;

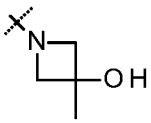
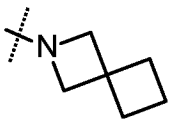
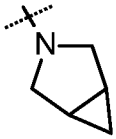
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^1 is a trifluoromethyl group

R^3 is

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

a  group, a  group, or a  group, and

R^4 is a methyl group;

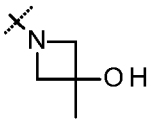
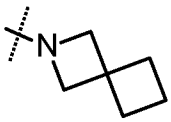
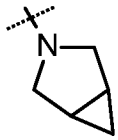
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^1 is a trifluoromethyl group

R^3 is

a 5- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group;

a  group, a  group, or a  group, and

R^4 is a methyl group;

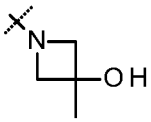
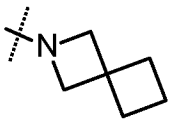
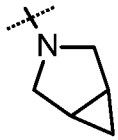
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^1 is a trifluoromethyl group

R^3 is

a 5-membered heterocycloalkyl group which is optionally substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group;

a  group, a  group, or a  group, and

R^4 is a methyl group;

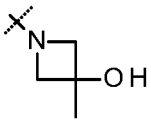
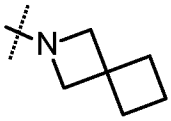
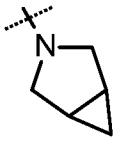
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^1 is a trifluoromethyl group

R^3 is

a 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group;

a  group, a  group, or a  group, and

R^4 is a methyl group;

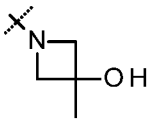
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^1 is a trifluoromethyl group

R^3 is

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

a  group, and

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is 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 trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is 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 trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5- to 6-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 trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5- to 6-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 trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5- to 6-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5- to 6-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5-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 trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5-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 trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 6-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 trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 6-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 trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 6-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 6-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5- to 10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a 5- to 10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, a R^3 is not an imodazolyl group, a pyridyl group and a furanyl group

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group, and

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

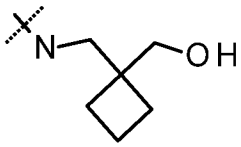
R^3 is a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 5- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group, and

R^4 is a methyl 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:

R^1 is a trifluoromethyl group

R^3 is a NR^5R^6 group, or a 

group,

R^4 is a methyl group;

R^5 is a hydrogen atom

R^6 is selected from

a C_1-C_3-alkyl group which is optionally substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

R^1 is a trifluoromethyl group

R^3 is a NR^5R^6 group,

R^4 is a methyl group;

R^5 is a hydrogen atom

R^6 is selected from

a C_1-C_3-alkyl group which is optionally substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

R^1 is a trifluoromethyl group

R^3 is a NR^5R^6 group,

R^4 is a methyl group;

R^5 is a hydrogen atom

R^6 is selected from

a C_1-C_3-alkyl group which is optionally substituted one or more times with a group selected from a C_1-C_3-alkoxy group and a hydroxy 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:

R^1 is a trifluoromethyl group

R^3 is a NR^5R^6 group,

R^4 is a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group

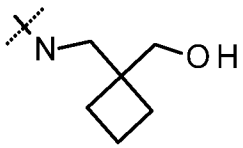
R^6 is selected from

a C_1-C_3-alkyl group which is optionally substituted one or more times with a group selected from a C_1-C_3-alkoxy group and a hydroxy 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:

R^1 is a trifluoromethyl group

R^3 is a  group,

R^4 is a methyl 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:

R^1 is a hydrogen atom, a halogen atom, a C_1-C_3-alkyl group, 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.

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 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:

R^1 is 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.

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

R^1 is a trifluormethyl 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:

R^3 is

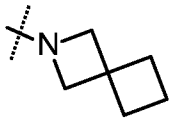
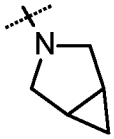
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that if R^4 and R^1 are hydrogen R^3 is not methyl;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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

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

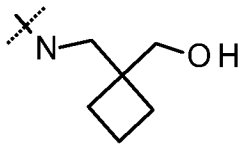
a  group, a  group,

a 5- to 10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are excluded,

a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group,

a NR^5R^6 group, and

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

R^3 is

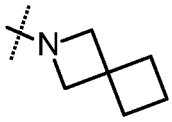
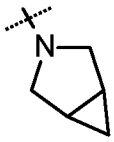
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that if R^4 and R^1 are hydrogen R^3 is not methyl;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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

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

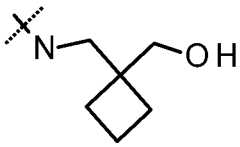
a  group, a  group,

a 5- to 10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,

with the proviso that if R^1 is a hydrogen atom, R^3 = an imidazolyl group, is excluded,

a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group,

a NR^5R^6 group, and

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

R^3 is a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl 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.

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

R^3 is a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy 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.

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

R^3 is 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:

R^3 is 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:

R^3 is a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl 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.

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

R^3 is a $-(CH_2)_3-O-CH_3$ group, a $–CH_2$-(morpholin-4-yl) group, a $-CH_2-N(CH_3)_2$ 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:

R^3 is a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-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:

R^3 is a phenyl group which is substituted one or more times with a group selected from a halogen atom, 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.

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:

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.

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.

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.

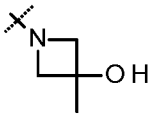
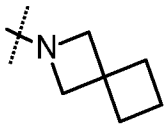
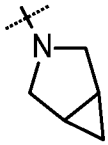
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

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

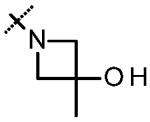
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^3 is a 4- to 6-membered heterocycloalkyl group which is substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a  group, a  group, 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.

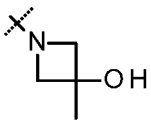
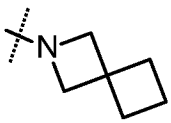
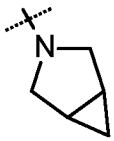
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^3 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.

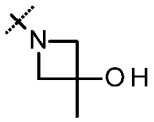
In a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^3 is a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

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

R^3 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 a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^3 is a 5- to 10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, a imidazolyl group, a pyridyl group and a furanyl group are 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:

R^3 is a 5- to 10-membered heteroaryl group which is substituted one or more times with a group selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group,
with the proviso that if R^1 is a hydrogen atom, R^3= an imidazolyl 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 the use of compounds of formula (I), *supra*, in which:

R^3 is an imidazolyl group, a pyridyl group and a furanyl 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 the treatment of hyperproliferative diseases, particularly cancer.

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

R^3 is a methyl group, an imidazolyl group, a pyridyl group and a furanyl 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 the treatment of hyperproliferative diseases, particularly cancer.

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

R^3 is a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5 to 6-membered heteroaryl 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:

R^3 is a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5 to 6-membered heteroaryl 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:

R^3 is a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy 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 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:

R^3 is a NR^5R^6 group, and

R^5 is a hydrogen atom;

R^6 is selected from

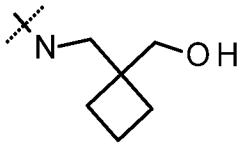
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-cycloalkyl group;

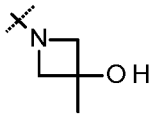
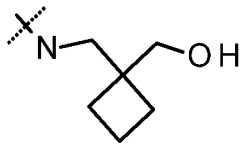
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a salt of a stereoisomer, a salt of a tautomer, a salt of an N-oxide or a mixture of same.

