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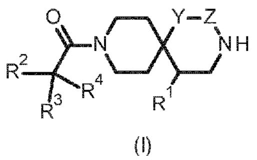
(54) Title: 5-HETEROARYL-3,9-DIAZASPIRO[5.5]UNDECANE COMPOUNDS



(I)

(57) Abstract: The present invention covers 5-heteroaryl-3,9-diazaspiro[5.5]undecane compounds of general formula (I), in which Y, Z, R^1, R^2, 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 and/or prophylaxis of diseases, in particular of hyperproliferative disorders, as a sole agent or in combination with other active ingredients.

5-HETEROARYL-3,9-DIAZASPIRO[5.5]UNDECANE COMPOUNDS

The present invention covers 5-heteroaryl-3,9-diazaspiro[5.5]undecane compounds of general formula (I) and general formula (I-1) as described and defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds, and the use of said compounds for manufacturing pharmaceutical compositions for the treatment or prophylaxis of diseases, in particular of hyperproliferative disorders, as a sole agent or in combination with other active ingredients.

BACKGROUND

The present invention covers 5-heteroaryl-3,9-diazaspiro[5.5]undecane compounds of general formula (I) and general formula (I-1) which inhibit the activity of geranylgeranyltransferase I (GGTase I), leading to inactivation of downstream YAP1 and/or TAZ and blockade of cancer cell proliferation.

Rho GTPases belong to the larger family of Ras GTPases, consisting of over 50 proteins with related characteristics. Rho GTPases are master regulators for signal transduction from the extracellular matrix to the cytoplasm and nucleus. They are involved in the regulation of cell proliferation, survival and differentiation by modulating cytoskeletal structure and properties of cell adhesion. Abberant Rho GTPase activity is observed in human cancer. Members of the pathway are therefore potential therapeutic targets. Activity of Rho GTPases is regulated by protein prenylation (farnesylation and geranylgeranylation) of the CAAX box motif. Prenylated Rho GTPases are primed for membrane localization and subsequent activitation. The three enzymes required of this post-translation modification are called protein prenyl-transferases (farnesyl-transferase, geranylgeranyl-transferase I and geranylgeranyl-transferase II). GGTase II is selective for Rab proteins and shows a different Mode of Action compared to GGTase I and FTase. Studies in mouse models have demonstrated that GGTase I inhibition reduces tumor formation of lung cancer as well as myeloproliferative disease and that the anti-tumor effect depended on the inhibition of protein geranyl-geranylation Sjogren AKM et al, J. Clin. Invest. 117:1294–1304 (2007). AKM et al, Leukemia (2011) 25, 186–189

A recently discovered downstream target of Rho GTPases are YAP1 and TAZ (gene name WWTR1). It has been shown that geranylgeranylated Rho GTPases such as RhoA activate downstream YAP1/TAZ in breast cancer (Mi W et al Oncogene 2015). YAP1 and TAZ (gene name WWTR1) are two highly related transcriptional coactivators that are frequently aberrantly activated in human cancers (Zanconato F, Cancer Cell. 2016 783-803). YAP1/TAZ are important for the activation of several hallmarks of cancer (Harvey KF, Nat Rev Cancer. 2013 246-57). Functionally, YAP1/TAZ shuttle between the cytoplasm and the cells´ nucleus, where they interact with TEAD transcription factors1-4 (TEAD1-4) to activate target genes important for cell survival and cell cycle progression (S. Piccolo Physiol. Rev., 2014 1287–1312. Zanconato F, et al. Nat Cell Biol. 2015 1218-27). Abberant YAP1/TAZ expression induces cell proliferation (Zhao B Genes Dev., 2007, 2747–2761). Moreover, high levels of YAP1/TAZ can overcome the induction of programmed cell death and apoptosis by upregulation of anti-apoptotic proteins (Rosenbluh J. Cell, 2012. 1457–1473). YAP1/TAZ also confers Cancer Stem Cells (CSC) traits and are required for CSC expansion within tumors (Cordenonsi M. Cell, 2011, 759–772). In line with this, the ability to initiate tumor formation and induce metastasis depends on YAP1/TAZ (Bartucci M, Oncogene, 2015, 681–690 Lau AN EMBO J. 2014, 468–481).Blockade of YAP1/TAZ function by RNAi-mediated knockdown reduces the viability of several cancer cells in vitro (Pan J Oncol. Rep., 2012 179–185). Moreover, it reduces the growth of tumor cells in mouse models of cancer in vivo (Nguyen LT Cancer Cell, 2015 797–808, He C, EMBO Mol. Med., 2015 1426–1449 Wang Q, Mol. Med. Rep., 2015 982–988 Feng X Cancer Cell, 2014 831–845).Given the crucial role various stages of tumor development, YAP1/TAZ may represent promising targets for therapeutic intervention of various diseases with uncontrolled cell proliferation, including cancer.

The present invention relates to chemical compounds that have been found to

- Inhibit the activity of GGTaseI
- inhibit the transcriptional regulation activity of YAP1 and/or TAZ
- block cell proliferation in tumor cells.

GGTase I inhibitors have been developed (reviewed in Ullah N et al Current Cancer Drug Targets 2016, 16, 563-571), but no GGTase I inhibitor is currently approved for treatment of patients. WO-03017939 , WO-2010088457. GGTI-2418 US 2012/0035184 A1.In cancer cell lines, GGTase I inhibitors cause cell cycle arrest in G0/G1 phase via blockade of cyclin-dependent kinases downstream of Rho Sun J et al, J. Biol. Chem., 1999, 274, 6930-; Vogt A et al, J. Biol. Chem., 1997, 272, 27224-27229. Furthermore, induction of apoptosis by GGTase I inhibitors has been reported Dan HC et al Oncogene, 2004, 23, 706-715.Morgan MA et al, Leukemia, 2003, 17, 1508-1520. Stark W et al, Am. J. Physiol., 1998, 275, L55-63. In Xenograft models of breast cancer, application of a GGTase I inhibitor caused tumor regression Kazi A et al, Cell Biol.,2009, 29, 2254-2263. Watanabe M et al (J. Biol. Chem. 2008, 283:9571-9579), described the identification of inhibitors of protein geranylgeranyltransferase I and Rab geranylgeranyltransferase from a Library of allenoate-derived compounds.

YAP1/TAZ small molecule modulators have been described in Johnson R et al, Nature Reviews Drug Discovery, 2014, 13, 63-79 and in Stahn L.C., Master Thesis, University

Rostock, 2017. Dey A et al, (Trends in Cancer, Vol. 5, No. 5, 297-307, 2019) reported on compounds to modulate hippo pathway activity, among them compounds that inhibit YAP-TEAD interaction or decrease YAP expressions. Cyclic peptides inhibiting the YAP1−TEAD protein−protein interaction have been described in Zhang Z. et al., ACS Med. Chem. Lett., 2014, 5, 993−998. A peptide mimicking VGLL4 function has been proposed to act as a YAP1 antagonist in preclinical models of gastric cancer in Jiao S, et al., Cancer Cell, 2014, 25, 166-180. A number of publications report inhibitors of YAP1, for example, the Tankyrase inhibitor XAV939 (Wang et al., Cell Reports, 2015, 13, 524-532) is reported to target YAP1 for cancer treatment. Peptide 17 has been reported to inhibit the YAP1-TEAD protein-protein interaction (Zhang Z. et al., ACS Med. Chem. Lett., 2014, 5, 993−998 and Zhou et al., FASEB J., 2015, 29, 724-732). Verteporfin has also reported to be a YAP1 inhibitor (Szeto et al., J. Am. Soc. Nephrol., 2016, 27, 3117-3128 and Liu-Chittenden et al., Gens Dev., 2012, 26, 1300-1305). Latrunculin A, Blebbistatin, Y27632 and ML7 have been reported to inhibit YAP1 nuclear localization as well as YAP1 and TEAD activity (see Nature Reviews Drug Discovery, 2014, 13, 63-79).

WO2019118973A1 describes 1-(piperidinocarbonylmethyl)-2-oxopiperazine derivatives for treating cancer.

EP2123652 relates to a heterocyclic compound having an acetyl-CoA carboxylase (ACC) inhibitory action.

WO2010138487 relates to benzoxazepines as inhibitors of mammalian target of rapamycin (mTOR).

WO2005040167A1 describes diazaspiroalkanes and their use for treatment of CCR8 mediated diseases.

WO2009037168A1 relates to 3,9-diaza-spiro[5.5]undecane and 3,9-diaza-spiro[5.5]undecan-2-one compounds useful for the treatment of a variety of disorders in which modulation of the CCR5 receptor ligand binding is beneficial.

WO2009135788A1 relates to 3,9-diaza-spiro[5.5]undecan-2-one compounds useful for thetreatment of a variety of disorders in which modulation of the CCR5 receptor ligand binding is beneficial.

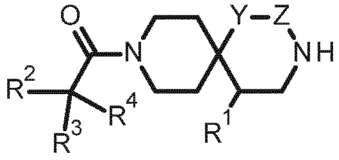
However, the state of the art does not describe the 5-heteroaryl-3,9-diazaspiro[5.5]undecane compounds of general formula (I) and general formula (I-1) of the present invention as described and defined herein.

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

In particular, the compounds of the present invention have surprisingly been found to effectively inhibit the activity of geranylgeranyltransferase I (GGTase I), leading to inactivation of downstream YAP1 and/or TAZ and blockade of cancer cell proliferation, and may therefore be used for the treatment or prophylaxis of hyperproliferative disorders, such as cancer, for example.

DESCRIPTION of the INVENTION

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



(I)

in which :

Y-Z represents a group selected from $-CH_2-CH_2-$, $-CH_2-C(=O)-$, and $-N(H)-C(=O)-$,

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_6-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_6-alkyl)-, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_6-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_6-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, $-N(R^5)(R^6)$ and $-(C_1\text{-}C_6\text{-alkyl})-N(R^5)(R^6)$,

R^2 represents a group selected from phenyl and naphthyl,

which phenyl and naphthyl group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-hydroxyalkoxy and hydroxy,

R^4 represents a hydrogen atom or a group selected from

C_1-C_6-alkyl and C_1-C_6-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

DEFINITIONS

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

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

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 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 part, *e.g.* (C_1-C_2-alkoxy)-(C_1-C_6-alkyl)-, it is possible for a given part to be attached at any suitable position of said composite substituent, *e.g.* it is possible for the C_1-C_2-alkoxy part to be attached to any suitable carbon atom of the C_1-C_6-alkyl part of said (C_1-C_2-alkoxy)-(C_1-C_6-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”.

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

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

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

The term “C_1-C_6-alkyl” means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, *neo*-pentyl, 1,1-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2,3-dimethylbutyl, 1,2-dimethylbutyl or 1,3-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms (“C_1-C_4-alkyl”), *e.g.* a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl isobutyl, or *tert*-butyl group, more particularly 1, 2 or 3 carbon atoms (“C_1-C_3-alkyl”), *e.g.* a methyl, ethyl, *n*-propyl or isopropyl group, more particularly 1 or 2 carbon atoms (“C_1-C_2-alkyl”), *e.g.* a methyl or ethyl group.

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 or 2 hydrogen atoms are replaced with a hydroxy group, *e.g.* a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-hydroxypropyl, 1-hydroxypropan-2-yl, 2-hydroxypropan-2-yl, 2,3-dihydroxypropyl, 1,3-dihydroxypropan-2-yl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl, 1-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl group, or an isomer thereof.

The term “C_2-C_6-hydroxyalkoxy” means a linear or branched, saturated, monovalent C_2-C_6-alkoxy group, as defined *supra*, in which group one of the hydrogen atoms is replaced with a hydroxy group. Particularly, said group contains 2, 3 or 4 carbon atoms (“C_2-C_4-hydroxyalkoxy”). Said C_2-C_4-hydoxyalkoxy group is, for example, a 2-hydroxyethoxy, 2-hydroxypropoxy, 3-hydroxypropoxy, 2-hydroxybutoxy, 3-hydroxybutoxy or 4-hydroxybutoxy group, or an isomer thereof.

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, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl or 1,3-difluoropropan-2-yl.

The term "C_1-C_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*, *e.g.* a methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, pentyloxy, isopentyloxy or *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, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy or pentafluoroethoxy.

The term "C_3-C_6-cycloalkyl" means a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms. Said C_3-C_6-cycloalkyl group is for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Particularly, said group has 3 or 4 carbon atoms ("C_3-C_4-cycloalkyl"), *e.g.* a cyclopropyl or cyclobutyl group.

The term "C_3-C_6-cycloalkyloxy" means a saturated, monovalent group of formula (C_3-C_6-cycloalkyl)-O-, in which the term "C_3-C_6-cycloalkyl" is as defined *supra*, *e.g.* a cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy group.

The term "nitrogen containing 4- to 7-membered heterocycloalkyl" group means a monocyclic, saturated heterocycle with 4, 5, 6 or 7 ring atoms in total, which contains one ring nitrogen atom and optionally one further ring heteroatom from the series N, O and S.

Said nitrogen containing 4- to 7-membered heterocycloalkyl group, without being limited thereto, can be a 4-membered ring, such as azetidinyl, for example; or a 5-membered ring, such as pyrrolidinyl, imidazolidinyl, pyrazolidinyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl or 1,3-thiazolidinyl, for example; or a 6-membered ring, such as piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, or 1,2-oxazinanyl, for example, or a 7-membered ring, such as azepanyl, 1,4-diazepanyl or 1,4-oxazepanyl, for example.

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

Said heteroaryl group can be a 5-membered heteroaryl group, such as, for example, thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl or tetrazolyl; or a 6-membered heteroaryl group, such as, for example, pyridinyl, pyridazinyl, pyrazinyl or triazinyl; or a 9-membered heteroaryl group, such as, for example, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzothiazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, indolizinyl or purinyl; or a 10-membered heteroaryl group, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxalinyl or pteridinyl.

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

The term “C_1-C_6”, as used in the present text, *e.g.* in the context of the definition of “C_1-C_6-alkyl”, “C_1-C_6-haloalkyl”, “C_1-C_6-hydroxyalkyl”, “C_1-C_6-alkoxy” or “C_1-C_6-haloalkoxy” means an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5 or 6 carbon atoms.

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

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

For example:

"C_1-C_6" encompasses C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

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

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

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

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

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

It is possible for the compounds of general formula (I) and general formula (I-1) to exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula (I) and general formula (I-1), particularly deuterium-containing compounds of general formula (I) and general formula (I-1).

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) and general formula (I-1)” is defined as a compound of general formula (I) or general formula (I-1) 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 disorders specified herein the isotopic variant(s) of the compounds of general formula (I) or general formula (I-1) preferably contain deuterium (“deuterium-containing compounds of general formula (I) or general formula (I-1)”). Isotopic variants of the compounds of general formula (I) or general formula (I-1) 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) or general formula (I-1). These isotopic variants of the compounds of general formula (I) or (I-1) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of general formula (I) or general formula (I-1) can be used in mass spectrometry analyses in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula (I) and general formula (I-1) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds. Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds and acetylenic bonds is a direct route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons. A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA.

The term “deuterium-containing compound of general formula (I) or general formula (I-1)” is defined as a compound of general formula (I) or general formula (I-1), 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) or general formula (I-1) is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula (I) or general formula (I-1) the abundance of deuterium at each deuterated position of the compound of general formula (I) or general formula (I-1) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) or general formula (I-1) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., J. Am. Chem. Soc., 2007, 129, 4490], basicity [C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I) or general formula (I-1). 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) or general formula (I-1) 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) or general formula (I-1) 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) or general formula (I-1) is/are attached to a carbon atom and/or is/are located at those positions of the compound of general formula (I) or general formula (I-1), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P_{450}.

In another embodiment the present invention concerns a deuterium-containing compound of general formula (I) or general formula (I-1) having 1, 2, 3 or 4 deuterium atoms, particularly with 1, 2 or 3 deuterium atoms.

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 of the structural formula (I) 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.

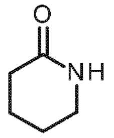
Preferred isomers are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of the present invention are also included within the scope of the present invention. The purification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

The optical isomers can be obtained by resolution of the 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. The optically active bases or acids are then liberated from the separated diastereomeric salts. 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. 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.

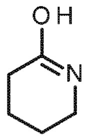
In order to distinguish different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

In case stereogenic centres are present, other than the one specified in the structural formula (I-1), the present invention includes all possible diastereomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, in any ratio. Isolation of a single stereoisomer, e.g. a single diastereomer, of a compound of the present invention may 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, the compounds of the present invention contain a piperidin-2-one moiety and can exist as a lactam, or a lactim, or even a mixture in any amount of the two tautomers, namely :



lactam



lactim

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 atom of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

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

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

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

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

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

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

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

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

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

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

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

As used herein, the term "*in vivo* hydrolysable ester" means an *in vivo* hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C_1-C_6 alkoxymethyl esters, *e.g.* methoxymethyl, C_1-C_6 alkanoyloxymethyl esters, *e.g.* pivaloyloxymethyl, phthalidyl esters, C_3-C_8 cycloalkyloxy-carbonyloxy-C_1-C_6 alkyl esters, *e.g.* 1-cyclohexyloxycarbonyloxyethyl ; 1,3-dioxolen-2-onylmethyl esters, *e.g.* 5-methyl-1,3-dioxolen-2-onylmethyl; and C_1-C_6-alkoxycarbonyloxyethyl esters, *e.g.* 1-methoxycarbonyloxyethyl, it being possible for said esters to be formed at any carboxy group in the compounds of the present invention.