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

R^3 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 a further embodiment of the first aspect, the present invention includes compounds of formula (I), *supra*, in which:

R^3 is a $-(CH_2)_3-O-CH_3$ group, a $-CH_2$-(morpholin-4-yl) group, a $-CH_2-N(CH_3)_2$ group, a $-CH=C(CH_3)_2$ group, a $-CH=CH-CH_2-O-CH_3$ group, a $-CH=CH-CH_2-O-CH_2-CH_3$ group, a cyclopent-1-en-1-yl 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 3-hydroxy-piperidin-1-yl group, a 4,4-difluoro-piperidin-1-yl group, a 4-ethyl-4-hydroxy-piperidin-1-yl group, a  group, a 3-hydroxy-3-methyl-pyrrolidin-1-yl group, a 4-methyl-piperazin-1-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 $-NH-CH_2$-(pyrazol-3-yl) group, a $-NH-CH_2$-(pyrazol-5-yl) group, a $-NH-CH_2$-pyrazin-2-yl group, a $-NH-CH_2-CH(OH)CF_3$ group, a  group, a NH-cyclopentyl

group, a -O-$(CH_2)_2$-CH_3 group, a -O-$(CH_2)_2$-$C(CH_3)_3$ group, a -O-(CH_2)-$CH(CH_3)$-OH group, a -O-(CH_2)-$C(CH_3)_2$-OH group, a -O-CH_2-(pyrazol-3-yl) group, a -O-$(CH_2)_2$-O-CH_3 group, a -O-CH_2-cyclobutyl group, a -O-CH_2-tetrahydofuran-2-yl group, a -O-$(CH_2)_2$-CF_3 group, a -O-$(CH_2)_3CH_3$ 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:

R^3 is 3-hydroxy-3-methylazetidin-1-yl, (2-methoxyethyl)amino, morpholin-4-yl, ethyl(methyl)amino, ethylamino, and 2-hydroxy-2-methylpropyl)amino

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 3-hydroxy-3-methylazetidin-1-yl, (2-methoxyethyl)amino, ethyl(methyl)amino, ethylamino, and 2-hydroxy-2-methylpropyl)amino

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 trifluoromethyl group and

R^3 is 3-hydroxy-3-methylazetidin-1-yl, (2-methoxyethyl)amino, morpholin-4-yl, ethyl(methyl)amino, ethylamino, and 2-hydroxy-2-methylpropyl)amino

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 trifluoromethyl group and

R^3 is 3-hydroxy-3-methylazetidin-1-yl, (2-methoxyethyl)amino, morpholin-4-yl, ethyl(methyl)amino, ethylamino, and 2-hydroxy-2-methylpropyl)amino

and

R^4 is a hydrogen 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:

R^4 is a hydrogen atom or 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.

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

R^4 is a hydrogen 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:

R^4 is 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.

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

R^4 is a methyl 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:

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5 to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl 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:

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5 to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-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:

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a C_1-C_3-alkoxy group, and a hydroxy 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 **(I)**, 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

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.

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.

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

In further embodiments, the present invention includes compounds of formula **(I)**, which are a 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".

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*.

The present invention includes any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of general formula (IV) and (V).

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

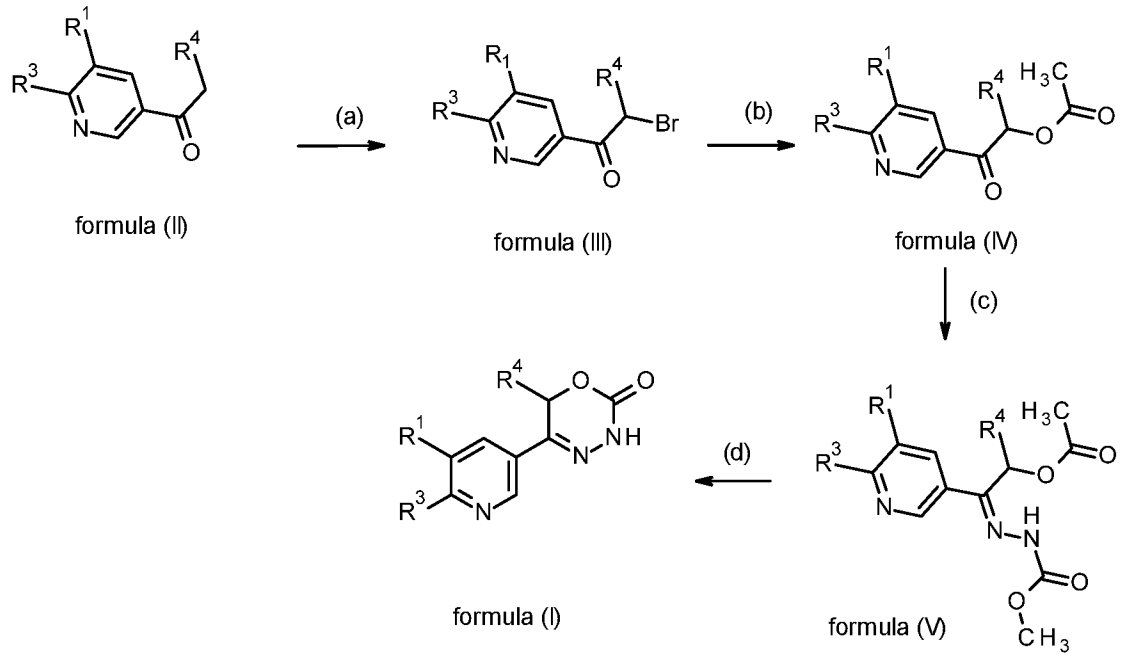
General synthesis of compounds of general formula (I)

A. General Synthesis Route

The compounds according to the invention of general formula (I) can be prepared according to the following schemes 1, 2, and 3. 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, and 3 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, R^2, R^3, or R^4 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.

Three routes for the preparation of compounds of general formula (I) are described in schemes 1, 2, 3, 4, and 5.

Route 1



Scheme 1

Scheme 1: Route for the preparation of compounds of general formula (I) from compounds of formulae (II), in which R^1, R^3 (potentially containing functional groups suitably protected), and R^4 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.

(a) acetic acid, bromine, hydrogen bromide, 18h, RT;

(b) potassium acetate, potassium iodide, 18h, RT;

(c) $H_2NNHCOOCH_3$, pTsOH, MeOH, RT, 5-18h;

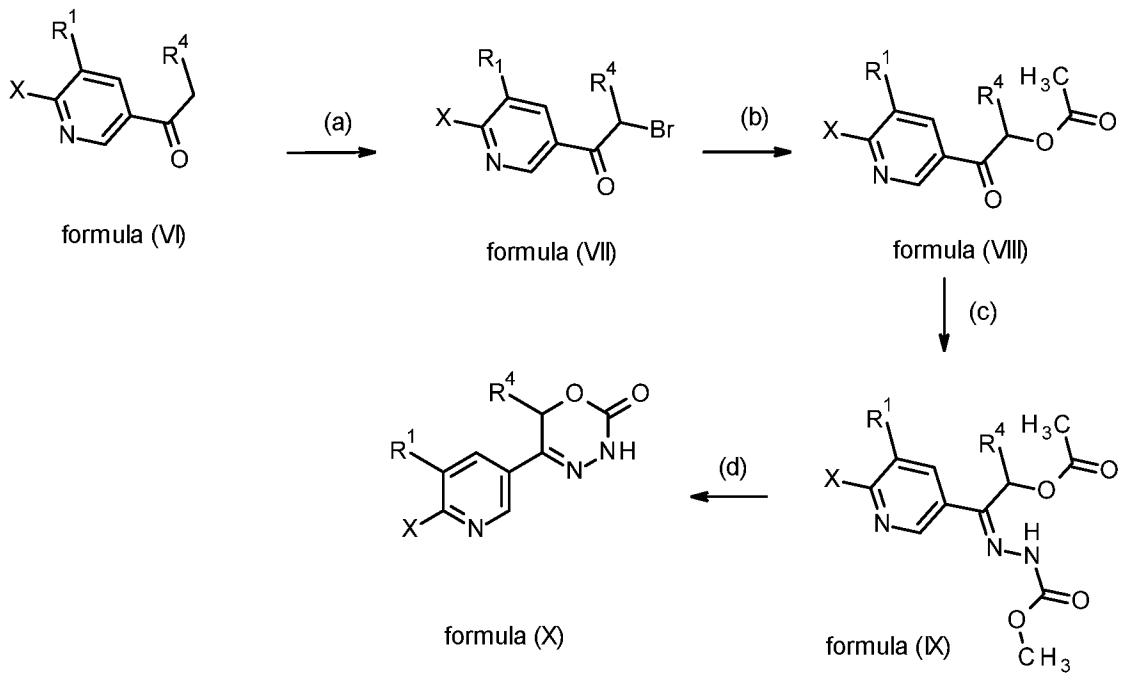
(d) NaH, EtOH, 0 °C, 4h, then aq. HCl;

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.

Compounds (II) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art.

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 (X)



Scheme 2

Scheme 2: Route for the preparation of intermediate compounds of formula (X), in which R^1 and R^4 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 (X).

(a) acetic acid, bromine, hydrogen bromide, 18h, RT;

(b) potassium acetate, potassium iodide, 18h, RT;

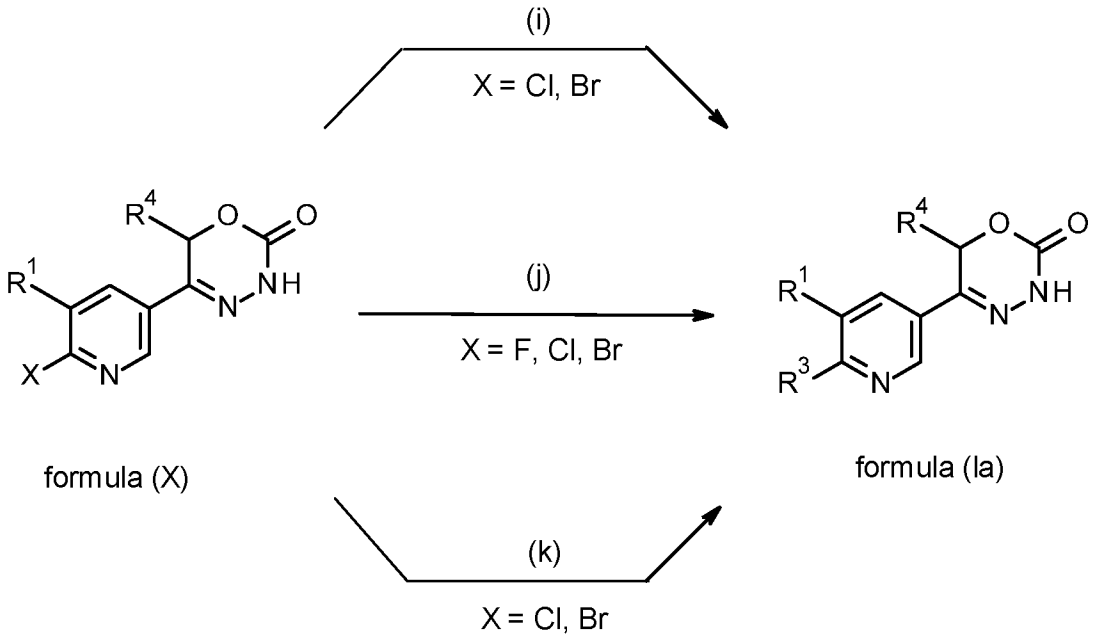
(c) $H_2NNHCOOCH_3$, pTsOH, MeOH, RT, 5-18h;

(d) NaH, EtOH, 0 °C, 4h, then aq. HCl ;

Compounds of formula (X) 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.

Compounds (II) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art.

<u>Part II: Conversion of the intermediate compounds of formula (X) into compounds of general formula (Ia):</u>



(**i**): R^3 = a substituted alkyl group, an optionally substituted alkenyl group, a cycloalkenyl group, a substituted phenyl group, or a substituted heteroaryl group,

(**j**), (**k**): R^3 = NR^5R^6, opt. subst. N-linked heterocycloalkyl, or subst. N-linked heteroaryl,

Scheme 3

Scheme 3: Route for the preparation of compounds of general formula (I) via formula (X) in which R^1 and R^4 have the meaning as defined *supra*, in which R^3 in general formula (Ia) is selected from a substituted methyl group, an optionally substituted alkenyl group, a cycloalkenyl group, a substituted phenyl group, and a substituted heteroaryl group as defined in more detail below in paragraph (i) for R^x; or R^3 is NR^5R^6, or an optionally substituted N-linked heterocycloalkyl group, or a substituted N-linked heteroaryl group, as defined in more detail below in paragraph (j) and (k), respectively; and in which the terms "N-linked heterocycloalkyl", and "N-linked heteroaryl" refer to a 4- to 6-membered 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, or heteroaryl group.

(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 (**XIa**), (**XIb**), and (**XIc**), can be obtained by reacting intermediate compounds of formula (X), in which

X is Cl, Br, (as reflected in scheme 3);

R^1 is as defined *supra* but different from Cl, Br, I, and

R^4 is as defined *supra*,

with boronic acids $R^xB(OH)_2$ (formula (**XIa**)), or boronic esters $R^xB(OR^y)_2$ (formula (**XIb**)), or tetrafluoroborate salts R^xBF_4 (formula (**XIc**)),

in the presence of

a base, such as potassium carbonate or potassium acetate,

a palladium catalyst, such as dichlorobis(triphenylphosphine)palladium, tetrakistriphenylphosphinepalladium(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 subtituted one or more times with a group selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and a NR^5R^6 group,
a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,
a C_5-C_6-cycloalkenyl group,
a phenyl group which is substituted one or more times with a group selcted from a fluorine atom, a chlorine atom, a methyl group, a trifluoromethyl group,
a 5- to10-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 trifluormethyl group, and a difluoromethyl group,
R^y is C_1-C_6-alkyl, or the two residues R^y together are a C_2-C_6-alkylene group, particularly $-C(CH_3)_2-C(CH_3)_2-$ 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 R^3 features a group comprising an olefinic double bond (*e.g.* if R^3 is alkenyl, cycloalkenyl or), can be readily converted into compounds in which R^3 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 R^3 substituents selected from -NR^5R^6, 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
R^3 is selected from -NR^5R^6, a N-linked 4- to 6-membered heterocycloalkyl group, a and 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 R^3, *supra*,

can be obtained by reacting intermediate compounds of formula (X), in which

R^1 and R^4 have the meaning as defined *supra*,

X is F, Cl, or Br (as reflected in scheme 3), particularly X is Cl;

with a corresponding amine, optionally as a free base or as a salt, such as a hydrochloride salt, selected from HNR^5R^6 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,

optionally in the presence of a base, such as triethylamine, DIPEA, potassium carbonate, or cesium carbonate, in an inert solvent, such as THF, CH_3CN, DMF or DMSO, at optionally elevated temperatures ranging from RT to 160 °C, particularly from 60°C to 150 °C, for 2h-7d;

whereby

R^5 is selected from H and a C_1-C_3-alkyl group, and

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group, and

a C_5-C_6-cycloalkyl group;

(k) Alternative Route *via* transition metal catalyzed, particularly palladium catalyzed amination, to introduce R^3 substituents selected from -NR^5R^6, 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 R^3 is selected from -NR^5R^6, 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 terms "4- to 6–membered heterocycloalkyl", and "heteroaryl" are constituted and optionally substituted as defined for R^3, *supra*,

can be obtained by reacting intermediate compounds of formula (X), in which

X is Cl or Br (as reflected in scheme 3);

R^1 is as defined *supra* but is different from Cl, Br; particularly, R^1 is $–CF_3$;

R^4 has the meaning as defined *supra*,

with a corresponding amine, optionally as a free base or as a salt, such as a hydrochloride salt, selected from HNR^5R^6 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,