An *in vivo* hydrolysable ester of a compound of the present invention containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted alkanoyl, benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), N,N-dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

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

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

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

Y-Z represents a group selected from $-CH_2-CH_2-$, $-CH_2-C(=O)-$, and $-N(H)-C(=O)-$,

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a hydrogen atom or a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

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

Y-Z represents a group selected from $-CH_2-CH_2-$, $-CH_2-C(=O)-$, and $-N(H)-C(=O)-$,

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl,

$(C_1\text{-}C_2\text{-alkoxy})\text{-}(C_1\text{-}C_4\text{-alkyl})\text{-}$, $C_1\text{-}C_4$-haloalkyl, $C_1\text{-}C_6$-alkoxy, $C_1\text{-}C_6$-haloalkoxy, $C_2\text{-}C_6$-hydroxyalkoxy, $(C_1\text{-}C_2\text{-alkoxy})\text{-}(C_2\text{-}C_4\text{-alkoxy})\text{-}$, $(C_1\text{-}C_2\text{-haloalkoxy})\text{-}(C_1\text{-}C_4\text{-alkyl})\text{-}$, $C_3\text{-}C_6$-cycloalkyloxy, -cyano, hydroxy, $-N(R^5)(R^6)$ and $-(C_1\text{-}C_6\text{-alkyl})\text{-}N(R^5)(R^6)$,

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

$C_1\text{-}C_4$-alkyl, $C_1\text{-}C_4$-haloalkyl and $C_1\text{-}C_4$-haloalkoxy,

R^3 represents a group selected from

$C_1\text{-}C_4$-alkyl, $C_1\text{-}C_4$-alkoxy, $C_2\text{-}C_4$-hydroxyalkoxy and hydroxy,

R^4 represents a group selected from

$C_1\text{-}C_4$-alkyl and $C_1\text{-}C_4$-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

$C_1\text{-}C_4$-alkyl and $C_3\text{-}C_4$-cycloalkyl,

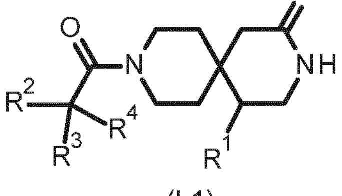
or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a $C_1\text{-}C_2$-alkyl group and oxo,

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

In accordance with a third embodiment of the first aspect, the present invention covers compounds of general formula (I-1):



(I-1) ,

in which :

R^1 represents a 5- to 10-membered heteroaryl group

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -$N(R^5)(R^6)$ and -(C_1-C_6-alkyl)-$N(R^5)(R^6)$,

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a hydrogen atom or a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

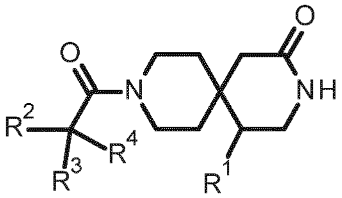
or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

In accordance with a variant of the third embodiment of the first aspect, the present invention covers compounds of general formula (I-1):



(I-1) ,

in which :

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

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

R^1 represents a 5- to 10-membered heteroaryl group, which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, C_3-C_6-cycloalkyloxy and hydroxy,

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

and

R^4 represents a hydrogen atom or a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

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

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)- and C_3-C_6-cycloalkyloxy,

R^2 represents a phenyl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,
and
R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

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

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
fluorine atom, chlorine atom, methyl, ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl and methoxy,
R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl ,
R^3 represents a group selected from C_1-C_4-alkyl, C_1-C_4-alkoxy and hydroxy,
and

R^4 represents a hydrogen atom or a C_1-C_4-haloalkyl group,

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

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

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
methyl and methoxy,
R^2 represents a phenyl group,
R^3 represents a C_1-C_4-alkoxy group,
and
R^4 represents a C_1-C_4-haloalkyl group,

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

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

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, 1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 5-chlorothiophen-2-yl, 4-methyl-1,3-thiazol-2-yl, 4-methyl-1,3-thiazol-5-yl, 3-fluoropyridin-2-yl, 5-methyl-1H-pyrazol-1-yl, 1-methyl-1H-pyrazol-3-yl, 1-methyl-1H-pyrazol-5-yl, 1-ethyl-1H-pyrazol-5-yl, 1-(2,2-difluoroethyl)-1H-pyrazol-5-yl, 1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl, pyridin-3-yl, 2-chloropyridin-3-yl, 2-methylpyridin-3-yl, 4-methylpyridin-3-yl, 2-methoxypyridin-3-yl, 4-methoxypyridin-3-yl, pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl and pyrazolo[1,5-a]pyridin-7-yl,

R^2 represents a group selected from phenyl2-(trifluoromethyl)phenyl, 3,3-dimethylphenyl and 1-naphthyl,

R^3 represents a group selected from methyl, methoxy and hydroxy,

and

R^4 represents a hydrogen atom or a trifluoromethyl group,

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

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

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl and pyrazolo[1,5-a]pyridin-4-yl,

R^2 represents a phenyl group,

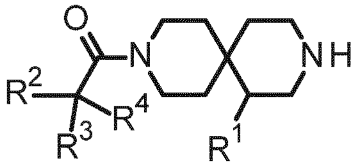
R^3 represents a methoxy group,

and

R^4 represents a trifluoromethyl group,

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

In accordance with a further embodiment of the first aspect, the present invention covers compounds of general formula (I-2),



(I-2) ,

in which :

R^1 represents a 5- to 10-membered heteroaryl group which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogenatom or a group selected from C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a group selected from phenyl and naphthyl, which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyland C_1-C_4-haloalkoxy,

R^3 represents a group selected from C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a group selected from C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group, wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

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

R^1 represents a 5- to 10-membered heteroaryl group
which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and hydroxy,

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

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

R^1 represents a group selected from
thiophenyl, pyrazolyl and pyridinyl,
which group is optionally substituted with a group selected from chlorine atom methyl, methoxy and hydroxy,

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_4-alkyl group,

R^3 represents a C_1-C_4-alkoxy group,

and

R^4 represents a C_1-C_4-haloalkyl group,

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

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

R^1 represents a group selected from
5-chlorothiophen-2-yl, 1-methyl-1H-pyrazol-5-yl, 2-hydroxypyridin-3-yl, 2-methylpyridin-3-yl and 2-methoxypyridin-3-yl,
R^2 represents a group selected from
phenyl, 3,3-dimethylphenyl and 1-naphthyl,
R^3 represents a methoxy group,
and
R^4 represents a trifluoromethyl group,

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

In accordance with a seventh embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, which are selected from the group consisting of:

5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),
(5R)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one, 5-(thiophen-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(thiophen-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(pyrazolo[1,5-a]pyridin-4-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(furan-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5S)-5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(pyridin-4-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(3-fluoropyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(2-chloropyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(2R)-3,3,3-trifluoro-2-methoxy-1-[7-(2-methylpyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-phenylpropan-1-one,

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-

diazaspiro[5.5]undecan-2-one,
(5S)-5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(2R)-3,3,3-trifluoro-2-methoxy-1-[7-(2-methoxypyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-phenylpropan-1-one,

(2R)-3,3,3-trifluoro-1-[7-(2-hydroxypyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-methoxy-2-phenylpropan-1-one,

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-hydroxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(4-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

(5S)-5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

(5S)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-

3,9-diazaspiro[5.5]undecan-2- one (mixture of stereosiomers),

(5S)-5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5R)-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-hydroxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

3,3,3-trifluoro-2-methoxy-1-[7-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-(naphthalen-1-yl)propan-1-one,

5-(1-methyl-1H-pyrazol-5-yl)-9-{2-[2-(trifluoromethyl)phenyl]propanoyl}-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

9-[2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoyl]-5-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-2-one,

2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxy-1-[7-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-3-yl]propan-1-one,

5-(1-ethyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(1-methyl-1H-pyrazol-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(5-methyl-1H-pyrazol-1-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(5-chlorothiophen-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-

diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(2R)-1-[7-(5-chlorothiophen-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropan-1-one (mixture of stereoisomers),

5-(4-methyl-1,3-thiazol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one, and
(5R)-5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

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

In accordance with a variant of the seventh embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, which are selected from the group consisting of:

5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),
(5R)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-

diazaspiro[5.5]undecan-2-one,

5-(thiophen-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

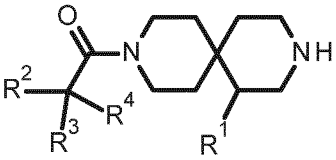
5-(thiophen-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(pyrazolo[1,5-a]pyridin-4-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers), and

5-(furan-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2),



(I-2)

in which:

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a phenyl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected

from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), in which:

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)- and C_3-C_6-cycloalkyloxy,

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

and

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), in which:

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
methyl and methoxy,
R^2 represents a phenyl group,
R^3 represents a C_1-C_4-alkoxy group,
and
R^4 represents a C_1-C_4-haloalkyl group,

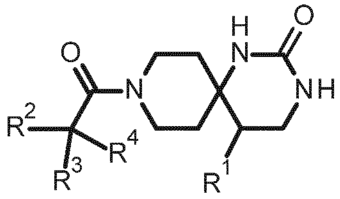
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), in which:

R^1 represents a group selected from
1-methyl-1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl and pyrazolo[1,5-a]pyridin-4-yl,
R^2 represents a phenyl group,
R^3 represents a methoxy group,
and
R^4 represents a trifluoromethyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3),



(I-3)

in which:

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), in which:

R^1 represents a 5- to 10-membered heteroaryl group,
    which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from
    C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy,
    (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)- and C_3-C_6-cycloalkyloxy,
R^2 represents a phenyl group,
    which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
    C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,
R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,
and
R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), in which:

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
    which group is optionally substituted with a group selected from
    methyl and methoxy,
R^2 represents a phenyl group,
R^3 represents a C_1-C_4-alkoxy group,
and

R^4 represents a C_1-C_4-haloalkyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), in which:

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl and pyrazolo[1,5-a]pyridin-4-yl,
R^2 represents a phenyl group,
R^3 represents a methoxy group,
and
R^4 represents a trifluoromethyl group,

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

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

Y-Z represents a group selected from $-CH_2-CH_2-$, $-CH_2-C(=O)-$, and $-N(H)-C(=O)-$,

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

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

Y-Z represents a group selected from $-CH_2-CH_2-$ and $-CH_2-C(=O)-$,

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

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

Y-Z represents a $-CH_2-CH_2-$ group,

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

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

Y-Z represents a -CH_2-C(=O)- group,

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

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

Y-Z represents a -N(H)-C(=O)- group,

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

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

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_6-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_6-alkyl)-, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_6-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_6-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

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

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

R^2 represents a group selected from phenyl and naphthyl, which phenyl and naphthyl group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

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

R^3 represents a group selected from
C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-hydroxyalkoxy and hydroxy,

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

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

R^4 represents a hydrogen atom or a group selected from
C_1-C_6-alkyl and C_1-C_6-haloalkyl,

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

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

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from
C_1-C_4-alkyl and C_3-C_4-cycloalkyl,
or
R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

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

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from
C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

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

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

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_6-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_6-alkyl)-, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_6-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_6-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -$N(R^5)(R^6)$ and -(C_1-C_6-alkyl)-$N(R^5)(R^6)$,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^2 represents a group selected from phenyl and naphthyl,

which phenyl and naphthyl group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^3 represents a group selected from
C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a hydrogen atom or a group selected from
C_1-C_6-alkyl and C_1-C_6-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from
C_1-C_4-alkyl and C_3-C_4-cycloalkyl,
or
R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

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

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-,

$(C_1$-C_2-haloalkoxy)-$(C_1$-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -$N(R^5)(R^6)$ and -$(C_1$-C_6-alkyl)-$N(R^5)(R^6)$,

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

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

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

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

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

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

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

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

R^4 represents a hydrogen atom or a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

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

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -$N(R^5)(R^6)$ and -(C_1-C_6-alkyl)-$N(R^5)(R^6)$,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected

from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a hydrogen atom or a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

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

R^1 represents a 5- to 10-membered heteroaryl group, which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, C_3-C_6-cycloalkyloxy and hydroxy,

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

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

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)- and C_3-C_6-cycloalkyloxy,

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

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

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from fluorine atom, chlorine atom, methyl, ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl and methoxy,

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

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

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
methyl and methoxy,

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

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

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each
substituent independently selected from a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl ,

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

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

R^2 represents a phenyl group,

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

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

R^3 represents a group selected from C_1-C_4-alkyl, C_1-C_4-alkoxy and hydroxy,

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

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

R^3 represents a C_1-C_4-alkoxy group,

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

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

R^4 represents a hydrogen atom or a C_1-C_4-haloalkyl group,

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

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

R^4 represents a C_1-C_4-haloalkyl group,

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

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

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, 1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 5-chlorothiophen-2-yl, 4-methyl-1,3-thiazol-2-yl, 4-methyl-1,3-thiazol-5-yl, 3-fluoropyridin-2-yl, 5-methyl-1H-pyrazol-1-yl, 1-methyl-1H-pyrazol-3-yl, 1-methyl-1H-pyrazol-5-yl, 1-ethyl-1H-pyrazol-5-yl, 1-(2,2-difluoroethyl)-1H-pyrazol-5-yl, 1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl, pyridin-3-yl, 2-chloropyridin-3-yl, 2-methylpyridin-3-yl, 4-methylpyridin-3-yl, 2-methoxypyridin-3-yl, 4-methoxypyridin-3-yl, pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl and pyrazolo[1,5-a]pyridin-7-yl,

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

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

R^1 represents a group selected from
1-methyl-1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl and pyrazolo[1,5-a]pyridin-4-yl,

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

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

R^2 represents a group selected from
phenyl, 2-(trifluoromethyl)phenyl, 3,3-dimethylphenyl and 1-naphthyl,

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

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

R^2 represents a phenyl group,

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

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

R^3 represents a group selected from methyl, methoxy and hydroxy,

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

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

R^3 represents a methoxy group,

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

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

R^4 represents a hydrogen atom or a trifluoromethyl group,

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

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

R^4 represents a trifluoromethyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group, which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, C_3-C_6-cycloalkyloxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group, which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)- and C_3-C_6-cycloalkyloxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a hydrogen atom or a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
fluorine atom, chlorine atom, methyl, ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl and methoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
methyl and methoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl ,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^2 represents a phenyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^3 represents a group selected from C_1-C_4-alkyl, C_1-C_4-alkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^3 represents a C_1-C_4-alkoxy group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a hydrogen atom or a C_1-C_4-haloalkyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a C_1-C_4-haloalkyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, 1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 5-chlorothiophen-2-yl, 4-methyl-1,3-thiazol-2-yl, 4-methyl-1,3-thiazol-5-yl, 3-fluoropyridin-2-yl, 5-methyl-1H-pyrazol-1-yl, 1-methyl-1H-pyrazol-3-yl, 1-methyl-1H-pyrazol-5-yl, 1-ethyl-1H-pyrazol-5-yl, 1-(2,2-difluoroethyl)-1H-pyrazol-5-yl, 1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl, pyridin-3-yl, 2-chloropyridin-3-yl, 2-methylpyridin-3-yl, 4-methylpyridin-3-yl, 2-methoxypyridin-3-yl, 4-methoxypyridin-3-yl, pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl and pyrazolo[1,5-a]pyridin-7-yl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl and pyrazolo[1,5-a]pyridin-4-yl,

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

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

R^2 represents a group selected from phenyl, 2-(trifluoromethyl)phenyl, 3,3-dimethylphenyl and 1-naphthyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^3 represents a group selected from methyl, methoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^3 represents a methoxy group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-1), *supra*, in which:

R^4 represents a trifluoromethyl group,

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

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

R^1 represents a 5- to 10-membered heteroaryl group

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogenatom or a group selected from C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

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

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

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyland C_1-C_4-haloalkoxy,

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

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

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

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

R^4 represents a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

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

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

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

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from
C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

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

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

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,
wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

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

R^1 represents a 5- to 10-membered heteroaryl group
which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and hydroxy,

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

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

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

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

R^1 represents a group selected from
thiophenyl, pyrazolyl and pyridinyl,
which group is optionally substituted with a group selected from chlorine atom methyl, methoxy and hydroxy,

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

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

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_4-alkyl group,

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

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

R^3 represents a C_1-C_4-alkoxy group,

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

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

R^4 represents a C_1-C_4-haloalkyl group,

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

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

R^1 represents a group selected from
thiophenyl, pyrazolyl and pyridinyl,
which group is optionally substituted with a group selected from chlorine atom methyl, methoxy and hydroxy,
R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_4-alkyl group,
R^3 represents a C_1-C_4-alkoxy group,
and
R^4 represents a C_1-C_4-haloalkyl group,

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

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

R^1 represents a group selected from
5-chlorothiophen-2-yl, 1-methyl-1H-pyrazol-5-yl, 2-hydroxypyridin-3-yl, 2-methylpyridin-3-yl and 2-methoxypyridin-3-yl,

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

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

R^2 represents a group selected from
phenyl, 3,3-dimethylphenyl and 1-naphthyl,

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

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

R^3 represents a methoxy group,

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

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

R^4 represents a trifluoromethyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogenatom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyland C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from
C_1-C_4-alkyl and C_3-C_4-cycloalkyl,
or
R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,
wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from
C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group, wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^2 represents a group selected from phenyl and naphthyl, which group is optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a group selected from
thiophenyl, pyrazolyl and pyridinyl,
which group is optionally substituted with a group selected from chlorine atom methyl, methoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_4-alkyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^3 represents a C_1-C_4-alkoxy group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^4 represents a C_1-C_4-haloalkyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a group selected from
5-chlorothiophen-2-yl, 1-methyl-1H-pyrazol-5-yl, 2-hydroxypyridin-3-yl, 2-methylpyridin-3-yl and 2-methoxypyridin-3-yl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^2 represents a group selected from
phenyl, 3,3-dimethylphenyl and 1-naphthyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^3 represents a methoxy group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^4 represents a trifluoromethyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-,

(C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^2 represents a phenyl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)- and C_3-C_6-cycloalkyloxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^2 represents a phenyl group,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
methyl and methoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^2 represents a phenyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^3 represents a C_1-C_4-alkoxy group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^4 represents a C_1-C_4-haloalkyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^1 represents a group selected from
1-methyl-1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl and pyrazolo[1,5-a]pyridin-4-yl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^3 represents a methoxy group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-2), *supra*, in which:

R^4 represents a trifluoromethyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected

from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^1 represents a 5- to 10-membered heteroaryl group,
which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)- and C_3-C_6-cycloalkyloxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^2 represents a phenyl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
methyl and methoxy,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^2 represents a phenyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^3 represents a C_1-C_4-alkoxy group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^4 represents a C_1-C_4-haloalkyl group,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl and pyrazolo[1,5-a]pyridin-4-yl,

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

In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

R^3 represents a methoxy group,

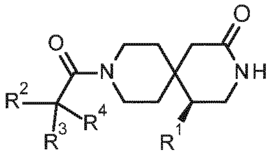
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

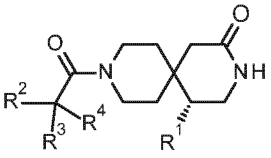
In a further embodiment of the first aspect, the present invention covers compounds of formula (I-3), *supra*, in which:

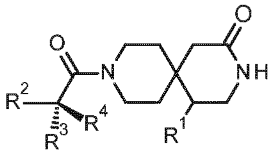
R^4 represents a trifluoromethyl group,

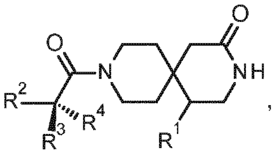
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

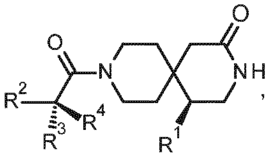
In accordance with an embodiment of the first aspect of the present invention, general formula (I-1) is divided into general sub-formulae (I-1a), (I-1b), (I-1c), (I-1d), (I-1e), (I-1f), (I-1g) and (I-1h):