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;

whereby

R^5 is selected from H and a C_1-C_3-alkyl group, and

R^6 is selected from

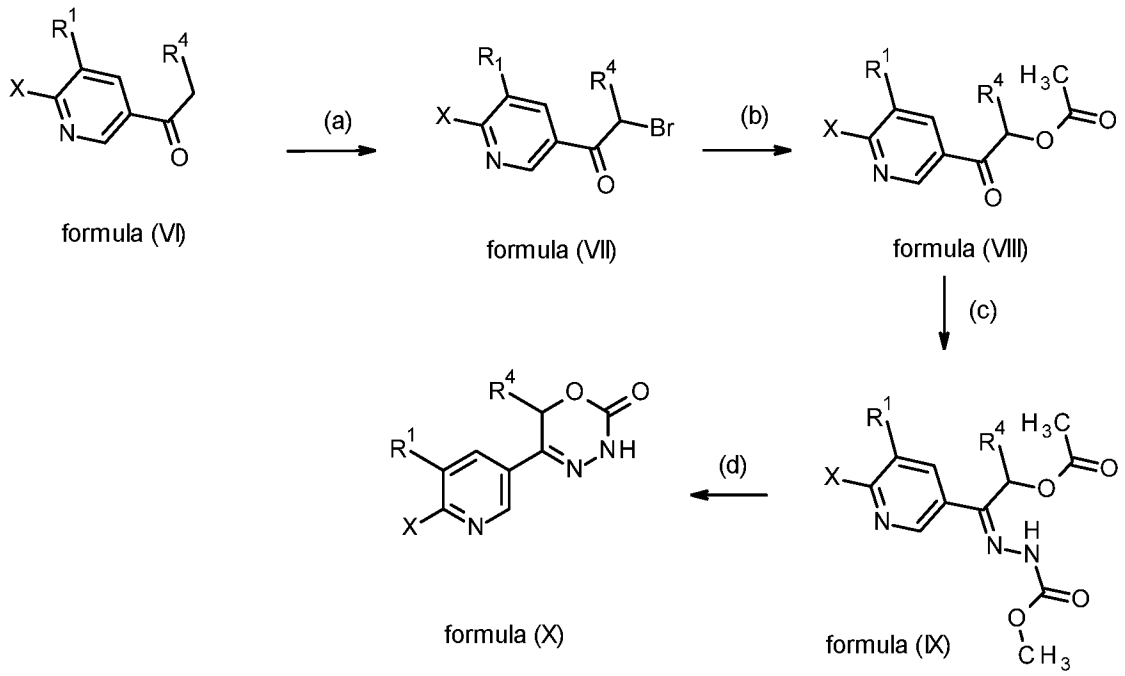
a C_1-C_3-alkyl group which is substituted one or more times with a group selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group, and

a C_5-C_6-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), compounds of general formula (Ib) wherein R^3 is an optionally substituted alkoxy group

Part I: Synthesis of intermediate compounds of formula (X)



Scheme 4

Scheme 4: Route for the preparation of intermediate compounds of formula (X), in which R^1 and R^4 have the meaning as defined *supra*; the meaning of X is as defined below in context of Scheme 5 and the paragraphs **(m)** and **(n)** for compounds of formula (X).

(a) acetic acid, bromine, hydrogen bromide, 18h, RT;

(b) potassium acetate, potassium iodide, 18h, RT;

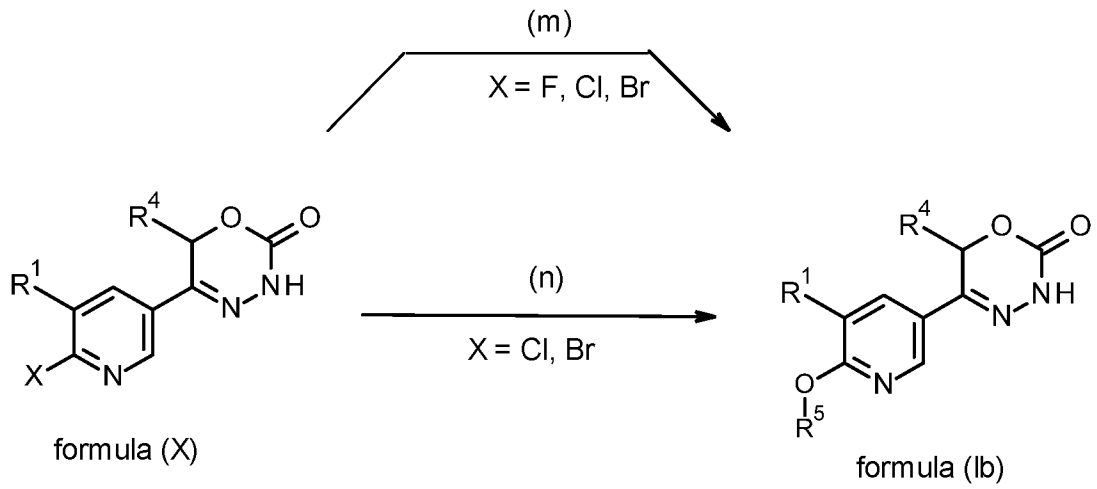
(c) $H_2NNHCOOCH_3$, pTsOH, MeOH, RT, 5-18h;

(d) NaH, EtOH, 0 °C, 4h, then aq. HCl ;

Compounds of formula (X) 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.

Compounds (II) are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art.

Part II: Conversion of the intermediate compounds of formula (X) into compounds of general formula (Ib):



R^5 = 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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group.

Scheme 5

Scheme 5: Route for the preparation of compounds of general formula (Ib) via formula (X) in which R^1 and R^4 have the meaning as defined *supra*, in which R^5 in general formula (Ib) is a C_1-C_6-alkoxy group which is optionally substituted with a group selected from C_1-C_3-haloalkyl group, a hydroxy group, a C_1-C_3-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group.

(m) Route 3 *via* nucleophilic aromatic substitution to introduce R^3 substituents, wherein R^3 is an optionally substituted alkoxy group

Compounds of general formula (Ib), can be obtained by reacting intermediate compounds of formula (X), in which

R^1 and R^4 have the meaning as defined *supra*,

X is F, Cl, or Br (as reflected in scheme 3), particularly X is Cl;

with a corresponding alcohol R^5-OH, optionally as the alcohol or as an alkoxide salt, such as a sodium or potassium salt,

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 60°C to 150 °C, for 2h-7d;

whereby

R^5 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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group.

(n) Alternative Route *via* transition metal catalyzed, particularly palladium catalyzed amination, to introduce R^3 substituents, wherein R^3 is an optionally substituted alkoxy group

Compounds of general formula (Ib), can be obtained by reacting intermediate compounds of formula (X), in which

X is Cl or Br (as reflected in scheme 5);

R^1 is as defined *supra* but is different from Cl, Br; particularly, R^1 is $-CF_3$;

R^4 has the meaning as defined *supra*,

with a corresponding alcohol R^5-OH,

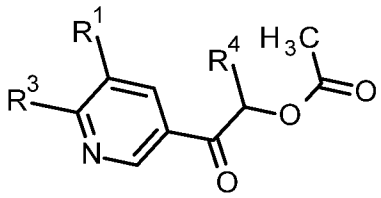
in the presence of a base, such as potassium phosphate or cesium carbonate, a palladium catalyst, such as [(2-Di-*tert*-butylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate or [(2-Di-*tert*-butylphosphino-3-methoxy-6-methyl-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2-aminobiphenyl)]palladium(II) methanesulfonate, optionally a ligand, such as 2-Di(tert-butyl)phosphino-2′,4′,6′-triisopropyl-3-methoxy-6-methylbiphenyl or 2-(Di-*tert*-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

R^5 = 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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group.

The thus obtained compounds of formula (I) containing chiral centers can be optionally separated by chiral chromatography to obtain individual enantiomers or diastereomers.