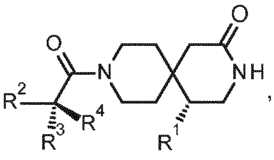

(I-1a),

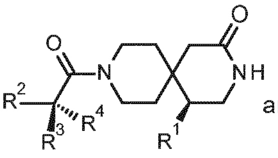

(I-1b),

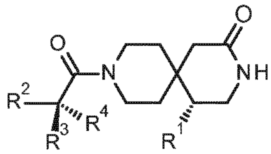

(I-1c),


(I-1d),


(I-1e),


(I-1f),

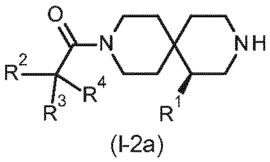

(I-1g) and

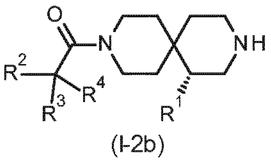

(I-1h),

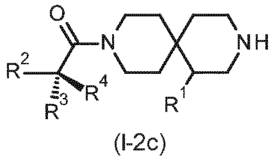
in which R^1, R^2, R^3 and R^4 are as defined above for the compounds of formula (I), *supra*,

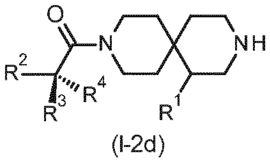
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

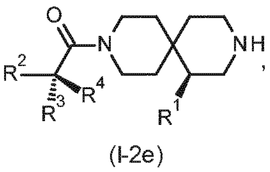
In accordance with a further embodiment of the first aspect of the present invention, general formula (I-2) is divided into general sub-formulae (I-2a), (I-2b), (I-2c), (I-2d), (I-2e), (I-2f), (I-2g) and (I-2h):

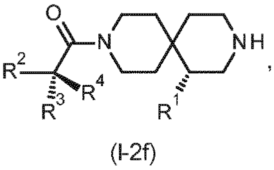

(I-2a),

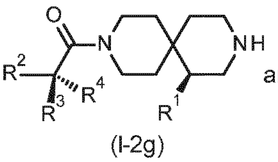

(I-2b),

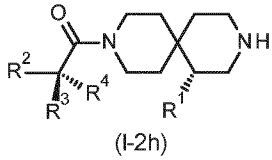

(I-2c),


(I-2d),


(I-2e),


(I-2f),

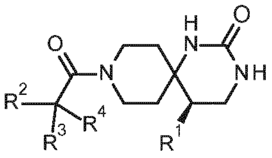

(I-2g) and

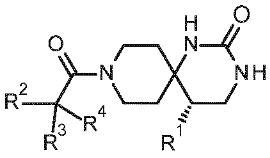

(I-2h),

in which R^1, R^2, R^3 and R^4 are as defined above for the compounds of formula (I), *supra*,

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

In accordance with a further embodiment of the first aspect of the present invention, general formula (I-3) is divided into general sub-formulae (I-3a), (I-3b), (I-3c), (I-3d), (I-3e), (I-3f), (I-3g) and (I-3h):


(I-3a)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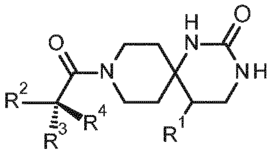
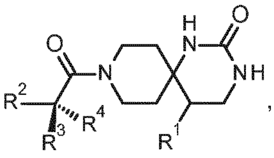
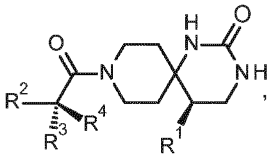
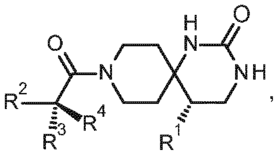
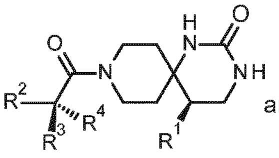

(I-3c)

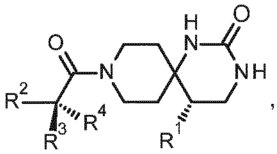

(I-3d)


(I-3e)


(I-3f)


(I-3g)

and


(I-3h)

in which R^1, R^2, R^3 and R^4 are as defined above for the compounds of formula (I), *supra*,

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

It is to be understood that all aspects, embodiments, pharmaceutical compositions, combinations, uses and/or methods of the present invention defined herein for the compounds of formula (I) also refer to more specific embodiments of the compounds of formula (I), such as, but not limited to, the compounds of formulae (I-1), (-2), (I-3), (I-3a), (I-3b), (I-3c), (I-3d), (I-3e), (I-3f), (I-3g), (I-3h), (I-2a), (I-2b), (I-2c), (I-2d), (I-2e), (I-2f), (I-2g), (I-2h), (I-3a), (I-3b), (I-3c), (I-3d), (I-3e), (I-3f), (I-3g) and/or (I-3h) for example.

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

The present invention covers any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I) and general formula (I-1), *supra*.

The present invention covers any sub-combination within any embodiment or aspect of the present invention of compounds of general formulae (I), (I-1), (-2), (I-3), (I-3a), (I-3b), (I-3c), (I-3d), (I-3e), (I-3f), (I-3g), (I-3h), (I-2a), (I-2b), (I-2c), (I-2d), (I-2e), (I-2f), (I-2g), (I-2h), (I-3a), (I-3b), (I-3c), (I-3d), (I-3e), (I-3f), (I-3g) and (I-3h), *supra*.

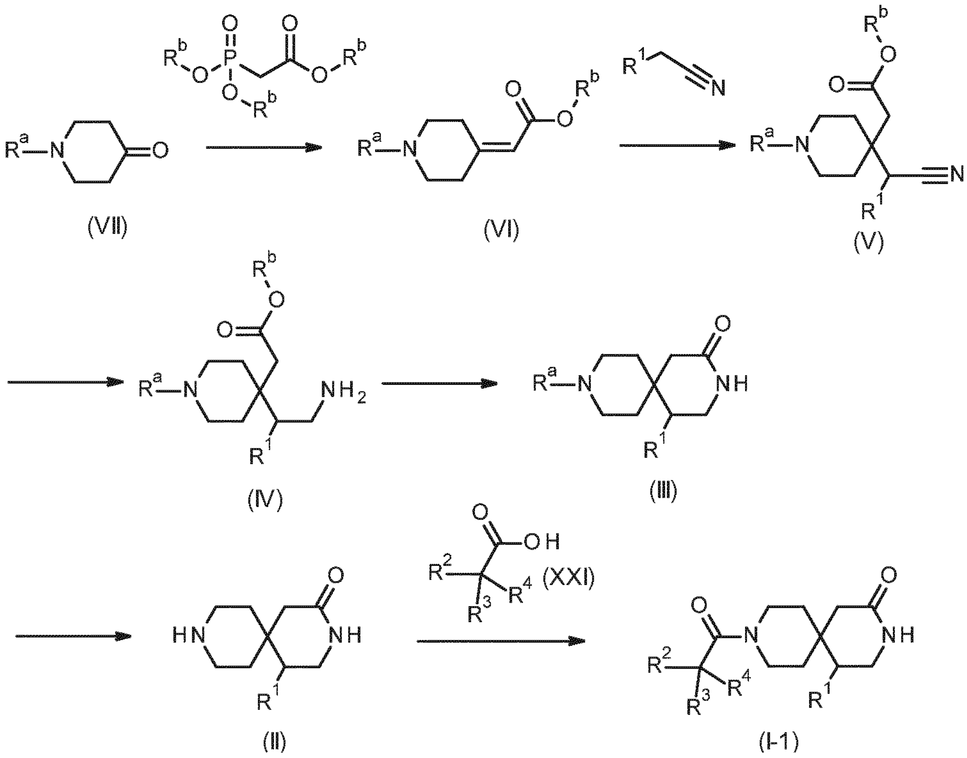
The present invention covers any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of general formulae (II), (II-a), (XVI), (XVII) and (XXI), *supra*.

The present invention covers the compounds of general formula (I) and and general formula (I-1) which are disclosed in the Example Section of this text, *infra*.

The compounds according to the invention of general formula (I) and general formulae (I-1), (I-2) and (I-3) can be prepared according to the following schemes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13. The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) and general formula (I-1) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in schemes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 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, R^4, R^a, R^b and X can be achieved before and/or after the exemplified transformations. These transformations 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*, 4th edition, Wiley 2006). Specific examples are described in the subsequent paragraphs.

Several routes for the preparation of compounds of general formula (I) and general formula (I-1), (I-2) and (I-3) are described in schemes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13.

Scheme 1



Scheme 1 Synthesis route for the preparation of compounds of general formula (I-1), which are compounds of general formula (I), in which -Y-Z- is a -CH$_2$-C(=O)- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a and R^b represent protecting groups.

R^a can be for example (not-limiting), *tert*-butoxycarbonyl (Boc), benzyl (Bn) and benzyloxycarboxybenzyl (Cbz) and R^b can be for example (not-limiting), methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and benzyl.

Compounds of general formula (VII) can be converted to compounds of general formula (VI) by numerous methods, such as, for example, Horner-Wandsworth-Emmons reaction (Sato et al., Heterocycles, 2001, 54, 747 – 755; Bradley et al., Bioorg. Med. Chem. Lett., 2003, 13, 629 – 632; Sugimoto et al., J. Med. Chem., 1990, 33, 1880 - 1887), Wittig reaction (Gilbert et al Bioorg. Med. Chem. Lett., 2010, 20, 608 – 611; Peschke et al., Eur. J. Med. Chem., 1999, 34, 363 - 380) and Peterson olefination (Sarkar et al, Tetrahedron Lett., 2011, 52, 923 - 927). These types of reactions are typically carried out with a base, such as for example, sodium hydride, in a solvent, such as for example, tetrahydrofuran, toluene in a temperature range ranging from -100℃ to the boiling point of the sol vent. Compounds of general formula (VI) can be converted to compounds of general formula (V) via a Michael addition with a nitrile under basic reaction conditions, such as for example, sodium hydride, potassium tert-butoxide, lithium hexamethyldisilazide, lithium diisopropylamide, sodium hexamethyldisilazide, in a solvent, such as for example, tetrahydrofuran, in a temperature range ranging from -78℃ to the boiling point of the solvent, these types of Michael addition reactions are known to those skilled and are available in the public domain (see the teachings of Grewe et al., Justus Liebis Ann. Chem., 1962, 653, 97 – 104; Hudkins et al., Bioorg. Med. Chem. Lett., 2012, 22, 194 – 198; Koelsch., J. Am. Chem. Soc., 1943, 65, 437; Banerjee et al., J. Indian Chem. Soc., 1983, 60, 1163 - 1168). Compounds of general formula (V) can be converted by reductive methods to compounds of general formula (IV), these compounds of general formula (IV) are usually formed in situ and are cyclized directly to give compounds of general formula (III), such reductive transformations are well-known to those skilled in the art, such transformations can be carried out with a catalyst, such as for example, Raney-Nickel with a base, such as for example, ammonia, under a pressurized atmosphere of hydrogen, in a solvent, such as for example, methanol or ethanol in a temperature range ranging from ambient temperature to the boiling point of the solvent or using other methods, such as for example, with a reducing agent, such as for example sodium borohydride, in the presence of a Lewis acid, such as for example, cobalt(II) chloride, in a solvent, such as for example, method or ethanol, in a temperature range ranging from -50℃ to the boiling point of the solvent (see the teachings of: e.g. pressurized catalytic hydrogenations using Nickel, Guengoer et al., J. Med. Chem., 1994, 37, 4307 – 4316; WO2005/97795 A1; MacKenzie et al., J. Med. Chem., 2002, 45, 5365 – 5377; WO2016/164284 A1; pressurized catalytic hydrogenations using Platinium or Platinium oxide (PtO_2), Petit et al., Eur. J. Med. Chem., 1990, 25, 641 - 652; Weinberg et al., Tetrahedron, 2013, 69, 4694 – 4707; sodium borohydride in the presence of cobalt chloride, Yang et al., Tetrahedron Lett., 2008, 49, 6371 – 6374; US2009/93501 A1; WO2015/96035;) and give compounds of general formula (III). Compounds of general formula (III) can be converted to compounds of general formula (II), using deprotection methods known to those skilled in the art, such as for example, using an acid, such as for example, hydrochloric acid or trifluoroacetic acid, in a solvent, such as for example, dioxane, methanol, dichloromethane, in a temperature range ranging from -50℃ to the boiling point of the solvent (see for example Greene's Protective Groups in Organic Synthesis, 4th edition, Editor P.G.M. Wuts in Wiley 200614), for such methods when R is *tert*-butoxycarbonyl (Boc) see the teachings of Bissantz et al., US2007/155761 A1 and WO2008/68159 A1, (hydrochloric acid in methanol); WO2015/96035 A1 and WO2015/100147 A1 (trifluoroacetic acid in dichloromethane); for such methods when R is benzyl (Bn), see the teachings of WO2005/97795 A1, Yang et al., Bioorg. Med. Chem. Lett., 2009, 19, 209 - 213 and Leonardi et al., J Med. Chem., 2004, 47, 1900 - 1918 (palladium on charcoal, hydrogen gas); US2009/281133 A1 and US2009/93501 A1 (palladium hydroxide, hydrogen gas). Compounds of general formula (II) can be converted to compounds of general formula (I-1) using carboxylic acids of general formula (XXI), using methods well known by those skilled in the art, such transformations can be carried out with a coupling reagent, such as for example, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-

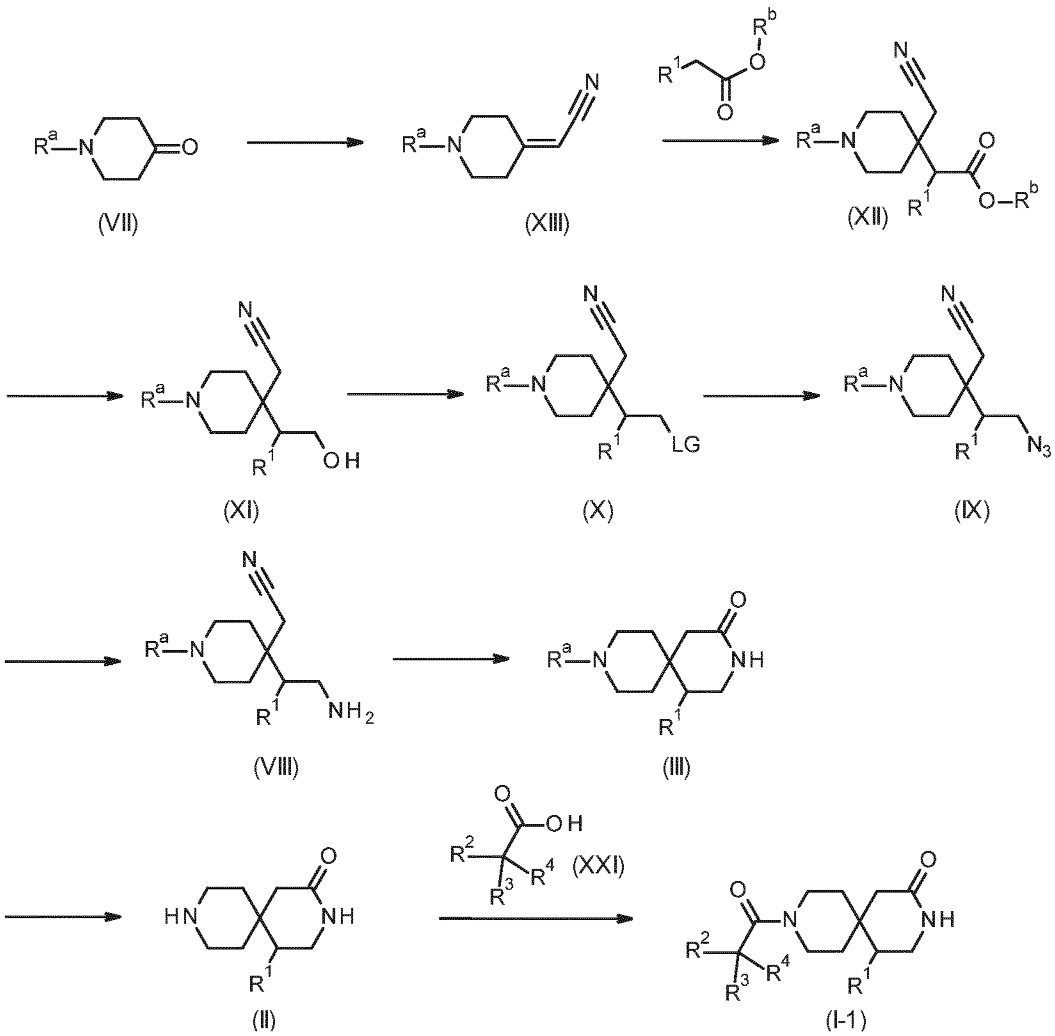
b]pyridinium 3-oxide hexafluorophosphate (HATU), with a base, such as for example, N,N-diisopropylethylamine, triethylamine, in a solvent, such as for example, dimethylformamide, in a temperature range ranging from 0℃ to the boiling point of the solvent. See the teachings listed below for such transformations of compounds of general formula (II) to compounds of general formula (I-1):

i. reacting with a carboxylic acid of general formula (XXI) and a coupling reagent, such as, for example, diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), 1-ethyl-(3-(3-dimethylamino)propyl)-carbodiimide hydrochloride (EDC), propanephosphonic acid anhydride (T3P), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), optionally in the presence of a base and optionally with 1-hydroxybenzotriazole (HOBt) or 1-hydroxy-7-azabenzotriazole (HOAt).

ii. reacting with a carboxylic acid anhydride in the presence of a base (e.g. Leonardi et al., J Med. Chem., 2004, 47, 1900 – 1918).

iii. reacting with an acid chloride in the presence of a base (e.g. Qiao et al., J Med. Chem., 2013, 56, 9275 - 9295).