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) :



formula (IV) ,

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) as defined *supra* or anyone of claims 1-8,

to react in a first step

with $H_2NNHCOOCH_3$,

wherein the reaction occurs under the following conditions:

acidic conditions (e.g. para-toluenesulfonic acid)

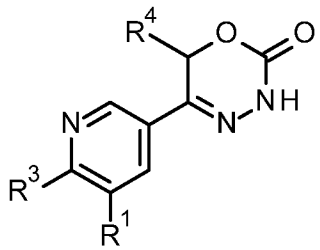
in an alcoholic solution e.g. in methanol,

at room temperature

and

in a second step reacting the product of the first step with sodiumhydride in alcoholic solution e.g. in ethanol at about 0°C and optionally acidic workup e.g. with aueous hydrochloric acid

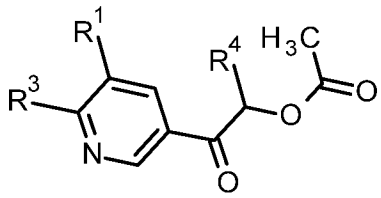
thereby giving a compound of general formula (I)



,

in which R^1, R^2, R^3 and R^4 are as defined *supra*.

In accordance with a third 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 (V) :



formula (IV) ,

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) as defined *supra* or anyone of claims 1-8,

to react in a first step

with $H_2NNHCOOCH_3$,

wherein the reaction occurs under the following conditions:

acidic conditions (e.g. para-toluenesulfonic acid)

in an alcoholic solution e.g. in methanol,

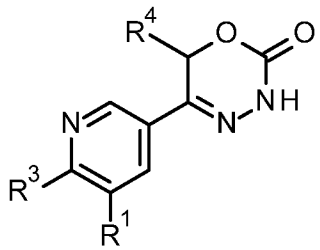
at room temperature

and

in a second step

reacting the product of the first step with sodiumhydride in alcoholic solution e.g. in ethanol at about 0°C and optionally acidic workup e.g. with aqueous hydrochloric acid

thereby giving a compound of general formula (I)

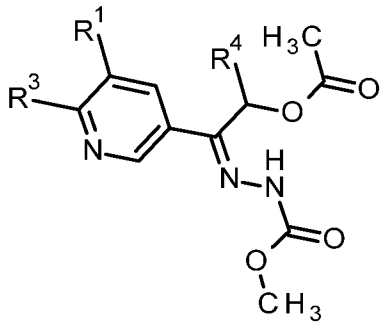


,

in which R^1, R^2, R^3 and R^4 are as defined *supra*.

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

In accordance with a third aspect, the present invention 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 (V) :

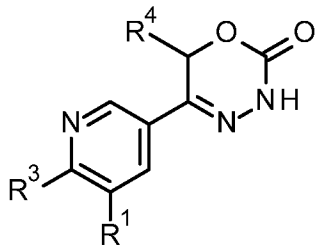


(V),

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) according to claim 1,

to react with sodiumhydride in alcoholic solution e.g. in methanol or ethanol at about 0°C and optionally acidic workup e.g. with aqueous hydrochloric acid

thereby giving a compound of general formula (I)



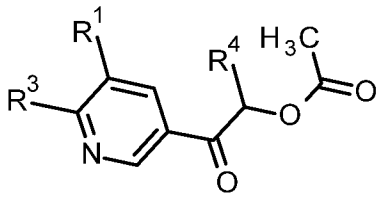
,

in which R^1, R^2, R^3 and R^4 are as defined *supra*.

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 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) :

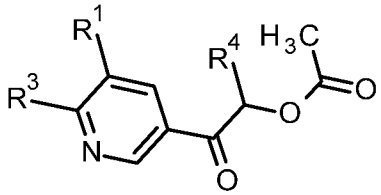


formula (IV)

in which R^1, R^3 and R^4 are as defined for the compound of general 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*.

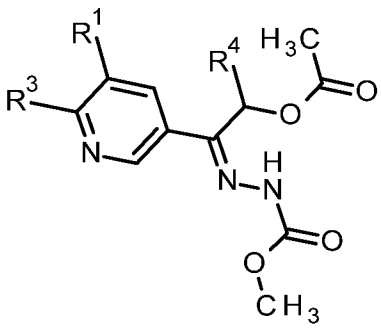
Particularly, the inventions includes the use of intermediate compounds of general formula (I) :



formula (IV)

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) *supra,* for the preparation of a compound of general formula (I) as defined *supra*.

Particularly, the inventions includes the intermediate compounds of general formula (V) :

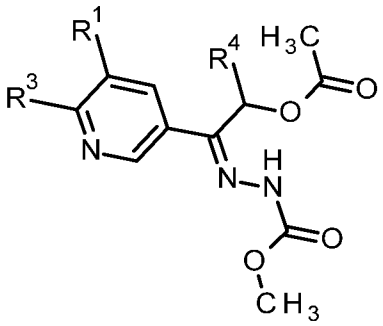


(V)

in which R^1, R^3 and R^4 are as defined for the compound of general 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 (V) :



(V)

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) *supra,* 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) and (V), *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, particularly 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- and/or PDE3B-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 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, particularly an about 25% change, more particularly an about 40% change, and most particularly 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, particularly a 25% or less (including 25%) change, more particularly a 40% or less (including 40%) change, and most particularly 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, particularly a 10%-25% (including 10% and 25%) change, more particularly a 25% - 40% (including 25% and 40%) change, and most particularly a 40%-50% (including 40% - 50%) or greater than 50% (including 50%) change in expression levels. In other certain embodiments an alteration includes a 9% - 11% (including 9% and 11 %) change in expression levels, particularly a 22%-28% (including 22% and 28%) change, more particularly a 35% - 45% (including 35% and 45%) change, and most particularly 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 contains, particularly, 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,

particularly, at least 9%-11% (including 9% and 11%), 18%-22% (including 18% ands 22%), 27%-33% (including 27% and 33%), 36%-44% (including 36% and 44%), 45%-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 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.

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 polypeptide to another agent. For example, a modulator may promote binding of a polypeptide to another polypeptide. In some embodiments, the modulator of PDE3A and/or 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 myoproliferative diseases include e.g.polycythemia vera, essential thrombocytosis, thrombocytosis, primary 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 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 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*.

Examples of *brain* cancers include, but are not limited to, brain stem and hypophtalmic glioma, glioblastoma, 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 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 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.

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.

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 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 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 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, 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.

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 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 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.

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 chemotherapeutic 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, 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.

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 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 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.

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 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 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.

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 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 cell with a compound of formula **(I)** according to any one of claims 1-6.

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 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 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 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 lest one compound of general formula **(I)** according to any one of claims 1-6.

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, using an effective amount of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

In accordance with a further aspect, the present invention includes the use of an effective amount of a compound of general formula (I), as described *supra*, including the disclaimed compounds, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, in a method of treatment or prophylaxis hyperproliferative diseases,

particularly cancer diseases, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

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 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., 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. comprising administering an effective amount of at least one compound of formula **(I)** according to any one of claims 1-6.

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 1-6.

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., 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.comprising administering an effective amount of at least one compound of formula **(I)** according to any one of claims 1-6.

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 1-6.

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.

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.

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.

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.

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.

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. 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.

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.

In some embodiments, the present invention includes compound of general formula (I) according to any one of claims 1 to 8 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 the cancer disease is cervix cancer and melanoma.

Particularly in some embodiments, the present invention includes compounds of general formula **(I),** including all compounds disclaimed in the compound claims, for use in a method of treating a hyperproliferative disease, more particularly wherein the

hyperproliferative disease is cancer, and yet even more particularly wherein 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.

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, particularly a medicament, for the prophylaxis or treatment of diseases, in particular hyperproloferative diseases, particularly cancer diseases.

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, including all compounds which are disclaimed in the compound claims, for the preparation of a pharmaceutical composition, particularly a medicament, for the prophylaxis or treatment of diseases, in particular hyperproloferative diseases, particularly cancer diseases.