Scheme 2



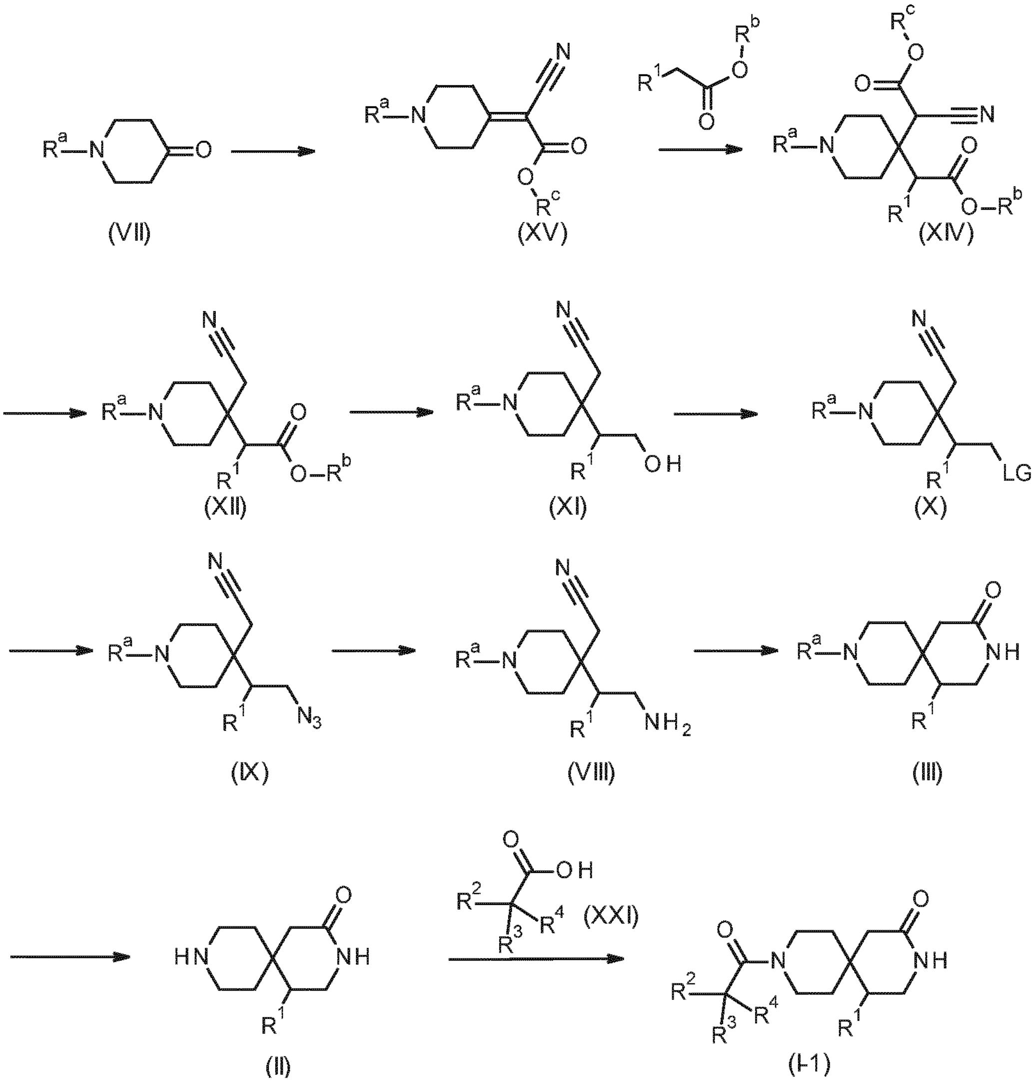
Scheme 2 Synthesis route for the preparation of compounds of general formula (I-1), which are compounds of general formula (I), in which -Y-Z- is a $-CH_2-C(=O)-$ group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a and R^b represent protecting groups, and LG represents a leaving group.

R^a can be for example (not-limiting), *tert*-butoxycarbonyl (Boc), benzyl (Bn) and benzyloxycarboxybenzyl (Cbz), and R^b can be for example (not-limiting), methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and benzyl. LG represents a leaving group, such as, for example, F, Cl, Br, I or aryl sulfonate such as for example p-toluene sulfonate (Tos), or alkyl sulfonate such as for example methane sulfonate (Ms) or trifluoromethane sulfonate (Tf).

Compounds of general formula (VII) can be converted to compounds of general formula (XIII) by numerous methods, such as for example, Horner-Wandsworth-Emmons reaction (Renslo et al., Bioorg. Med. Chem. Lett., 2007, 17, 5036 - 5040; Contreras et al., J. Med. Chem., 1999, 42, 730 – 741). Compounds of general formula (XIII) can be converted to compounds of general formula (XII) via a Michael addition with an ester under basic reaction conditions, these types of Michael addition reactions are known to those skilled in the art and are available in the public domain (see the teachings of Hutchison et al., J. Med. Chem., 1989, 32, 2221 - 2226). Compounds of general formula (XII) can be converted by reductive methods to compounds of general formula (XI), such reductive transformations are known using lithium pyrrolidinoborohydride (Yang et al., Tetrahedron Lett., 2008, 49, 6371 – 6374). Compounds of general formula (XI) can be converted to intermediates of general formula (X) using methods well-known to those skilled in the art (selected literature examples are: Vila et al., RSC Advances, 2016, 6, 46170 – 46185 and Meyers et al., Bioorg. Med. Chem. Lett., 2011, 21, 6545 – 6553 (X = Br); Nencini et al., Eur. J. Med. Chem., 2014, 78, 401 – 418 (X = OTos); Brown et al., J Med. Chem., 2014, 57, 733 – 758 and WO2010/58318 A1 (X = OMs); WO2009/131631 A1, (X = OTf)). Intermediates of general formula (X) can be converted to compounds of general formula (IX) using nucleophilic substitution methods to introduce an azide into a molecule are well-known to those skilled in the art (see: US2006/69123 A1; Ogino et al., Bioorg. Med. Chem. Lett., 2003, 13, 2167 – 2172; Askew et al., J. Med. Chem., 1997, 40, 1779 – 1788). Compounds of general formula (XI) can also be converted to compounds of general formula (IX) using known methods, such as, for example, diphenylphosphoryl azide, diethylazodicarboxylate and triphenylphosphine (Yang et al., Tetrahedron Lett., 2008, 49, 6371 – 6374). Compounds of general formula (IX) can be converted to compounds of general formula (VIII) using reductive methods which known to those skilled and are available in the public domain (see the teachings of Askew et al., J. Med. Chem., 1997, 40, 1779 – 1788 and Adang et al., Bioorg. Med. Chem. Lett., 1999, 9, 1227 – 1232 (palladium on charcoal, hydrogen gas) and US2011/212963 A1 and Chen et al., Bioorg. Med. Chem. Lett., 2012, 22, 363 – 366 (triphenylphospine, THF and water)).

Compounds of general formula (VIII) are usually generated in situ and cyclize to give compounds of general formula (III) as described *supra*, as well as the conversion of compounds of general formula (III) to compounds of general formula (II) and their transformation to compounds of general formula (I-1).

Scheme 3



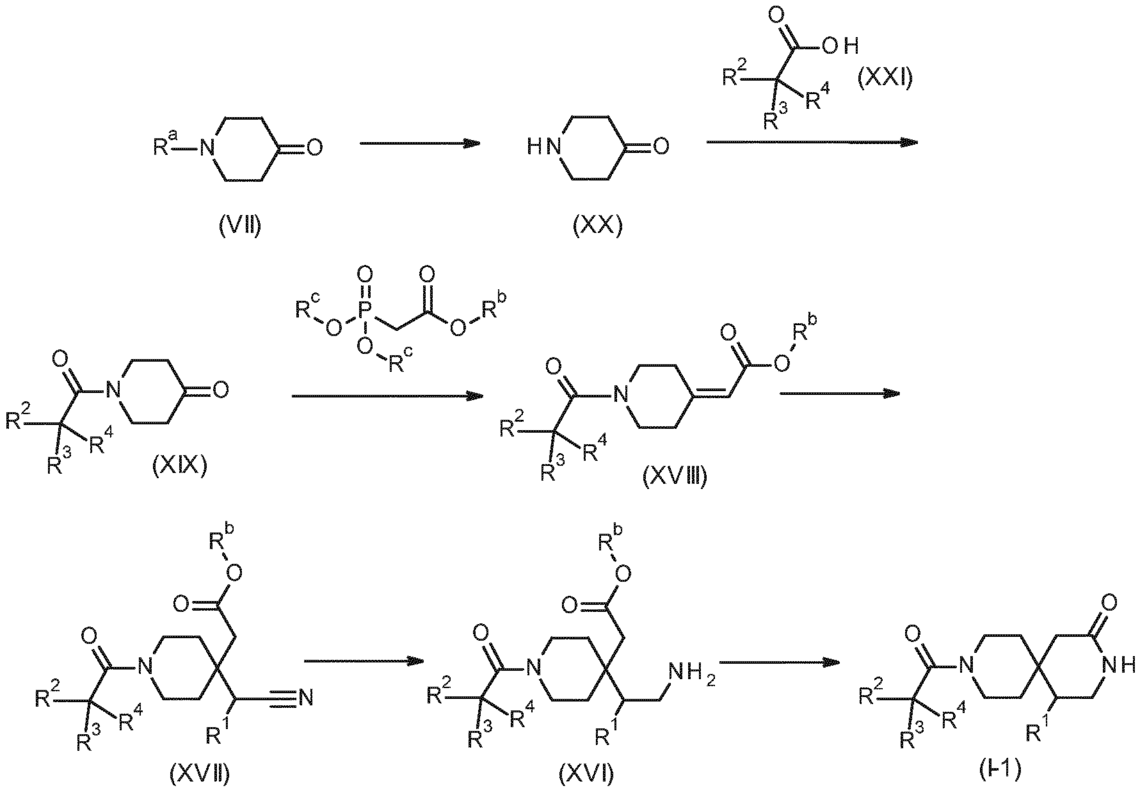
Scheme 3 Synthesis route for the preparation of compounds of general formula (I-1), which are compounds of general formula (I), in which -Y-Z- is a -CH$_2$-C(=O)- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a, R^b and R^c represent protecting groups, and LG represents a leaving group.

R^a can be for example (not-limiting), *tert*-butoxycarbonyl (Boc), benzyl (Bn) and benzyloxycarboxybenzyl (Cbz), and R^b and R^c can be for example (not-limiting), methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and benzyl. LG represents a leaving group, such as, for example, F, Cl, Br, I or aryl sulfonate such as for example p-toluene sulfonate, or alkyl sulfonate such as for example methane sulfonate or trifluoromethane sulfonate.

Compounds of general formula (VII) can be converted to compounds of general formula (XV) by numerous methods, such as for example, Horner-Wandsworth-Emmons reaction as described in the literature (see the teachings of Yang et al., Tetrahedron Lett., 2008, 49, 6371 and US2009/281133). Compounds of general formula (XV) can be converted to compounds of general formula (XIV) via a Michael addition with an ester under basic reaction conditions, these types of Michael addition reactions are known (see the teachings of Yang et al., Tetrahedron Lett., 2008, 49, 6371 and US2009/281133). Compounds of general formula (XIV) can be converted to compounds of general formula (XII) using decarboxylation methods such as using hexafluoroisopropanol at elevated temperatures, optionally using microwave heating conditions (Yang et al., Tetrahedron Lett., 2008, 49, 6371). This decarboxylation step to form compounds of general formula (XII) is also known to those skilled in the art and has been described for similar lower alkyl chain esters using the Krapcho conditions, e.g. lithium chloride, in DMSO, water at elevated temperatures (see the teachings of Yang et al., Tetrahedron Lett., 2008, 49, 6371 and US2009/281133).

The remaining steps within Scheme 3 follow the same route and methods as described in Scheme 2 to generate compounds of general formula (I).

Scheme 4



Scheme 4 Synthesis route for the preparation of compounds of general formula (I-1), which are compounds of general formula (I), in which -Y-Z- is a -CH_2-C(=O)- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a, R^b and R^c represent protecting groups.

R^a can be for example (not-limiting), *tert*-butoxycarbonyl (Boc), benzyl (Bn) and benzyloxycarboxybenzyl (Cbz), and R^b and R^c can be for example (not-limiting), methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and benzyl.

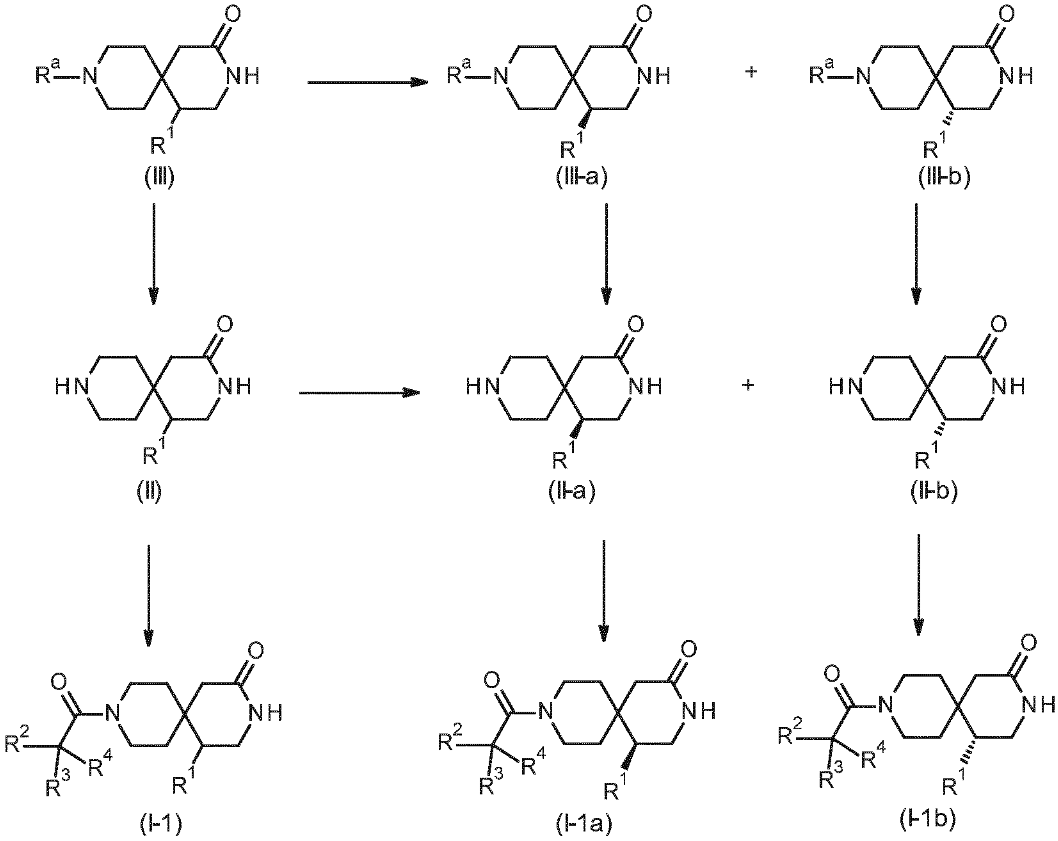
Compounds of general formula (VII) can be converted to compound (XX) by methods described in the literature, such as for example, using an acid, such as for example, hydrochloric acid or trifluoroacetic acid, in a solvent, such as for example, dioxane, methanol, dichloromethane, in a temperature range ranging from -50℃ to the boiling point of the solvent (see the teachings of: Evelyn et al., Bioorg. Med. Chem. Lett., 2010, 20, 665 – 672 and WO2009/76387 A1 (R = Boc), Yoo et al., Archiv der Pharmazie, 2003, 336, 208 – 215 and Li et al., Synth. Commun., 2006, 36, 925 – 928 (R = Bn), Felpin et al., Chem. Eur. J., 2010, 16, 12440 – 12445 (R = Cbz) or compound (XX) is commercially available (CAS No.: 41661-74-6) and as the hydrate (CAS No.: 709046-15-1) or the hydrochloric acid salt (CAS No.: 41979-39-9).

Compounds of general formula (XX) can be converted to compounds of general formula (XIX) using carboxylic acids of general formula (XXI), using methods well known by those skilled in the art, and are previously described in Scheme 1, such as, for example,

i. reacting with a carboxylic acid of general formula (XXI) and a coupling reagent, such as, for example, diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), 1-ethyl-(3-(3-dimethylamino)propyl)-carbodiimide hydrochloride (EDC), propanephosphonic acid anhydride (T3P), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), optionally in the presence of a base and optionally with 1-hydroxybenzotriazole (HOBt) or 1-hydroxy-7-azabenzotriazole (HOAt). See the teachings of Mangana et al., Tetrahedron Lett., 2015, 56, 1960 – 1963; WO2007/3934 A2; WO2008/124756 A1 and US2016/318866 A1).
ii. reacting with a carboxylic acid anhydride in the presence of a base (e.g. WO2007/124136 A1).
iii. reacting with an acid chloride in the presence of a base (e.g. WO2005/95402 A1; Van Der Klein et al., J Med. Chem., 1999, 42, 3629 – 3635; WO2015/74123).

The remaining steps within Scheme 4 follow similar routes and methods as described in Scheme 1 and 2 to generate compounds of general formula (I). For example, the methods used to convert compounds of general formula (XIX) to compounds of general formula (XVIII) are similar as those described in Scheme 1 to convert compounds of general formula (VII) to compounds of general formula (VI). In addition, the methods used to convert compounds of general formula (XVIII) to compounds of general formula (XVII) are similar as those described in Scheme 1 to convert compounds of general formula (VI) to compounds of general formula (V). Additionally, the methods used to convert compounds of general formula (XVII) via compounds of general formula (XVI) to compounds of general formula (I) are similar as those described in Scheme 1 to convert compounds of general formula (V) via compounds of general formula (IV) to compounds of general formula (III), whereby compounds of general formula (XVI) are generally formed in situ and then cyclize to give compounds of general formula (I-1).

Scheme 5



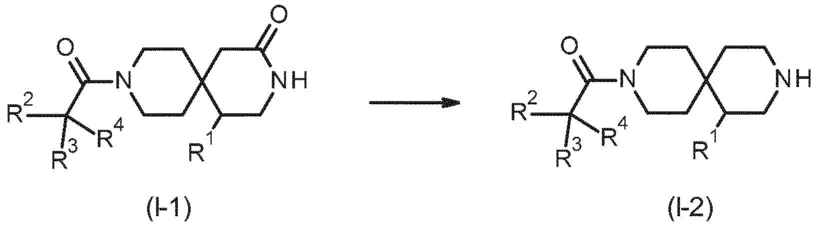
Scheme 5 Synthesis route for the preparation of compounds of general formula (I-1) and general formulae (I-1a) and (I-1b), which are compounds of general formula (I), in which -X-Y- is a $-CH_2-C(=O)-$ group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I) or general formula (I-1), *supra*, and R^a represents a protecting group.

R^a can be for example (not-limiting), *tert*-butoxycarbonyl (Boc), benzyl (Bn) and benzyloxycarboxybenzyl (Cbz).

Compounds of general formula (I-1), (II) and (III) can be a mixture of stereoisomers.

To those skilled in the art it is possible to carry out the chemical reactions described in Schemes 1, 2, 3 and 4, where the stereoisomers can be separated using various methods known to those skilled in the art, such as, for example, separation using chiral HPLC purification. The separation of these stereoisomers can be carried out on compounds of general formula (I-1), to give stereoisomers of general formula (I-1a) and (I-1b). Alternatively, the separation of these stereoisomers can be carried at an earlier stage in the synthetic route, such as, for example, the separation of the stereoisomers of compounds of general formula (II) or stereoisomers of compounds of general formula (III) to give compounds of general formula (II-a) and (II-b) or stereoisomers of compounds of general formula (III-a) and (III-b), respectively. The subsequent chemistry transformations using these stereoisomers can be carried out in analogy to the racemic mixtures described earlier. For example, compounds of general formula (III-a) can be converted to compounds of general formula (II-a) using the methods described for converting compounds of general formula (III) to compounds of the general formula (II) (see Schemes 1, 2 and 3). Analogously, compounds of general formula (II-a) can be converted to compounds of general formula (I-1a) using the methods described for converting compounds of general formula (II) to compounds of the general formula (I-1) (see Schemes 1, 2 and 3).

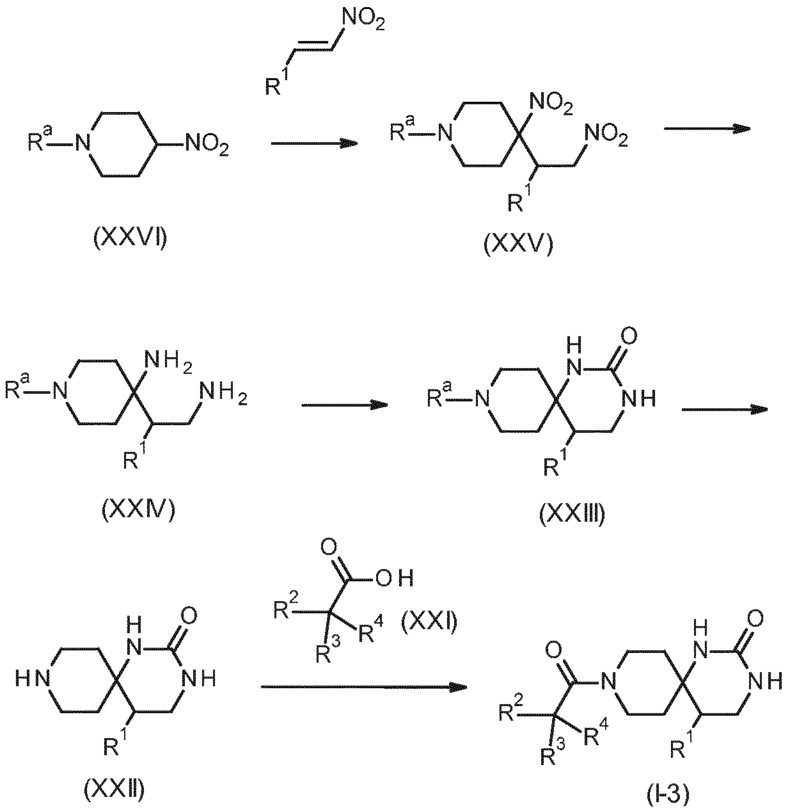
Scheme 6



Scheme 6 Synthesis route for the preparation of compounds of general formula (I-2), which are compounds of general formula (I), in which -Y-Z- is a -CH_2- CH_2- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra.*

Compounds of general formula (I-1) can be converted to compounds of general formula (I-2) by numerous methods, such as, for example, reductive methods. These reductive methods for converting a lactam to an amine have been described widely in the public domain. The commonly used method is with lithium aluminium hydride (see the teachings of Yang et al., Tetrahedron Lett., 2008, 49, 6371 – 6374; WO2015/96035, 2015, A1). Other reductive methods use borane-THF (WO2015/192053, 2015, A1; WO2009/109608, 2009, A1); dimethylsulfide borane complex (Oueslati et al., Org. Lett., 2007, 9, 153) and sodium tetrahydroborate in the presence of boron trifluoride diethyl etherate (EP1200406, 2004, B1).

Scheme 7



Scheme 7 Synthesis route for the preparation of compounds of general formula (I-3), which are compounds of general formula (I), in which -Y-Z- is a –N(H)-C(=O)- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a represent protecting groups. R^a can be for example (not-limiting), *tert*-butoxycarbonyl (Boc), benzyl (Bn) and benzyloxycarboxybenzyl (Cbz).

Compounds of general formula (XXVI) can be converted to compounds of general formula (XXV) by numerous methods, such as for example, Michael addition and such transformations are described in the literature under a variety of reaction conditions: see the teachings of Bora et al., Can. J. Chem., 2017, 95, 1261 – 1266 (aqueous phosphate buffer at pH 7); Fierro et al., J. Chem. Res. Part S, 2001, 294 – 296 (sodium bicarbonate at elevated temperature); Mahboobi and Grothus, Archiv der Pharmazie, 1994, 327, 349 – 358 (phase transfer catalysis); Singha et al.,.Chem. Commun., 2013, 50, 121 – 123 (alumina oxide at elevated temperatures); Meyers and Sircar, J. Org. Chem., 1967, 32, 4134 – 4136 (sodium hydroxide in water and acetonitrile); using organic bases (Alcantara et al., Synthesis, 1996, 64 - 70; Zenz et al., J. Org. Chem., 2011, 76, 9370 – 9378; Andrés et al., Beilstein J. Org. Chem., 2016, 12, 628 – 635). These transformations can be carried out in the presence of a base, such as for example (non-limiting), lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, preferably, potassium hydroxide, in a solvent, such as for example (non-limiting), methanol, ethanol, isopropanol, tetrahydrofuran, preferably ethanol, in a temperature range ranging from -78℃ to the boili ng point of the solvent preferably at ambient temperature.

Compounds of general formula (XXV) can be converted by reductive methods to compounds of general formula (XXIV), such reductive transformations are well-known to those skilled in the art, such transformations can be carried out with a catalyst, such as for example (non-limiting), palladium hydroxide, platinium oxide, Raney-Nickel with a base, such as for example, ammonia, under a pressurized atmosphere of hydrogen, in a solvent, such as for example, methanol or ethanol in a temperature range ranging from ambient temperature to the boiling point of the solvent (see the teachings of Yang et al., Chem. Commun., 2011, 47, 12706 – 12708; Kwiatkowski and Lu., Chem. Commun., 2014, 50, 9313 – 9316; WO2017/106064, 2017, A1; US2013/310394, 2013, A1).

Compounds of general formula (XXIV) can be converted to compounds of general formula (XXIII) via cyclization reaction. These types of transformations are well-described in the public domain can be carried out with (non-limiting) phosgene, trichlorophosgene, carbonyl di-imidiazole, phenyl carbonate, 4-nitrophenyl carbonate, in the presence of a base, in a solvent, in a temperature range ranging from ambient temperature to the boiling point of the solvent. For such transformations please see the teachings of Mecozzi et al., J. Org. Chem., 2001, 24, 8264 – 8267; Skinner et al. J. Am. Chem. Soc., 1957, 79, 3786; US2016/244460, 2016, A1; Shchepin et al., ACS Med. Chem. Lett., 2013, 4, 710 – 714).

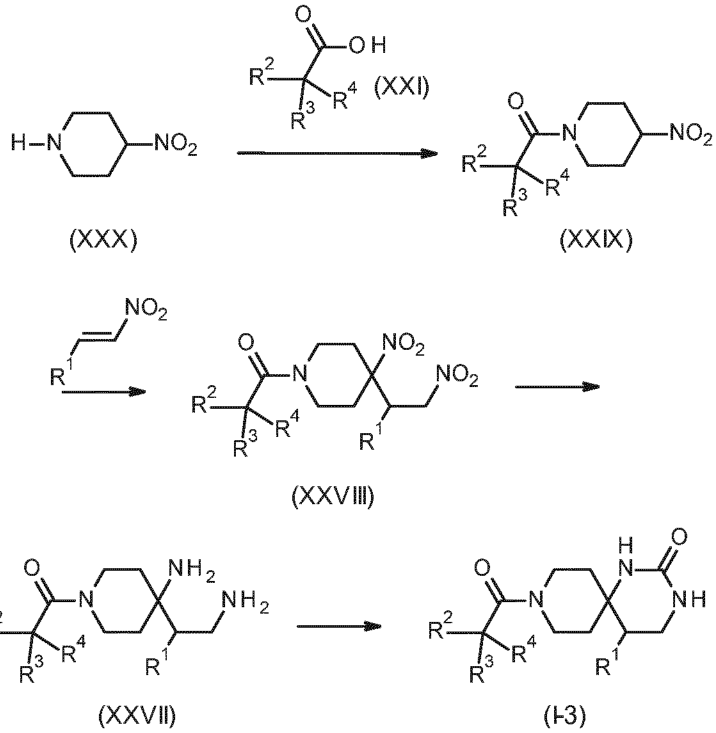
Compounds of general formula (XXIII) can be converted to compounds of general formula (XXII), using protection methods known to those skilled in the art, such as for example, see for example Greene's Protective Groups in Organic Synthesis, 4th edition, Editor P.G.M. Wuts in Wiley 2014. For such methods when R^a is *tert*-butoxycarbonyl (Boc) see the teachings of Dong et al., WO2015/96035, 2015, A1; WO2007/30061, 2007, A1; Yang et al., Bioorg. Med. Chem. Lett., 2009, 19, 209. For such methods when R^a is benzyl (Bn) or analogs like para-methoxybenzyl (PMB) see the teachings of Lv et al., see the teachings of Mercer et al., Eur. J. Med. Chem., 2008, 43, 1304 – 1308; Nagase et al., Bioorg. Med. Chem. Lett., 2010, 20, 6302 – 6305; EP892802, 2003, B1 and EP1679069, 2006, A1Compounds of general formula (II) can be converted to compounds of general formula (I) using carboxylic acids of general formula (XXI), using methods well known by those skilled in the art, such transformations can be carried out with a coupling reagent, such as for example, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), with a base, such as for example, N,N-diisopropylethylamine, triethylamine, in a solvent, such as for example, dimethylformamide, in a temperature range ranging from 0℃ to the boiling point of the solvent. See the teachings listed below for such transformations of compounds of general formula (XXII) to compounds of general formula (I-3):

i. reacting with a carboxylic acid of general formula (XXI) and a coupling reagent (non-limiting), such as, for example, diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), 1-ethyl-(3-(3-dimethylamino)propyl)-carbodiimide hydrochloride (EDC), propanephosphonic acid anhydride (T3P), benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), optionally in the presence of a base and optionally with 1-hydroxybenzotriazole (HOBt) or 1-hydroxy-7-azabenzotriazole (HOAt).

ii. reacting with a carboxylic acid anhydride in the presence of a base (e.g. Leonardi et al., J Med. Chem., 2004, 47, 1900 – 1918).

iii. reacting with an acid chloride in the presence of a base (e.g. Qiao et al., J Med. Chem., 2013, 56, 9275 - 9295).

Scheme 8



Scheme 8 Synthesis route for the preparation of compounds of general formula (I-3), which are compounds of general formula (I), in which -Y-Z- is a –N(H)-C(=O)- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a represent protecting groups.

Compounds of general formula (XXX) are known in the public domain or are commercially available (hydrochloride salt CAS No.: 1881295-85-7).

Compounds of general formula (XXX) can be converted to compounds of general formula (XXIX) using carboxylic acids of general formula (XXI), using methods well known by those skilled in the art, and are previously described in Scheme 1, such as, for example,

i. reacting with a carboxylic acid of general formula (XXI) and a coupling reagent (non-limiting), such as, for example, diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), 1-ethyl-(3-(3-dimethylamino)propyl)-carbodiimide hydrochloride (EDC), propanephosphonic acid anhydride (T3P), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), optionally in the presence of a base and optionally with 1-hydroxybenzotriazole (HOBt) or 1-hydroxy-7-azabenzotriazole (HOAt). See the teachings of Mangana et al., Tetrahedron Lett., 2015, 56, 1960 – 1963; WO2007/3934 A2; WO2008/124756 A1 and US2016/318866 A1).

ii. reacting with a carboxylic acid anhydride in the presence of a base (e.g. WO2007/124136 A1).

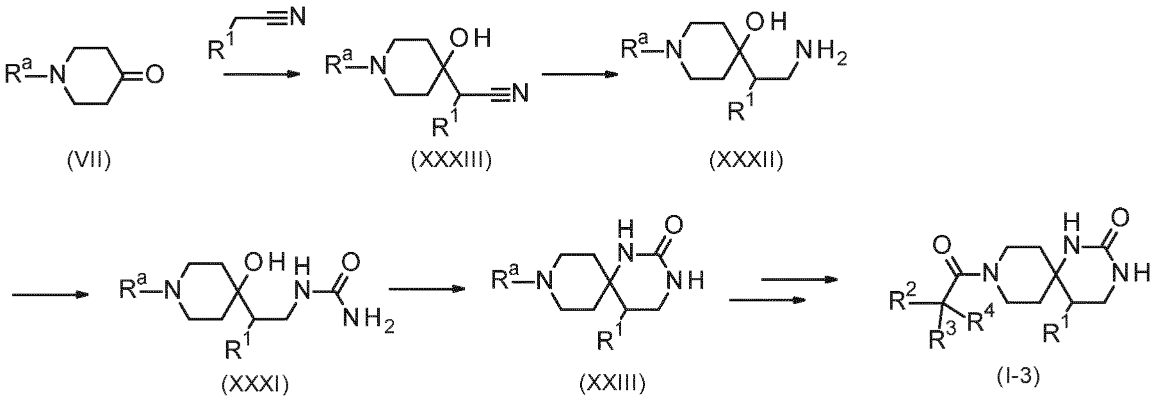
iii. reacting with an acid chloride in the presence of a base (e.g. WO2005/95402 A1; Van Der Klein et al., J Med. Chem., 1999, 42, 3629 – 3635; WO2015/74123).

Compounds of general formula (XXIX) can be converted to compounds of general formula (XXVIII) via a Michael addition under basic reaction conditions and such methods have been described in Scheme 7 for the conversion of compounds of general formula (XXVI) to compounds of general formula (XXV).

Compounds of general formula (XXVIII) can be converted to compounds of general formula (XXVII) by numerous methods, such as, for example, reductive methods. These reductive methods have been outlined in Scheme 7 for the conversion of compounds of general formula (XXV) to compounds of general formula (XXIV).

Compounds of general formula (XXVII) can be converted to compounds of general formula (I-3) via a cyclization reaction and such methods have been described in Scheme 7 for the conversion of compounds of general formula (XXIV) to compounds of general formula (XXIII).

Scheme 9



Scheme 9 Synthesis route for the preparation of compounds of general formula (I-3), which are compounds of general formula (I), in which -Y-Z- is a –N(H)-C(=O)- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a represent protecting groups.

Compounds of general formula (VII) could be converted to compounds of general formula (XXXIII) by reaction with nitrile compounds under basic conditions using, such as, for example, n-butyllithium (WO2014/210354 A1, WO2010/56564 A1), lithium hexamethyldisilazide (US2017/101406 A1) lithium diisopropylamide (WO2017/16669 A1) and potassium tert-butoxide. These types of reactions are typically carried out, in a solvent, such as for example, tetrahydrofuran, toluene, hexane, ethyl benzene, preferably tetrahydrofuran, in a temperature range ranging from -100℃ to the boiling point of the solvent.

Compounds of general formula (XXXIII) could be converted to compounds of general formula (XXXII) by reaction with nitrile compounds under basic conditions using, such as, for example, n-butyllithium (WO2014/210354 A1, WO2010/56564 A1), lithium hexamethyldisilazide (US2017/101406 A1) lithium diisopropylamide (WO2017/16669 A1) and potassium tert-butoxide. These types of reactions are typically carried out, in a solvent, such as for example, tetrahydrofuran, toluene, hexane, ethyl benzene, preferably tetrahydrofuran, in a temperature range ranging from -100℃ to the boiling point of the solvent.

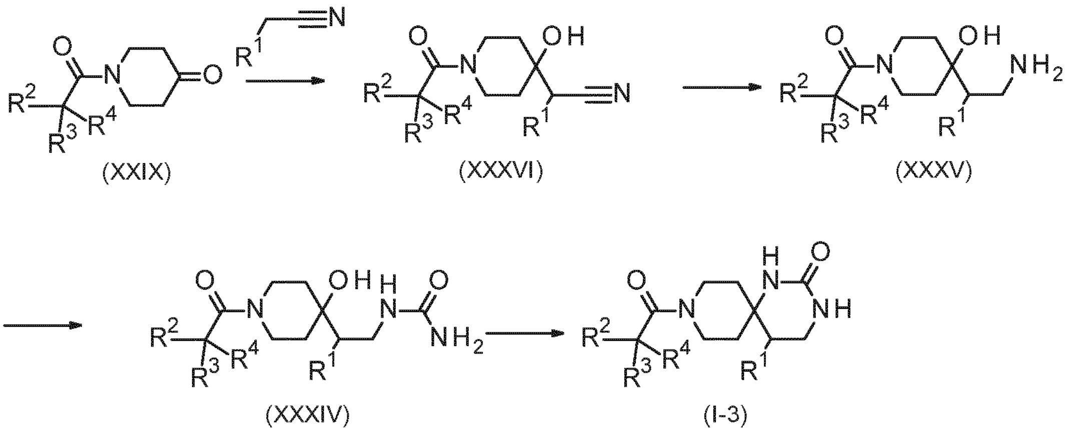
Compounds of general formula (XXXIII) could be converted by reductive methods to compounds of general formula (XXXII), such reductive transformations are well-known to those skilled in the art, such transformations can be carried out with a catalyst, such as for example, Raney-Nickel with a base, such as for example, ammonia, under an optionally over-pressurized atmosphere of hydrogen, in a solvent, such as for example, methanol or ethanol in a temperature range ranging from ambient temperature to the boiling point of the solvent or using other methods, such as for example, with a reducing agent, such as for example sodium borohydride, lithium aluminiumborohydride, optionally in the presence of a Lewis acid, such as for example, cobalt(II) chloride, in a solvent, such as for example, methanol or ethanol, in a temperature range ranging from -50℃ to the boiling point of the solvent (see the teachings of: e.g. pressurized catalytic hydrogenations using Nickel, WO2006/94934 A1; sodium borohydride in the presence of cobalt chloride, Rotstein et al., Bioorg. Med. Chem. Lett., 2009, 19, 5401 - 5406; US2005/176703 A1; lithium aluminium borohydride, Rotstein et al., Bioorg. Med. Chem. Lett., 2009, 19, 5401 - 5406; US2005/176703 A1; WO2017/79641 A1) and give compounds of general formula (XXXII).

Compounds of general formula (XXXII) could be converted to compounds of general formula (XXXI) using isocyanates, such as, for example, trimethylsilylisocyanate under basic conditions, such transformations being known to those skilled in the art (see the teachings of Coffey et al., J. Am. Chem. Soc., 2000, 122, 4893; WO2006/7540 and US5605923, 1997), or using sodium cyanate or potassium cyanate, such transformations being known to those skilled in the art (see the teachings of Yau et al., ACS Med. Chem. Lett., 2016, 7, 1179 and Lickefett et al., Tetrahedron Asymmetry, 1993, 4, 1129).