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, conventionally together with one or more pharmaceutically suitable excipients, and to their use for the above mentioned purposes.

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

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

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

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

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

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

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),

- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- solvents (for example water, ethanol, isopropanol, glycerol, propylene glycol, medium chain-length triglycerides, fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example, Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),
- buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),
- isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas),
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),
- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross- linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®)),
- flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),
- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropylmethylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),

- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

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

In accordance with another aspect, the present invention 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 hyperproloferative disease, e.g. cancer.

Particularly, the present invention includes a pharmaceutical combination, which comprises:

- one or more first active ingredients, in particular compounds of general formula (I) as defined *supra,* and
- one or more further active ingredients, in particular 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 combination or a kit-of-parts.

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

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

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also 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, alpharadin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, apalutamide, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, avelumab, 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 levofolinate,

capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cemiplimab, 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 diftitox, 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 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, 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, 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, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, 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, 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, orilotimod, osimertinib,

oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, 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, 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, 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, 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, tislelizumab, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, 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.

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 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.

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 particularly 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 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 techniques will particularly be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will particularly be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will particularly be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will particularly be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will particularly be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will particularly 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 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 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.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (300 or 400 MHz ^{1}H, 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).

The ^{1}H-NMR data of selected compounds are listed in the form of ^{1}H-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 (intensity$_1$), δ_2 (intensity$_2$), ... , δ_i (intensity$_i$), ... , δ_n (intensity$_n$).

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 ^{1}H-NMR peaklist is similar to a classical ^{1}H-NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation. Moreover, similar to classical ^{1}H-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 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 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 ^{1}H-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. 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
pTsOH	para-toluenesulfonic acid
q	quartet (NMR coupling pattern)
R_t	retention time
RT	room temperature
s	singlet (NMR coupling pattern)
t	triplet (NMR coupling pattern)
tBuOH	*tert*-butanol

THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
UPLC	Ultra Performance Liquid Chromatography
UPLC-MS	Ultra High Preformance 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.

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 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 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 cartidges 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 UPLC-MS was performed as described below. The masses (m/z) are reported from the positive mode electrospray ionisation unless the negative mode is indicated (ESIneg). In most of the cases method 1 is used. If not, it is indicated.

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 3µm, 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.

Preparative HPLC Methods:

Method 4:

Instrument: Waters Acquity UPLC-MS SingleQuad; Colum: Acquity UPLC BEH C18 1.7 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 5:

Instrument: Waters Acquity UPLC-MS SingleQuad; Column: Acquity UPLC BEH C18 1.7 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

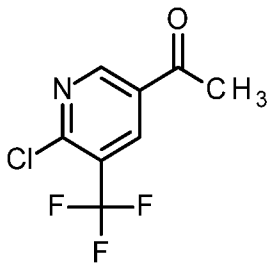
Method 6:

[Column: XBridge, RP18 OBD 19*150mm; Mobile Phase A: Waters(0.1% NH4HCO3), Mobile Phase B: ACN; Flow rate: 20 mL/min; 254 & 220 nm]

EXPERIMENTAL SECTION – INTERMEDIATES

Intermediate 1

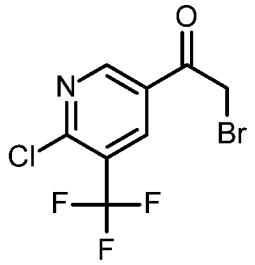
1-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]ethan-1-one



To a solution of 5-bromo-2-chloro-3-(trifluoromethyl)pyridine (6.0 g, 23 mmol), in 100 mL of 1,4-dioxane were added tributyl(1-ethoxyvinyl)stannane (8.32 g, 23 mmol), and tetrakis(triphenylphosphine)palladium(0) (1.33 g, 1.15 mmol). The resulting mixture was stirred at 110 °C overnight. The mixture was cooled to room temperature, then 60 mL of aqueous hydrochloric acid (1N) was added. The resulting mixture was stirred at room temperature for 3 hours. Upon completion of the reaction, the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified with silica gel column chromatography (petroleum ester: ethyl acetate= 30:1) to give 5.27 g (81%) of the product as a yellow solid. MS (ESIpos):m/z = 224 (M+H)+.

Intermediate 2

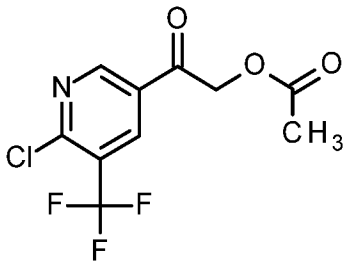
2-bromo-1-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]ethan-1-one



To a solution of 1-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]ethan-1-one (5 g, 22.4 mmol, Intermediate 1), in 80 mL of AcOH were added hydrobromic acid, 0.06 mL (1.1 mmol) and bromine (1.15 mL, 22.4 mmol). The resulting mixture was stirred at room temperature overnight. Upon completion of the reaction, ice water was added and the resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give 6.5 g(crude) of the product as a yellow oil. MS (ESIpos):m/z = 302 (M+H)+

Intermediate 3

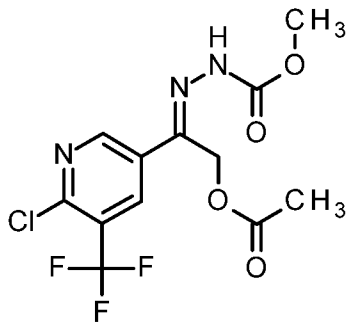
2-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]-2-oxoethyl acetate



To a solution of 2-bromo-1-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]ethan-1-one (6.50 g, 17 mmol, Intermediate 2) in 70 mL of N,N-dimethylformamide were added potassium acetate (3.4 g, 34 mmol), and potassium iodide (2.9 g, 17 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to give 5.6 g (crude) of the product as a yellow solid. MS(ESIpos): m/z = 382 (M+H)+.

Intermediate 4

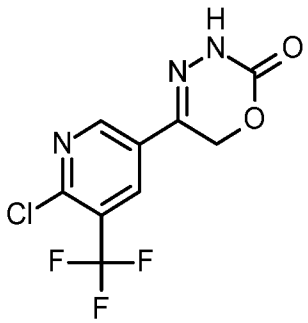
methyl -2-{2-(acetyloxy)-1-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]ethylidene}hydrazine-1-carboxylate



To a solution of 2-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]-2-oxoethyl acetate (4.70 g, 16.7 mmol, Intermediate 3) in 100 mL of methanol were added methyl hydrazinecarboxylate (1.50 g, 16.9 mmol) and 4-Toluenesulfonic acid (0.29 g, 1.7 mmol). The mixture was stirred at room temperature overnight. Upon completion of the reaction, the solvent was removed in vacuo directly to give 6.4 g (crude) of the product as a yellow solid. MS (ESIpos):m/z = 354 (M+H)+

Intermediate 5

5-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one



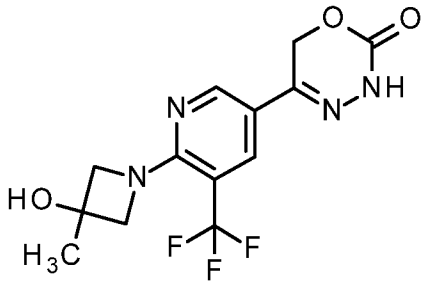
To a solution of methyl -2-{2-(acetyloxy)-1-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]ethylidene}hydrazine-1-carboxylate (6.4 g, Intermediate 4), in 180 mL of ethanol, was added sodium hydride (0.38 g, 9.5 mmol, 60% purity), then the resulting mixture was stirred at 0 ºC for 4 hours under nitrogen atmosphere. Upon completion of the reaction, the mixture was acidified to pH=1 with aqueous hydrochloric acid (1N). The resulting mixture was extracted with ethyl acetate (twice). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give 5.0 g (98% purity) of the product as a white solid. MS (ESIpos):m/z = 280 (M+H)+.