Compounds of general formula (XXXI) could be converted to compounds of general formula (XXIII) using acid and/or oxidizing conditions, such as, for example, carboxylic acids in sulfuric acid, or Jones reagent in a solvent. Such transformations are known to those skilled in the art and can be found in the public domain (see teachings of Denis et al., Synth. Commun., 1997, 27, 2345).

Compounds of general formula (XXIII) could be converted to compounds of general formula (I-3) following the methods described in Scheme 7.

Scheme 10



Scheme 10 Synthesis route for the preparation of compounds of general formula (I-3), which are compounds of general formula (I), in which -Y-Z- is a –N(H)-C(=O)- group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a represent protecting groups.

Compounds of general formula (XXIX) and there synthesis are described previously in Scheme 4.

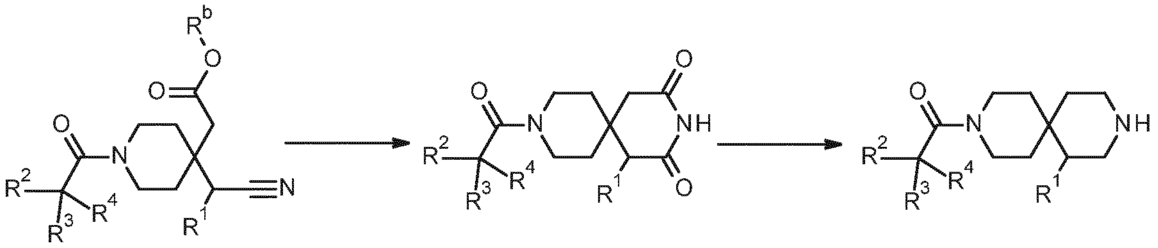
Compounds of general formula (XXIX) could be converted to compounds of general formula (XXXVI) using the same methods described in Scheme 9 for converting compounds of general formula (VII) to compounds of general formula (XXXIII).

Compounds of general formula (XXXVI) could be converted to compounds of general formula (XXXV) using the same methods described in Scheme 9 for converting compounds of general formula (XXXIII) to compounds of general formula (XXXII).

Compounds of general formula (XXXV) could be converted to compounds of general formula (XXXIV) using the same methods described in Scheme 9 for converting compounds of general formula (XXXII) to compounds of general formula (XXXI).

Compounds of general formula (XXXI) could be converted to compounds of general formula (I-3) using the same methods described in Scheme 9 for converting compounds of general formula (XXXI) to compounds of general formula (XXIII).

Scheme 11



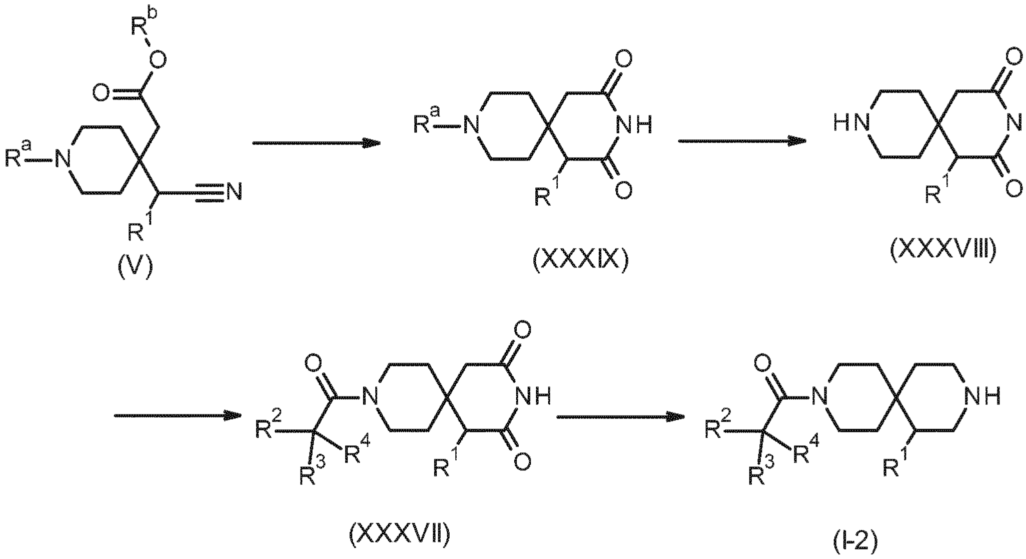
Scheme 11 Synthesis route for the preparation of compounds of general formula (I-2), which are compounds of general formula (I), in which -Y-Z- is a $–CH_2-CH_2-$ group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a and R^b represent protecting groups.

Compounds of general formula (XVII) and there synthesis are described previously in Scheme 4.

Compounds of general formula (XVII) could be converted to compounds of general formula (XXXVII) under acidic conditions, such, for example, sulfuric acid, acetic acid, trifluoroacetic anhydride, or mixtures thereof. Reactions are usually carried out at elevated temperatures (see teachings of Hammond et al., J. Fluorine Chem., 1988, 40, 81; Basavaiah et al., Org. Biomol. Chem., 2008, 6, 1034 and Roehnert, Chem. Ber., 1957, 90, 118). Such transformations can also be carried out under basic conditions (see teachings of Gensler et al., J. Org. Chem., 1975, 40, 733) and lewis acid conditions (see teachings of Singh et al., Tetrahedron, 2006, 37, 8731).

Compounds of general formula (XXXVII) could be converted to compounds of general formula (I-2) using reductive methods. Such methods are well known to those skilled in the art, such as using borane (See: WO2007/22936, 2007; WO2015/151001, 2015; Kormos et al., Bioorg. Med. Chem., 2016, 24, 3842), lithium aluminium hydride (See: EP2557082, 2013; WO2007/140383; Mimura et al., Chem. Pharm. Bull., 1993, 41, 1971) and Red-Al (See: Epstein et al., J. Med. Chem., 1981, 24, 481).

Scheme 12



Scheme 12 Synthesis route for the preparation of compounds of general formula (I-2), which are compounds of general formula (I), in which -Y-Z- is a $–CH_2-CH_2-$ group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a and R^b represent protecting groups.

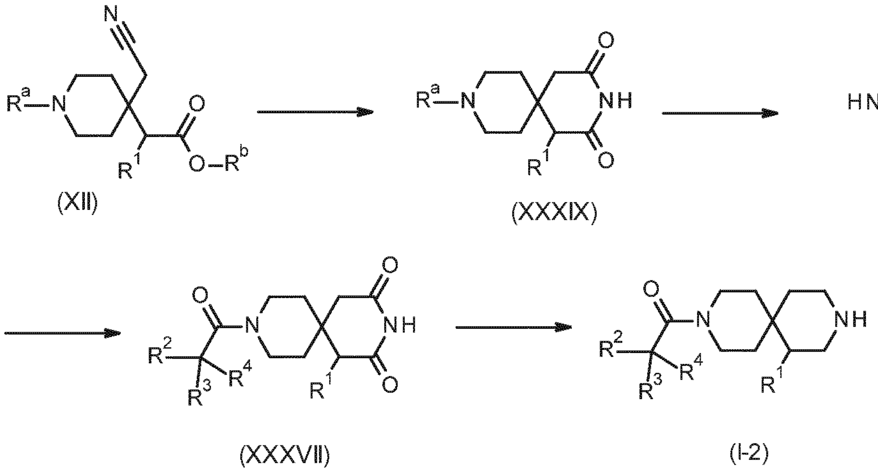
Compounds of general formula (V) could be converted to compounds of general formula (XXXIX) using methods well known by those skilled in the art, and are previously described in Scheme 11 for transforming compounds general formula (XVII) into compounds of general formula (XXXVII).

Compounds of general formula (XXXIX) could be converted to compounds of general formula (XXXVIII) using methods well known by those skilled in the art, and are previously described in Schemes 1, 2 and 3 for transforming compounds general formula (III) into compounds of general formula (II).

Compounds of general formula (XXXVIII) could be converted to compounds of general formula (XXXVII) using methods well known by those skilled in the art, and are previously described in detail in Scheme 1.

Compounds of general formula (XXXVII) could be converted to compounds of general formula (I-2) using methods well known by those skilled in the art, and are previously described in detail in Scheme 11.

Scheme 13



Scheme 13 Synthesis route for the preparation of compounds of general formula (I-2), which are compounds of general formula (I), in which -Y-Z- is a $–CH_2-CH_2-$ group, and in which R^1, R^2, R^3 and R^4 have the meaning as given for general formula (I), *supra*, and R^a and R^b represent protecting groups.

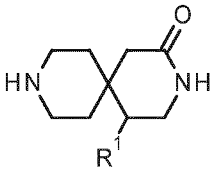
Compounds of general formula (XII) could be converted to compounds of general formula (XXXIX) using methods well known by those skilled in the art, and are previously described in Scheme 11.

The various subsequent transformations of compounds of general formula (XXXIX) through to compounds of general formula (I-2) have been described in Schemes 11 and 12.

Compounds VI, VII, XIII, XV, XX, XXI, XXVI and XXX are either commercially available or can be prepared according to procedures which are known to the person skilled in the art. Specific examples are described in the Experimental Section.

In accordance with a second aspect, the present invention covers methods of preparing compounds of general formula (I-1) as defined *supra*,

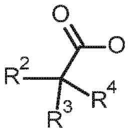
said methods comprising the step of allowing an intermediate compound of general formula (II) :



(II),

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

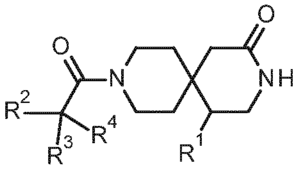
to react with a compound of general formula (XXI) :



(XXI),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*,

thereby giving a compound of general formula (I-1) :

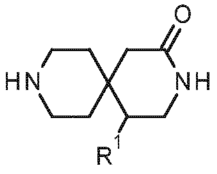


(I-1),

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

In accordance with a third aspect, the present invention covers methods of preparing compounds of general formula (I-1) as defined *supra,*

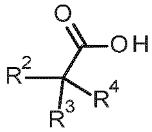
said methods comprising the step of allowing an intermediate compound of general formula (II) :



(II),

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

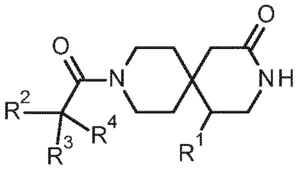
to react with a compound of general formula (XXI) :



(XXI),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*,

thereby giving a compound of general formula (I-1) :



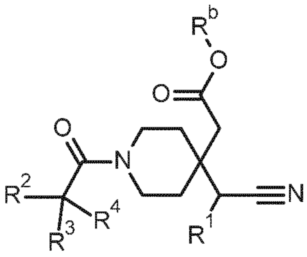
(I),

in which R^1, R^2 and R^3 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 fourth aspect, the present invention covers methods of preparing compounds of general formula (I-1) as defined *supra*,

said methods comprising the step of allowing an intermediate compound of general formula (XVII) :

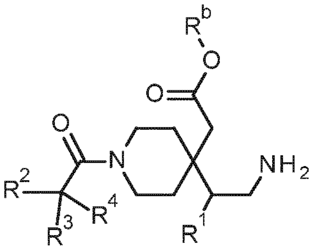


(XVII),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*, and R^b represents a group, such as for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or benzyl,

to react with a reducing agent, such as for example Raney-Nickel, with a base, such as for example ammonia, under a hydrogen atmosphere,

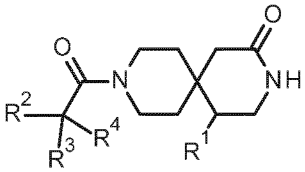
or to react with a reducing agent, such as for example sodium borohydride, in the presence of a Lewis acid, such as for example cobalt(II) chloride, thereby giving a compound of general formula (XVI) :



(XVI),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*, and R^b represents a group, such as for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or benzyl,

which compound of general formula (XVI) cyclizes, thereby giving a compound of general formula (I-1) :

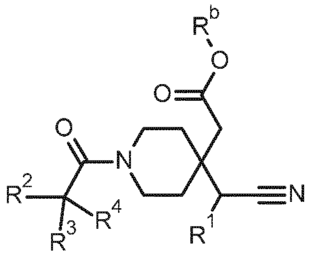


(I-1),

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

In accordance with a fifth aspect, the present invention covers methods of preparing compounds of general formula (I-1) as defined *supra*,

said methods comprising the step of allowing an intermediate compound of general formula (XVII) :

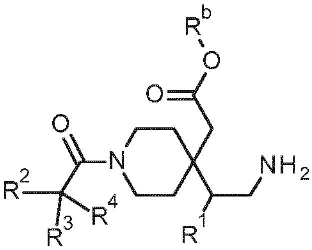


(XVII),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*, and R^b represents a group, such as for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or benzyl, to react with a reducing agent, such as for example Raney-Nickel, with a base, such as for example ammonia, under a hydrogen atmosphere,

or to react with a reducing agent, such as for example sodium borohydride, in the presence of a Lewis acid, such as for example cobalt(II) chloride,

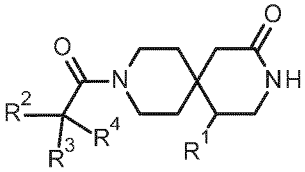
thereby giving a compound of general formula (XVI) :



(XVI),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*, and R^b represents a group, such as for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or benzyl,

which compound of general formula (XVI) cyclizes, thereby giving a compound of general formula (I-1) :



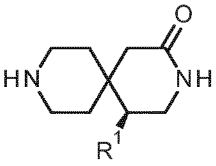
(I-1),

in which R^1, R^2 and R^3 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 sixth aspect, the present invention covers methods of preparing compounds of general formula (I-1a) as defined *supra*,

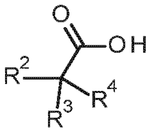
said methods comprising the step of allowing an intermediate compound of general formula (II-a) :



(II-a),

in which R^1 is as defined for the compound of general formula (I-1) as defined *supra*,

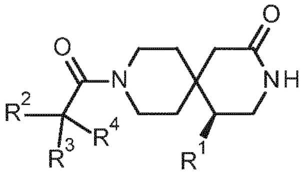
to react with a compound of general formula (XXI) :



(XXI),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I-1) as defined *supra*,

thereby giving a compound of general formula (I-1a) :

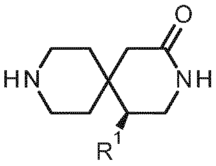


(I-1a),

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

In accordance with a seventh aspect, the present invention covers methods of preparing compounds of general formula (I-1) as defined *supra,*

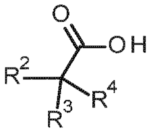
said methods comprising the step of allowing an intermediate compound of general formula (II-a) :



(II-a),

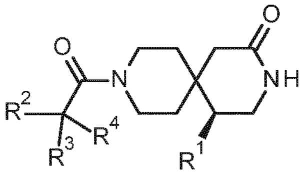
in which R^1 is as defined for the compound of general formula (I-1) as defined *supra*,

to react with a compound of general formula (XXI) :



(XXI),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I-1) as defined *supra*, thereby giving a compound of general formula (I-1a) :



(I-1a),

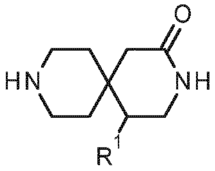
in which R^1, R^2 and R^3 are as defined *supra*,

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.

The present invention covers methods of preparing compounds of the present invention of general formula (I) and general formula (I-1), said methods comprising the steps as described in the Experimental Section herein.

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

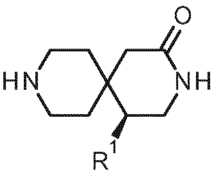
In accordance with a ninth aspect, the present invention covers intermediate compounds which are useful for the preparation of the compounds of general formula (I-1a), *supra*.Particularly, the inventions covers the intermediate compounds of general formula (II) :



(II),

in which R^1 is as defined for the compound of general formula (I) as defined *supra*.

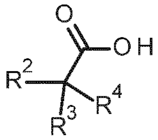
Particularly, the inventions covers the intermediate compounds of general formula (II-a) :



(II-a),

in which R^1 is as defined for the compound of general formula (I-1a) as defined *supra*.

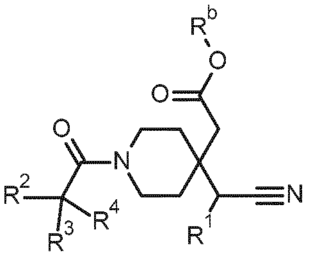
Particularly, the inventions covers the intermediate compounds of general formula (XXI) :



(XXI),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*.

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



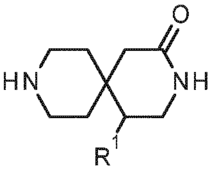
(XVII),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*, and R^b represents a group, such as for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or benzyl.

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

In accordance with an eleventh aspect, the present invention covers the use of said intermediate compounds for the preparation of a compound of general formula (I-1) as defined *supra*.

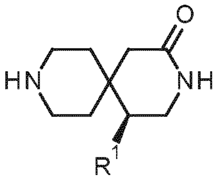
Particularly, the inventions covers the use of intermediate compounds of general formula (II) :



(II),

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

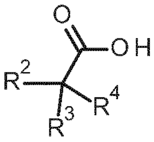
Particularly, the inventions covers the use of intermediate compounds of general formula (II-a) :



(II-a),

in which R^1 is as defined for the compound of general formula (I-1a) as defined *supra*, for the preparation of a compound of general formula (I-1a) as defined *supra*.

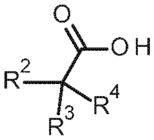
Particularly, the inventions covers the use of intermediate compounds of general formula (XXI) :



(XXI),

in which R^1, R^2 and $R^3$are as defined for the compound of general formula (I) as defined *supra*, for the preparation of a compound of general formula (I) as defined *supra*.

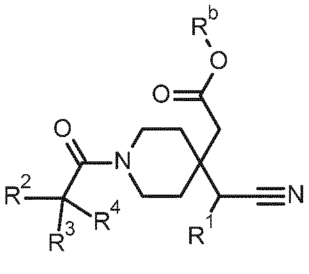
Particularly, the inventions covers the use of intermediate compounds of general formula (XXI) :



(XXI),

in which R^2 and A are as defined for the compound of general formula (I-1a) as defined *supra*, for the preparation of a compound of general formula (I-1a) as defined *supra*.

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



(XVII),

in which R^1, R^2 and R^3 are as defined for the compound of general formula (I) as defined *supra*, and R^b represents a group, such as for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or benzyl, for the preparation of a compound of general formula (I) as defined *supra*.

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

The present invention covers any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of general formulae (II), (II-a), (XVI), (XVII) and (XXI), *supra*.

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

Compounds of general formula (I) and general formula (I-1) 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 the activity of geranylgeranyltransferase I (GGTase I), leading to inactivation of downstream YAP1 and/or TAZ and blockade of cancer cell proliferation; and it is possible therefore that said compounds be used for the treatment or prophylaxis of diseases, preferably hyperproliferative disorders in humans and animals.

Compounds of the present invention can be utilized to effectively inhibit the activity of geranylgeranyltransferase I (GGTase I), leading to inactivation of downstream YAP1 and/or TAZ and blockade of cancer cell proliferation. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of general formula (I) or general formula (I-1) of the present invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof, which is effective to treat the disorder.

Another aspect of the invention is a method of inhibiting proliferation of a cell, comprising contacting the cell with a compound of formula (I) or general formula (I-1).

Hyperproliferative disorders include, but are not limited to, for example : hematological tumors such as leukemia, lymphoma, multiple myeloma, benign prostate hyperplasia (BPH), solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include sarcomas.

One aspect of the invention is the use of the compounds of formula (I) or general formula (I-1) for the treatment of cancer, the compounds of formula (I) or general formula (I-1) for use in the treatment of cancer as well as a method of treatment of cancer diseases comprising administering a specific amout of a compound of formula (I) or general formula (I-1).

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 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.

Examples of brain cancers include, but are not limited to, brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

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 digestive tract include, but are not limited to, anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumours of the urinary tract include, but are not limited to, bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to, intraocular melanoma and retinoblastoma.

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.

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.

Head-and-neck cancers include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell.

Sarcomas include, but are not limited to, sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Lung cancers include, but are not limited to, Bronchogenic Carcinoma Small Cell Lung Carcinoma, Non-small cell lung carcinoma, Lung Anaplastic Carcinoma, Lung Squamous Cell Carcinoma.

Mesothelioma include, but are not limited to, Mesothelioma I sarcomatoid and Mesothelioma I biphasic mesothelioma.

Endocrine cancers include, but are not limited to, Adrenal gland and Thyroid cancers.

Hematopoietic and lymphoid cancers include, but are not limited to Acute T cell leukemia, multiple Myeloma and Mantle cell lymphoma.

Another aspect of the invention is a method for controlling cancer in humans and animals by administering an effective amount of at least one compound of general formula (I) or general formula (I-1) of the present invention, or a pharmaceutically acceptable salt, polymorph, metabolite, hydrate, solvate or ester thereof, or of a medicament, comprising at least one compound of general formula (I) or general formula (I-1) of the present invention.

In another aspect, the present invention provides the use of a compound of general formula (I) or general formula (I-1) of the present invention, or a pharmaceutically acceptable salt, polymorph, metabolite, hydrate, solvate or ester thereof, for the preparation of a medicament for the treatment or prophylaxis of a disease.

Compounds of the present invention can be utilized to inhibit the activity of geranylgeranyltransferase I (GGTase I), leading to inactivation of downstream YAP1 and/or TAZ and blockade of cancer cell proliferation.

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 disorder.

In another aspect, the present invention provides methods of treating cancer, which cancer is selected from skin cancer, liposarcoma, cervical cancer, brain cancer, bladder cancer, endocrine cancer, lung cancer, gliosarcoma, colorectal carcinoma, head & neck cancer, hepatocellular carcinoma, breast cancer, ovarian cancer, gastric cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, sarcoma, lymphoma and leukemia.

In another aspect, the present invention provides methods of treating cancer, which cancer is selected from breast cancer, melanoma and ovarian cancer.

In another aspect, the present invention provides the use of a compound of general formula (I) or general formula (I-1) of the present invention, or a pharmaceutically acceptable salt, polymorph, metabolite, hydrate, solvate or ester thereof, for the treatment of cancer, which cancer is selected from skin cancer, liposarcoma, cervical cancer, brain cancer, bladder cancer, endocrine cancer, lung cancer, gliosarcoma, colorectal carcinoma, head & neck cancer, hepatocellular carcinoma, breast cancer, ovarian cancer, gastric cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, sarcoma, lymphoma and leukemia.

In another aspect, the present invention provides the use of a compound of general formula (I) or general formula (I-1) of the present invention, or a pharmaceutically acceptable salt, polymorph, metabolite, hydrate, solvate or ester thereof, for the treatment of cancer, which cancer is selected from breast cancer, melanoma and ovarian cancer.

These disorders 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 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 disorder, 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,
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 cancer agent combinations produce antagonistic effects.

In addition, the compounds of general formula (I) and general formula (I-1) 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) and general formula (I-1) 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) or general formula (I-1) 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) or general formula (I-1) 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) or general formula (I-1) 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) or general formula (I-1) 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) or general formula (I-1) 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.

In the context of the present invention, the term „treating" or “treatment” means combatting, inhibiting, delaying, hindering, alleviating, diminishing, limiting, reducing, suppressing, repressing or curing of a disease, of a complaint, of an illness, of an injury or of a health disorder, or of the development, the course or the progression of same.

In the context of the present invention, the term “prevention” or “prophylaxis” means avoiding or decreasing of the risk of getting, suffering from, sustaining or having a disease, a complaint, an illness, an injury or health disorder, or the development, the course, the progression or the symtoms of same.

Said treatment and/or prevention of a disease, a complaint, an illness, an injury or health disorder can be carried out partially or totally.

The compounds of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of hyperproliferative disorders, more particularly cancer.

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

In accordance with a further aspect, the present invention covers compounds of general formula (I-1), as described *supra*, or stereoisomers, tautomers, hydrates, and solvates thereof, or mixtures of same, for use in the treatment or prophylaxis of diseases, in particular hyperproliferative disorders, particularly benign hyperproliferative disorders, more particularly cancer.

In accordance with a further aspect, the present invention covers compounds of general formula (I) and general formula (I-1), 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 disorders, particularly benign hyperproliferative disorders, more particularly cancer.

The pharmacological activity of the compounds according to the invention can be explained by their ability to effectively inhibit the activity of geranylgeranyltransferase I (GGTase I), leading to inactivation of downstream YAP1 and/or TAZ and blockade of cancer cell proliferation.

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

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I-1), as described *supra*, or stereoisomers, tautomers, hydrates or solvates thereof, or mixtures of same, for the treatment and/or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I) and general formula (I-1), 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 and/or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, in a method of treatment and/or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer disorders.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I-1), as described *supra*, tautomers, hydrates or solvates thereof, or mixtures of same, in a method of treatment and/or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer disorders.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I) and general formula (I-1), 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 and/or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer disorders.

In accordance with a further aspect, the present invention covers use of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the preparation of a pharmaceutical composition, preferably a medicament, for the prophylaxis or treatment of diseases, in particular hyperproliferative disorders, particularly cancer disorders.

In accordance with a further aspect, the present invention covers use of a compound of general formula (I-1), as described *supra*, or stereoisomers, tautomers, hydrates or solvates thereof, or mixtures of same, for the preparation of a pharmaceutical composition, preferably a medicament, for the prophylaxis or treatment of diseases, in particular hyperproliferative disorders, particularly cancer disorders.

In accordance with a further aspect, the present invention covers use of a compound of general formula (I) or general formula (I-1), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the preparation of a pharmaceutical composition, preferably a medicament, for the prophylaxis or treatment of diseases, in particular hyperproliferative disorders, particularly cancer disorders.

In accordance with a further aspect, the present invention covers a method of treatment or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer, using an effective amount of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

In accordance with a further aspect, the present invention covers a method of treatment or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer, using an effective amount of a compound of general formula (I-1), as described *supra*, or stereoisomers, tautomers, hydrates or solvates thereof, or mixtures of same.

In accordance with a further aspect, the present invention covers a method of treatment or prophylaxis of diseases, in particular hyperproliferative disorders, particularly cancer, using an effective amount of a compound of general formula (I) or general formula (I-1), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular medicaments, comprising compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, salts thereof, particularly pharmaceutically acceptable salts, or mixtures of same, and one or more excipient(s), in particular one or more pharmaceutically acceptable excipient(s).

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular medicaments, comprising compounds of general formula (I-1), as described *supra*, or stereoisomers, tautomers, hydrates or solvates thereof, or mixtures of same, and one or more excipient(s), in particular one or more pharmaceutically acceptable excipient(s).

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular medicaments, comprising compounds of general formula (I) and general formula (I-1), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, salts thereof, particularly pharmaceutically acceptable salts, or mixtures of same, and one or more excipient(s), in particular one or more pharmaceutically acceptable excipient(s).

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

In accordance with another aspect, the present invention covers pharmaceutical combinations, in particular medicaments, comprising at least one compound of general formula (I) or general formula (I-1) of the present invention and at least one or more further active ingredients, in particular for the treatment and/or prophylaxis of a hyperproliferative disorder, particularly cancer.

Particularly, the present invention covers 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 agents.

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) or general formula (I-1) of the present invention, and a further active ingredient are present together in one unit dosage or in one single entity. One example of a “fixed combination” is a pharmaceutical composition wherein a first active ingredient and a further active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical combination wherein a first active ingredient and a further active ingredient are present in one unit without being in admixture.

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

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

Examples of anti-cancer agents include:

131I-chTNT, abarelix, abemaciclib, abiraterone, acalabrutinib, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, 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, 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, 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.

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more medical therapeutic means (e.g. surgical intervention, irradiation) and/or medical devices or appliances (e.g. breathing apparatuses, pacemaker implants, electrostimulation, stents).

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyperproliferative disorders, 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 preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Therapeutically 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 preferably be from 0.01 to 200 mg/kg body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg body weight.

Nevertheless, it may be necessary to deviate from the stated amounts, depending on the body weight, the route of administration, the individual behavior towards the active substance, the type of preparation and the time or interval at which the application takes place. Thus, in some cases, it may be sufficient to get by with less than the aforementioned minimum quantity, while in other cases the above-mentioned upper limit must be exceeded. In the case of the application of larger quantities, it may be advisable to distribute these in several doses throughout the day.

Nevertheless, it may be necessary to deviate from the stated amounts, depending on the body weight, the route of administration, the individual behavior towards the active substance, the type of formulation and the time or interval at which the application takes place. Thus, in some cases, it may be possible to achieve the desired effect with less than the aforementioned minimum quantity, while in other cases the above-mentioned upper limit must be exceeded. In the case of the application of larger quantities, it may be advisable to distribute these in several doses throughout the day.

Description of the Figures

Figure 1: Firefly luciferase reporter under control of a TEAD-promoter, as described under SEQ ID No. 1.

Figure 2: Firefly luciferase reporter under control of a TEAD-promoter (base pairs 27-304), as described under SEQ ID No. 2.

Figure 3: Recognition sequence of geranylgeranyl pyrophosphate (GGPP), as described under SEQ ID No. 3.

EXPERIMENTAL SECTION

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.

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

Abbreviation	**Meaning**
DAD	Diode Array Detector
DMEM	Dulbecco's Modified Eagle's Medium
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
ESI	electrospray (ES) ionization
FBS	Fetal bovine serum
h, hr (hrs)	hour(s)
Ham's F12	Ham's F-12 liquid medium developed by Ham
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]-pyridinium 3-oxide hexafluorophosphate
HCl	hydrogen chloride, hydrochloric acid
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography–mass spectrometry
min	minute(s)
MS	mass spectrometry
MTP	microtiter plate
MWD	Multiple wavelength detector
NMR	Nuclear Magnetic Resonance spectroscopy : chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50 ppm using unless otherwise stated.
PG	Protecting Group
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
rpm	rounds per minute
rt	room temperature
R_t, Rt	retention time
THF	tetrahydrofuran
δ	chemical shift

Other abbreviations have their meanings customary *per se* to the skilled person.

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.

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 removed by trituration using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartridges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or dichloromethane/methanol. In flash column chromatography, unmodified ("regular") silica gel may be used as well as aminophase functionalized silica gel. If reference is made to flash column chromatography or to flash chromatography in the experimenta section without specification of a stationary phase, regular silica gel was used.

In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

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

Analytical LC-MS Methods:

Method 1:

Instrument: Waters Acquity UPLCMS 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 ℃; DAD scan: 210-400 nm.

Method 2:

Instrument: Waters Acquity UPLCMS 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 ℃; DAD scan: 210-400 nm.

Method 3:

Instrument: Waters Acquity UPLCMS 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 ℃; DAD scan: 210-400 nm.

Method 4:

Instrument: Waters Acquity UPLCMS 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 ℃; DAD scan: 210-400 nm

Preparative LC-MS Methods:

Method 5:

Instrument: Waters Autopurification MS SingleQuad; Colum: Waters XBrigde C18 5µ 100x30mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-5.5 min 5-100% B; flow 70 ml/min; temperature: 25 ℃; DAD scan: 210-400 nm

Method 6:

Instrument: pump: Labomatic HD-5000 or HD-3000, head HDK 280, lowpressure gradient module ND-B1000; manual injection valve: Rheodyne 3725i038; detector: Knauer Azura UVD 2.15; collector: Labomatic Labocol Vario-4000; column: Chromatorex RP C-18 10 µm, 125x30mm; solvent A: water + 0.1 vol-% formic acid, solvent B: acetonitrile; gradient: 0.00-0.50 min 30% B (150 ml/min), 0.50–6.00 min 30-70% B (150 ml/min), 6.00-6.10 min 70-100% B (150 ml/min), 6.10-8.00 min 100% B (150 ml/min); UV-Detection.

Specific Optial Rotation Methods:

Method OR1:

Instrument: JASCO P2000 Polarimeter; wavelength 589 nm; temperature: 20 ℃; integration time 10 s; path length 100 mm.

NMR Spectra:

The multiplicities of proton signals in ^{1}H NMR spectra given in the following paragraphs reflect the observed signal form and do not take into account any higher-order signal phenomena. As a rule, the chemical shift data refers to the center of the signal in question. In the case of wide multiplets, a range is specified. Signals hidden by solvent or water were either assigned tentatively or are not listed. Strongly broadened signals - e.g. caused by rapid rotation of molecular moieties or by interchanging protons - have also been assigned tentatively (often referred to as a broad multiplet or broad singlet) or are not shown.

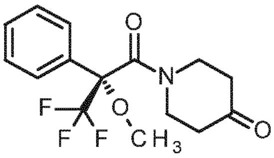
The ^{1}H-NMR data of selected compounds are listed in the form of ^{1}H-NMR peaklists. Therein, for each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, 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%.

EXPERIMENTAL SECTION – INTERMEDIATES

Intermediate 1

1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-one



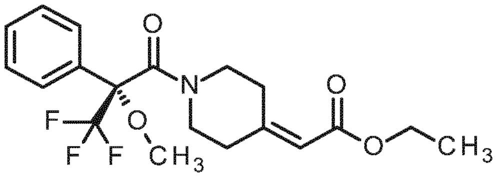
To a solution of (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (15.5 g, 66.2 mmol) in DMF (61 ml) under Argon was added HATU (25.2 g, 66.2 mmol) and N,N-diisopropylethylamine (42 ml, 241 mmol) and the reaction mixture was stirred at room temperature for 10 min. To the reaction mixture was added piperidin-4-one hydrochloride (8.16 g, 60.2 mmol) and stirred at room temperature for 24h. The reaction mixture was concentrated in vacuo to remove the excess N,N-diisopropylethylamine . The reaction was dissolved in ethyl acetate and washed with sat. sodium bicarbonate solution and brine, filtered through a hydrophobic filter and concentrated in vacuo. The residue was purified by flash chromatography (hexane: ethyl acetate) to give the title compound (15.8 g, 83%).

Optical rotation (method OR1): 73.0°(methanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.321 (1.05), 1.341 (2.39), 1.360 (2.23), 1.380 (2.64), 1.399 (1.21), 1.904 (1.07), 1.916 (2.32), 1.927 (1.14), 1.943 (1.02), 1.955 (2.13), 1.967 (0.99), 1.988 (0.56), 2.413 (4.31), 2.427 (7.08), 2.446 (2.96), 2.518 (2.58), 2.523 (1.78), 3.498 (3.98), 3.509 (4.43), 3.517 (4.36), 3.529 (3.80), 3.549 (1.41), 3.565 (1.69), 3.568 (1.85), 3.582 (2.20), 3.598 (1.83), 3.601 (2.09), 3.616 (1.47), 3.669 (6.37), 3.673 (16.00), 3.677 (15.43), 4.082 (1.09), 4.096 (2.35), 4.111 (1.47), 4.129 (2.07), 4.144 (0.94), 7.458 (0.86), 7.464 (4.32), 7.471 (4.11), 7.474 (6.57), 7.483 (15.58), 7.490 (12.47), 7.504 (2.65).

Intermediate 2

ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate

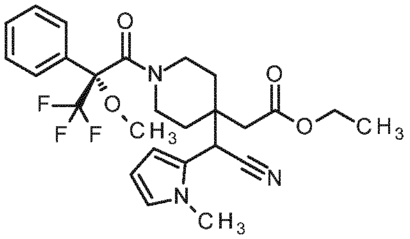


To a solution of ethyl (diethoxyphosphoryl)acetate (8.56 g, 38.2 mmol) in THF (60 ml) was added slowly sodium hydride (1.47 g, 60 % suspension in mineral oil, 36.7 mmol) maintaining a temperature of 5 to 10℃ and the mixture was stir red for 30 min at that temperature. A solution of 1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-one (Intermediate 1, 9.63 g, 30.5 mmol)in THF (60 ml) was added slowly at that temperature. Upon complete addition the mixture was allowed to warm to room temperature and stirred at that temperature for 1h. For the work-up, ethyl acetate and water were added, the phases were separted and the aqeous phase was extracted with ethyl acetate (2x). The combined organic phases were washed with brine, filtered through a hydrophobic filter and then concentrated to give the title compound (12.48 g) which was used in the next step without further purification.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.112 (0.61), 1.117 (3.94), 1.130 (1.30), 1.135 (8.99), 1.148 (4.08), 1.152 (5.03), 1.166 (7.79), 1.171 (3.17), 1.184 (3.66), 1.187 (1.72), 1.189 (1.58), 1.204 (0.62), 1.214 (0.77), 1.232 (1.88), 1.250 (0.79), 1.302 (0.45), 1.352 (0.46), 1.474 (0.42), 1.872 (0.46), 1.907 (0.41), 1.986 (4.33), 2.271 (0.44), 2.369 (0.55), 2.518 (1.01), 2.522 (0.65), 2.741 (0.50), 2.778 (0.47), 3.074 (0.47), 3.127 (0.50), 3.189 (0.96), 3.192 (0.89), 3.217 (1.40), 3.225 (1.50), 3.235 (1.01), 3.242 (1.19), 3.257 (1.10), 3.268 (0.88), 3.281 (0.64), 3.370 (0.74), 3.380 (0.79), 3.392 (0.53), 3.403 (0.56), 3.415 (0.56), 3.637 (9.54), 3.640 (9.24), 3.972 (1.16), 3.990 (3.77), 3.999 (1.00), 4.008 (4.43), 4.017 (1.77), 4.022 (1.89), 4.026 (1.99), 4.035 (1.97), 4.040 (4.21), 4.053 (1.05), 4.057 (3.59), 4.075 (1.01), 5.609 (1.69), 5.707 (1.76), 7.451 (0.97), 7.460 (1.14), 7.466 (2.57), 7.473 (12.28), 7.478 (16.00), 7.490 (1.11).