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm] = 11.41 (s, 1H), 8.98 (d, 1H), 8.48 (d, 1H), 5.45 (s, 2H).

EXPERIMENTAL SECTION – EXAMPLES

Example 1

5-[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one

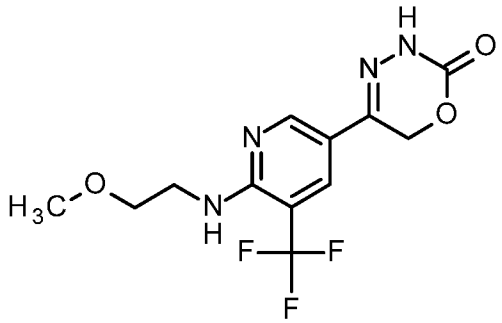


To a solution of 5-[6-chloro-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (400 mg, 1.4 mmol, Intermediate 5) in 10 mL of DMF were added potassium carbonate (593 mg, 4.3 mmol) and 3-methylazetidin-3-ol hydrochloride (354 mg, 2.9 mmol). The resulting mixture was stirred at 50 °C for 6 hours. Upon completion of the reaction ice water was added and the resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, the residue was purified by Prep-HPLC (Method 6, Gradient: 25% B to 38% B, Rt: 5.87 min) to give 75.5 mg, 15.8%) of the product as a white solid. MS (ESIpos):m/z = 331 (M+H)+.

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm] = 11.01 (s, 1H), 8.63 (d, 1H), 8.10 (d, 1H), 5.68 (s, 1H), 5.33 (s, 2H), 4.09-3.99 (m, 4H), 1.44 (s, 3H)

Example 2

5-{6-[(2-methoxyethyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one



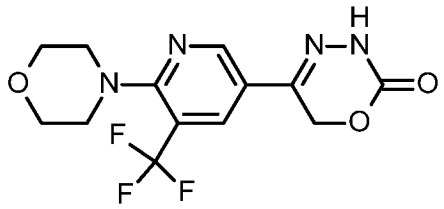
Synthesized in analogy to Example 1 from Intermediate 5 and 2-methoxyethan-1-amine.

Purified using Method 6; Gradient: 30% B to 50% B in 8 min; Rt: 6.72 min to give 18.1 mg (3.9%) of the product as a white solid. MS (ESIpos):m/z = 319 (M+H)+.

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm] = 10.99 (s, 1H), 8.61-8.56 (m, 1H), 8.07-8.02 (m, 1H), 6.90 (br t, 1H), 5.32 (s, 2H), 3.64 (q, 2H), 3.54-3.44 (m, 2H), 3.26 (s, 3H).

Example 3

5-[6-(morpholin-4-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one

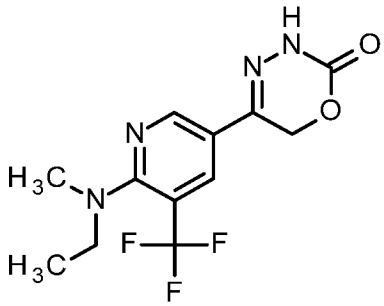


Synthesized in analogy to Example 1 from Intermediate 5 and morpholine.

Purified using Method 6; Gradient: 30% B to 40% B in 8 min, hold 1.5 min; 254 & 220 nm Rt: 6.52 min to give 34.6 mg (16.2%) of the product as a white solid. MS (ESIpos):m/z = 331 (M+H)+.

Example 4

5-{6-[ethyl(methyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one

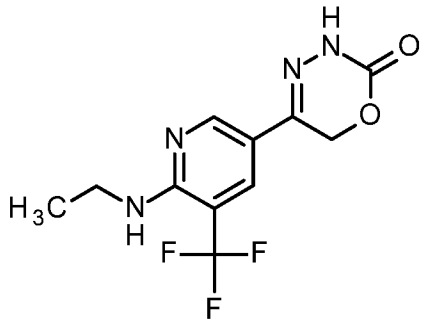


Synthesized in analogy to Example 1 from Intermediate 5 and N-methylethanamine.

Purified using Method 6; Gradient: 30% B to 65% B in 8 min; 254 & 220 nm Rt: 7.33 min] to give 40.5 mg (9.3%) of the product as a white solid. MS (ESIpos):m/z = 303 (M+H)+.

Example 5

5-[6-(ethylamino)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one

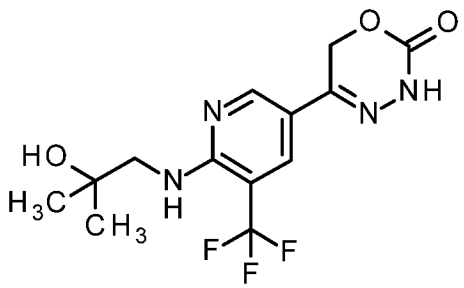


Synthesized in analogy to Example 1 from Intermediate 5 and ethanamine hydrogen chloride (1/1).

Purified using Method 6; Gradient: 23% B to 50% B in 8 min; 254 & 220 nm Rt: 7.50 min] to give 47.4 mg (11.5%) of the product as a white solid. MS (ESIpos):m/z = 289 (M+H)+.

Example 6

5-{6-[(2-hydroxy-2-methylpropyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one



Synthesized in analogy to Example 1 from Intermediate 5 and 1-amino-2-methylpropan-2-ol.

Purified using Method 6; Gradient: 30% B to 65% B in 8 min; 254 & 220 nm Rt: 7.32 min] to give 23.5 mg (4.9%) of the product as a white solid. MS (ESIpos):m/z = 333 (M+H)+.

EXPERIMENTAL SECTION – BIOLOGICAL ASSAYS

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

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

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

The *in vitro* activity of the compounds of the present invention 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;) 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)) 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. Inhibitory activity for several examples is shown in Table 2.

Table 2: Anti-proliferation IC_{50} values of several examples *in vitro* in different cell lines

Example	HeLa	SK-MEL-3
	IC_{50} [nM]	IC_{50} [nM]
1	10	24
2	12	22
3	22	47
4	14	38
5	38	58
6	57	>100

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.

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.

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.

Assay 2

Method for PDE3A 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 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 overexpressing human full length PDE3A (SB Drug Discovery, UK) in buffer A (50 mM Tris/HCl pH 7.5, 8.3 mM $MgCl_2$, 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 [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). IC_{50} values were determined from sigmoidal curves by plotting percentage PDE3A activity vs log compound concentration.

Assay 3

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 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 $MgCl_2$, 1.7 mM EDTA, 0.2% BSA) was added. The dilution of 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 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 IC_{50} values of < 100 nM in e.g. HeLa cells while IC_{50} values for enzymatic PDE3A or PDE3B inhibition are often > 10 times higher than IC_{50} values for tumor cell proliferation.

Another aspect of the invention are compounds of formula (I) which effectively inhibit tumor cell proliferation with IC_{50} values of < 100 nM in e.g. HeLa cells while IC_{50} values for enzymatic PDE3A or PDE3B inhibition are often > 30 times higher than IC_{50}

values for tumor cell proliferation.Inhibitory activity for several examples is shown in Table 3.

Table 3: Inhibition of PDE3A and PDE3B

Example	PDE3A IC_{50} [nM]	PDE3B IC_{50} [nM]
1	380	580
2	685	877
3	850	930
4	310	390
5	510	790
6	690	760

Assay 4

Validation of PDE3A modulator-induced PDE3A protein interactions using immunoprecipitation and immunoblotting

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 µM 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 5

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 mm^2 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 6

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.

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 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.

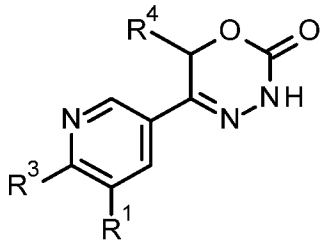
Other Embodiments

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.

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.

CLAIMS

1. A compound of formula (I)



formula (I)

wherein

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

R^3 is

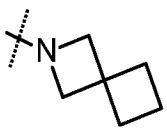
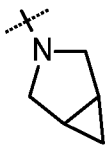
a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are a hydrogen atom;

a C_2-C_6-alkenyl group, which is optionally substituted with a C_1-C_3-alkoxy group,

a C_5-C_6-cycloalkenyl group,

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,

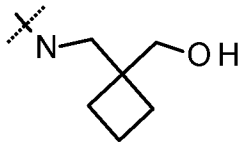
a 4- to 6-membered heterocycloalkyl group which is optionally substituted one or more times with a group independently selected from a fluorine atom, a hydroxy group, and a C_1-C_3-alkyl group,

a  group, a  group,

a 5- to 10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, R^3 is not an imidazolyl 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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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.

2. The compound according to claim 1, wherein:

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

R^3 is

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkyl group, a C_1-C_3-alkoxy group, a 4- to 6-membered heterocycloalkyl group, and an amino group which is substituted once or twice with a C_1-C_3-alkyl group, with the proviso that R^3 is not methyl if R^1 and R^4 are a hydrogen atom;

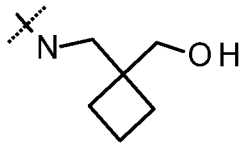
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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

a 5- to10-membered heteroaryl group which is optionally substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, R^3 is not an imidazolyl 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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a C_1-C_3-alkyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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:

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

R^3 is

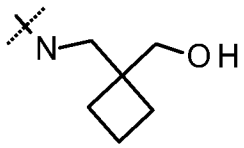
a phenyl group which is substituted one or more times with a group independently selected from halogen atom, C_1-C_3-alkyl group, and a C_1-C_3-haloalkyl group,

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, and a C_1-C_3-alkyl group,

a 5 to10-membered heteroaryl group which is substituted one or more times with a group independently selected from an amino group, a chlorine atom, a fluorine atom, a trifluormethyl group, and a difluoromethyl group, with the proviso that if R^1 is a hydrogen atom, R^3 is not an imidazolyl 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-alkyoxy group, a C_4-C_6-cycloalkyl group, a 4- to 6-membered heterocycloalkyl group, a 5- to 6-membered heteroaryl group;

a NR^5R^6 group, and

a  group,

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is selected from

a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a 5- to 6-membered heteroaryl group, a C_1-C_3-alkoxy group, a hydroxy group, a C_1-C_3-haloalkyl group, and a C_4-C_6-cycloalkyl group which itself is optionally substituted with a C_1-C_3-hydroxyalkyl group,

and

a C_5-C_6-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.

4. The compound according to claim 1 or 2, wherein:

R^1 is a trifluormethyl group;

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, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom or a methyl group;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, a hydroxy 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.

5. The compound according to claim 1 or 2, wherein:

R^1 is a trifluormethyl group;

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, and a C_1-C_3-alkyl group,

or

a NR^5R^6 group,

R^4 is a hydrogen atom;

R^5 is a hydrogen atom or a C_1-C_3-alkyl group;

R^6 is a C_1-C_3-alkyl group which is substituted one or more times with a group independently selected from a C_1-C_3-alkoxy group, and a hydroxy 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.

6. The compound according to claim 1 to 4 which is selected from the group consisting of:

5-[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[(2-methoxyethyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-[6-(morpholin-4-yl)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

5-{6-[ethyl(methyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-one,

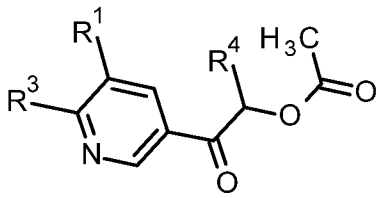
5-[6-(ethylamino)-5-(trifluoromethyl)pyridin-3-yl]-3,6-dihydro-2H-1,3,4-oxadiazin-2-one and

5-{6-[(2-hydroxy-2-methylpropyl)amino]-5-(trifluoromethyl)pyridin-3-yl}-3,6-dihydro-2H-1,3,4-oxadiazin-2-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.

7. A method of preparing a compound of general formula (I) according to any one of claims 1 to 6, said method comprising the step of allowing an intermediate compound of general formula (IV):

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) :



formula (IV) ,

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) as defined *supra* or anyone of claims 1-8,

to react in a first step

with $H_2NNHCOOCH_3$,

wherein the reaction occurs under the following conditions:

acidic conditions (e.g. para-toluenesulfonic acid)

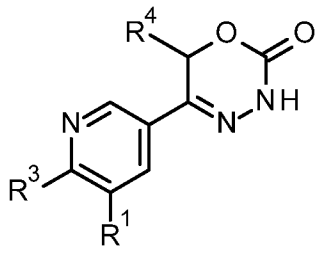
in an alcoholic solution e.g. in methanol,

at room temperature

and

in a second step

reacting the product of the first step with sodiumhydride in alcoholic solution e.g. in ethanol at about 0°C and optionally acidic workup e.g. with aqueous hydrochloric acid thereby giving a compound of general formula (I)



(I)

in which R^1, R^2, R^3 and R^4 are as defined *supra*.

8. A pharmaceutical composition comprising a compound of general formula (I) according to any one of claims 1 to 6 and one or more pharmaceutically acceptable excipients.

9. 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 6, and
- one or more further active ingredients, in particular anti-cancer agents.

10. Use of a compound of general formula (I) according to any one of claims 1-6 for the preparation of a pharmaceutical composition according to claim 8 or 9.

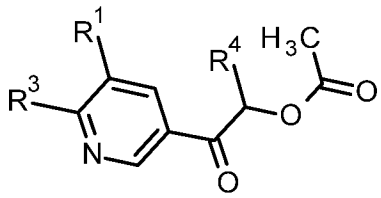
11. Use of a compound of general formula (I) according to any one of claims 1 to 6 for the treatment or prophylaxis of a disease.

12. Use according to claim 11, wherein the disease is a hyperproliferative disease.

13. Use according to claim 12, wherein the disease is a cancer disease.

14. Use according to claim 13 wherein the cancer disease is cervix cancer or melanoma.

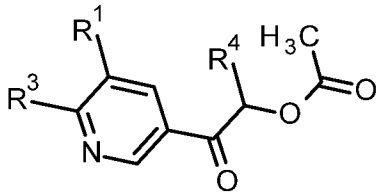
15. An intermediate compound of formula (IV)



formula (IV) ,

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) according to any of the claims 1-6.

16. Use of intermediate compound of general formula (IV)



formula (IV)

in which R^1, R^3 and R^4 are as defined for the compound of general formula (I) according to any one of claims 1 to 6,

for the preparation of a compound of general formula (I) according to any one of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/052355

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/04 C07D413/14 A61P35/00 A61K31/5395
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, 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.
A	WO 2017/134231 A1 (BAYER PHARMA AG [DE]; BROAD INST INC [US] ET AL.) 10 August 2017 (2017-08-10) claims; examples -----	1-16
A	EP 0 255 704 A2 (BOEHRINGER MANNHEIM GMBH [DE]) 10 February 1988 (1988-02-10) cited in the application claims -----	1-16
A	WO 03/037349 A1 (MERCK PATENT GMBH [DE]; EGGENWEILER HANS-MICHAEL [DE] ET AL.) 8 May 2003 (2003-05-08) claims; examples -----	1-16
A	EP 2 253 625 A1 (SHANGHAI INST MATERIA MEDICA C [CN]) 24 November 2010 (2010-11-24) claims; examples -----	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2020	02/04/2020

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/052355

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 2017134231	A1	10-08-2017	AR	107529	A1	09-05-2018
			CA	3013402	A1	10-08-2017
			CN	108883112	A	23-11-2018
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EP 0255704	A2	10-02-1988	DE	3626865	A1	11-02-1988
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