Intermediate 3

ethyl {4-[cyano(1-methyl-1H-pyrrol-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)

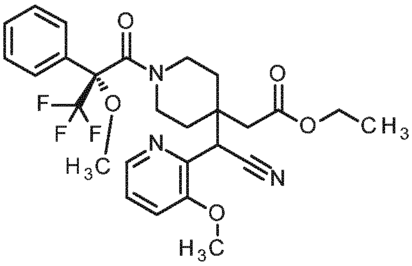


To a solution of ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol, Intermediate 2) and (1-methyl-1H-pyrrol-2-yl)acetonitrile (300 µl, 2.6 mmol) in THF (3.5 ml) under an Argon atmosphere was added a solution of potassium tert-butoxide (1M in THF, 1.3 ml) and then stirred at 0℃ for 30 min. The reaction mixture was poured onto ice-water/brine mixture and extracted with ethyl acetate. The organics phases were combined and washed with brine, filtered through an hydrophobic filter and concentrated *in vacuo*. The residue was purified by silica chromatography (Biotage hexane:ethyl acetate) to give the title compound 200 mg (90 % purity, 27 % yield) which was used directly in the next step without further purification.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.112 (0.48), 1.130 (1.12), 1.147 (1.81), 1.154 (4.54), 1.164 (3.17), 1.168 (2.28), 1.172 (8.75), 1.183 (1.67), 1.187 (3.13), 1.190 (4.66), 1.204 (1.16), 1.988 (16.00), 2.428 (0.52), 2.518 (1.71), 2.522 (1.11), 2.809 (0.52), 2.845 (0.46), 2.850 (0.46), 3.266 (3.72), 3.413 (0.54), 3.457 (3.39), 3.486 (0.79), 3.537 (1.65), 3.542 (1.73), 3.552 (0.99), 3.585 (2.45), 3.590 (1.91), 3.992 (0.44), 4.000 (1.29), 4.010 (0.48), 4.017 (4.03), 4.035 (4.40), 4.053 (1.98), 4.065 (0.67), 4.069 (0.68), 4.437 (1.14), 4.480 (1.02), 4.615 (0.40), 4.626 (0.41), 5.782 (0.41), 5.978 (0.45), 5.983 (0.50), 5.988 (0.70), 5.992 (0.71), 6.070 (0.46), 6.077 (0.54), 6.114 (0.48), 6.765 (0.54), 6.770 (0.50), 6.815 (0.43), 6.819 (0.52), 6.826 (0.41), 7.242 (1.95), 7.258 (0.81), 7.304 (0.45), 7.322 (0.58), 7.442 (1.14), 7.449 (0.92), 7.462 (0.92), 7.482 (0.50), 7.524 (0.42).

Intermediate 4

ethyl {4-[cyano(3-methoxypyridin-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)

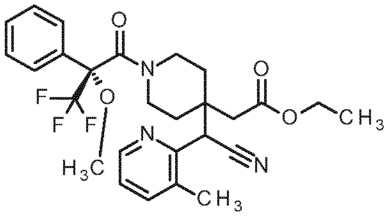


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from Intermediate 2 (500mg) and (3-methoxypyridin-2-yl)acetonitrile (280 µl, 2.6 mmol) to give the title compound 640 mg (69 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.161 (0.55), 1.179 (0.82), 1.197 (0.74), 1.202 (1.11), 1.209 (1.57), 1.220 (2.62), 1.227 (2.85), 1.236 (2.24), 1.246 (1.53), 1.253 (0.86), 2.043 (5.40), 2.573 (1.07), 2.578 (0.81), 3.494 (0.48), 3.567 (0.60), 3.628 (1.49), 3.637 (1.21), 3.698 (3.33), 3.811 (2.52), 3.871 (1.24), 3.880 (1.24), 3.917 (16.00), 4.047 (0.41), 4.055 (0.50), 4.073 (1.32), 4.078 (0.44), 4.090 (1.42), 4.097 (0.73), 4.111 (0.72), 4.115 (0.84), 4.131 (8.75), 4.857 (1.17), 4.886 (0.89), 5.067 (0.42), 5.079 (0.40), 7.167 (0.55), 7.185 (0.45), 7.218 (0.57), 7.332 (0.45), 7.413 (0.44), 7.419 (0.76), 7.425 (1.19), 7.437 (1.32), 7.446 (1.44), 7.458 (1.38), 7.484 (0.49), 7.493 (0.62), 7.500 (0.42), 7.534 (1.52), 7.538 (1.54), 7.555 (1.19), 7.559 (1.24), 7.569 (1.01), 7.579 (0.54), 7.590 (0.54), 7.600 (0.47), 7.603 (0.50), 8.171 (1.37), 8.175 (1.35), 8.183 (1.31), 8.187 (1.23), 8.234 (0.47), 8.238 (0.42), 8.291 (0.41).

Intermediate 5

ethyl {4-[cyano(3-methylpyridin-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)

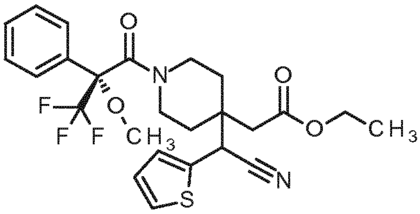


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from Intermediate 2 (500 mg) and (3-methylpyridin-2-yl)acetonitrile (330 µl, 2.6 mmol) to give the title compound 255 mg (34 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) delta [ppm]: -0.034 (0.30), -0.011 (0.50), 0.000 (0.50), 0.023 (0.30), 1.013 (0.22), 1.023 (0.25), 1.032 (0.23), 1.045 (0.49), 1.057 (0.46), 1.077 (0.58), 1.089 (0.58), 1.094 (0.59), 1.112 (1.21), 1.121 (0.48), 1.130 (0.49), 1.143 (0.32), 1.170 (0.78), 1.179 (1.96), 1.196 (4.14), 1.214 (1.88), 1.232 (6.74), 1.238 (4.56), 1.250 (16.00), 1.255 (9.61), 1.267 (10.40), 1.273 (4.47), 1.284 (3.53), 1.331 (0.78), 1.360 (0.61), 1.550 (0.20), 1.585 (0.23), 1.774 (0.71), 1.809 (0.84), 1.859 (0.30), 1.895 (0.19), 1.931 (0.23), 1.999 (0.61), 2.015 (0.48), 2.042 (1.08), 2.070 (0.58), 2.082 (11.86), 2.127 (0.63), 2.158 (10.55), 2.241 (0.23), 2.353 (8.50), 2.371 (7.04), 2.417 (6.25), 2.612 (4.04), 2.617 (3.39), 2.664 (1.63), 2.759 (0.61), 2.764 (0.82), 2.768 (0.61), 2.829 (0.55), 2.870 (0.42), 2.893 (0.55), 2.933 (0.46), 2.959 (0.49), 2.993 (1.99), 3.034 (1.53), 3.051 (1.62), 3.061 (0.85), 3.092 (1.56), 3.142 (0.22), 3.179 (0.38), 3.210 (0.69), 3.243 (0.42), 3.283 (0.32), 3.313 (0.53), 3.344 (0.35), 3.384 (1.88), 3.464 (0.22), 3.477 (0.23), 3.511 (0.19), 3.580 (2.29), 3.609 (0.49), 3.624 (0.68), 3.662 (7.14), 3.676 (5.76), 3.994 (0.29), 4.000 (0.16), 4.011 (0.16), 4.032 (0.46), 4.049 (1.44), 4.067 (1.41), 4.085 (0.52), 4.094 (1.92), 4.104 (0.92), 4.109 (3.00), 4.112 (5.35), 4.122 (2.37), 4.127 (4.57), 4.130 (5.32), 4.139 (2.39), 4.144 (2.86), 4.148 (1.88), 4.156 (0.84), 4.162 (0.61), 4.172 (0.23), 4.272 (0.22), 4.299 (5.35), 4.364 (0.62), 4.401 (0.46), 4.436 (0.52), 4.470 (0.49), 4.778 (4.52), 4.795 (3.87), 4.902 (0.23), 4.918 (1.56), 4.928 (0.23), 4.945 (1.63), 7.153 (1.07), 7.173 (2.52), 7.192 (1.90), 7.250 (2.42), 7.270 (1.59), 7.345 (1.08), 7.348 (0.76), 7.363 (2.83), 7.377 (3.16), 7.396 (1.33), 7.404 (0.68), 7.408 (0.63), 7.416 (0.63), 7.436 (1.54), 7.447 (1.75), 7.455 (1.92), 7.467 (3.30), 7.486 (2.68), 7.495 (1.69), 7.507 (2.70), 7.515 (1.77), 7.526 (3.26), 7.533 (1.77), 7.538 (2.50), 7.543 (2.41), 7.551 (0.98), 7.555 (0.85), 7.565 (0.25), 7.610 (0.92), 7.629 (1.40), 7.647 (0.55), 7.718 (0.75), 7.720 (0.75), 7.737 (0.69), 7.739 (0.69), 7.762 (1.39), 7.771 (1.99), 7.776 (2.03), 7.782 (1.30), 7.789 (1.67), 8.464 (0.68), 8.476 (0.63), 8.516 (1.92), 8.528 (1.77), 8.589 (1.23), 8.592 (1.27), 8.600 (1.26), 8.603 (1.17).

Intermediate 6

ethyl {4-[cyano(thiophen-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-piperidin-4-yl}acetate (mixture of stereoisomers)

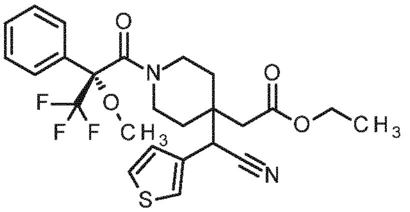


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from Intermediate 2 (500 mg) and (thiophen-2-yl)acetonitrile (280 µl, 2.6 mmol) to give the title compound 450 mg (61 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.133 (0.76), 1.138 (0.81), 1.150 (1.94), 1.155 (5.92), 1.163 (1.64), 1.168 (1.17), 1.173 (11.97), 1.181 (3.39), 1.190 (5.82), 1.199 (1.50), 1.238 (0.41), 1.988 (16.00), 2.299 (0.45), 2.322 (0.64), 2.327 (0.95), 2.332 (0.76), 2.337 (0.76), 2.518 (3.09), 2.523 (2.33), 2.627 (0.67), 2.665 (1.08), 2.669 (1.28), 2.673 (0.70), 3.606 (3.18), 3.627 (0.84), 3.643 (0.75), 3.912 (0.53), 4.000 (1.36), 4.012 (0.59), 4.017 (3.57), 4.023 (0.94), 4.026 (0.62), 4.030 (0.95), 4.035 (3.39), 4.041 (0.92), 4.044 (1.40), 4.048 (0.78), 4.053 (1.11), 4.062 (1.23), 4.725 (1.12), 4.780 (1.08), 5.051 (0.59), 5.058 (0.53), 6.917 (0.47), 6.919 (0.42), 6.974 (0.42), 6.981 (0.50), 6.982 (0.47), 7.021 (0.42), 7.054 (0.87), 7.060 (0.42), 7.063 (0.78), 7.067 (0.89), 7.076 (0.92), 7.078 (0.87), 7.087 (0.58), 7.091 (0.66), 7.100 (0.50), 7.379 (2.25), 7.386 (1.08), 7.389 (1.22), 7.392 (1.81), 7.402 (0.95), 7.405 (0.83), 7.414 (0.84), 7.418 (0.80), 7.426 (0.64), 7.430 (0.72), 7.434 (1.39), 7.439 (1.19), 7.442 (0.67), 7.447 (0.69), 7.451 (1.45), 7.466 (0.61), 7.470 (0.62), 7.488 (0.42), 7.595 (0.70), 7.597 (1.00), 7.608 (0.55), 7.611 (1.06), 7.615 (0.70), 7.625 (0.52), 7.628 (0.47).

Intermediate 7

ethyl {4-[cyano(thiophen-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-piperidin-4-yl}acetate (mixture of stereoisomers)

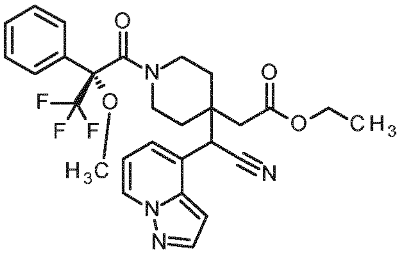


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from Intermediate 2 (500 mg) and (thiophen-3-yl)acetonitrile (300 µl, 2.6 mmol) to give the title compound 225 mg (31 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.137 (0.86), 1.155 (5.35), 1.161 (0.89), 1.168 (0.99), 1.173 (8.56), 1.179 (1.80), 1.186 (1.74), 1.191 (4.12), 1.196 (0.81), 1.204 (0.77), 1.988 (16.00), 2.518 (1.36), 2.523 (0.92), 3.602 (2.36), 3.616 (0.57), 3.712 (0.43), 4.000 (1.22), 4.012 (0.54), 4.018 (3.58), 4.030 (0.73), 4.035 (3.57), 4.047 (0.82), 4.053 (1.22), 4.056 (0.43), 4.065 (0.63), 4.450 (0.62), 4.470 (0.61), 7.353 (0.42), 7.357 (0.45), 7.363 (0.75), 7.366 (0.75), 7.370 (0.81), 7.373 (0.70), 7.382 (0.91), 7.400 (0.75), 7.410 (0.44), 7.414 (0.44), 7.429 (0.78), 7.431 (0.78), 7.448 (0.78), 7.455 (0.54), 7.607 (0.45), 7.627 (0.48).

Intermediate 8

ethyl {4-[cyano(pyrazolo[1,5-a]pyridin-4-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)

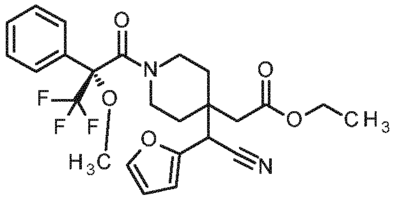


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from Intermediate 2 (250 mg) and (pyrazolo[1,5-a]pyridin-4-yl)acetonitrile (153 mg, 973 µmol) to give the title compound 200 mg (47 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.019 (0.48), 1.080 (0.43), 1.097 (0.95), 1.115 (0.53), 1.119 (0.60), 1.137 (1.23), 1.153 (5.03), 1.162 (2.32), 1.172 (9.51), 1.180 (4.85), 1.189 (5.01), 1.198 (2.32), 1.235 (0.46), 1.987 (16.00), 2.518 (1.69), 2.523 (1.13), 2.529 (0.76), 2.551 (0.47), 2.576 (0.59), 2.617 (0.66), 2.789 (0.42), 2.846 (0.43), 3.095 (0.43), 3.474 (0.82), 3.555 (3.94), 3.575 (2.06), 3.987 (0.53), 3.999 (1.29), 4.004 (0.68), 4.016 (3.75), 4.034 (3.76), 4.046 (0.61), 4.052 (1.43), 4.064 (1.36), 4.080 (1.25), 4.082 (1.20), 4.098 (0.42), 4.274 (3.06), 4.713 (1.19), 4.726 (2.01), 4.914 (0.50), 6.336 (1.02), 6.340 (0.99), 6.556 (0.61), 6.559 (0.59), 6.724 (0.89), 6.727 (0.99), 6.730 (0.94), 6.732 (0.93), 6.899 (0.59), 6.916 (1.30), 6.934 (0.83), 6.981 (1.30), 6.998 (1.87), 7.004 (2.02), 7.011 (0.96), 7.016 (1.37), 7.111 (0.92), 7.128 (0.72), 7.151 (0.99), 7.169 (0.85), 7.226 (0.74), 7.228 (0.72), 7.243 (0.65), 7.245 (0.65), 7.302 (0.45), 7.319 (0.97), 7.334 (0.57), 7.353 (0.92), 7.373 (0.64), 7.422 (0.74), 7.429 (0.76), 7.437 (0.60), 8.004 (1.49), 8.009 (1.43), 8.051 (0.99), 8.057 (1.15), 8.060 (1.53), 8.066 (1.44), 8.682 (0.74), 8.700 (0.72), 8.835 (0.89), 8.852 (0.86).

Intermediate 9

ethyl {4-cyano(furan-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-piperidin-4-yl}acetate (mixture of stereoisomers)

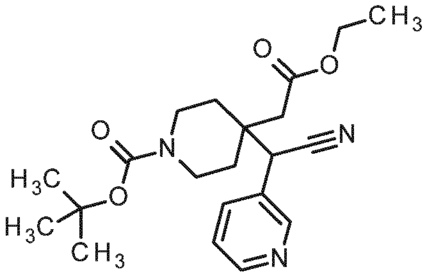


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from Intermediate 2 (500 mg) and (furan-2-yl)acetonitrile (260 µl, 2.6 mmol) to give the title compound 340 mg (48 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.537 (0.57), 0.548 (0.59), 0.568 (0.62), 0.578 (0.59), 1.034 (0.48), 1.125 (4.13), 1.143 (9.78), 1.147 (7.66), 1.154 (2.73), 1.161 (5.93), 1.165 (16.00), 1.172 (4.12), 1.183 (7.45), 1.190 (2.42), 1.237 (0.82), 1.371 (0.43), 1.394 (0.66), 1.425 (0.48), 1.483 (0.52), 1.507 (0.57), 1.647 (0.71), 1.677 (0.41), 1.784 (0.71), 1.987 (5.36), 2.199 (0.59), 2.230 (0.66), 2.237 (0.80), 2.268 (0.80), 2.322 (0.75), 2.326 (1.09), 2.332 (1.19), 2.364 (0.98), 2.375 (1.12), 2.404 (1.19), 2.439 (0.80), 2.449 (0.78), 2.518 (4.15), 2.522 (2.76), 2.593 (1.37), 2.619 (1.23), 2.634 (1.05), 2.660 (1.28), 2.664 (1.02), 2.668 (1.14), 2.673 (0.80), 3.028 (0.55), 3.060 (0.53), 3.095 (0.50), 3.199 (0.64), 3.237 (0.71), 3.466 (0.89), 3.503 (0.78), 3.555 (0.41), 3.604 (11.19), 3.623 (2.65), 3.967 (0.59), 3.972 (0.41), 3.977 (0.46), 3.984 (1.94), 3.990 (1.14), 3.995 (1.41), 4.002 (3.22), 4.008 (1.35), 4.012 (2.23), 4.019 (5.63), 4.029 (2.03), 4.037 (5.04), 4.047 (0.82), 4.055 (1.48), 4.247 (0.66), 4.272 (0.62), 4.586 (3.67), 4.613 (3.30), 4.912 (1.87), 4.931 (1.82), 6.302 (1.50), 6.309 (1.64), 6.323 (1.66), 6.330 (1.78), 6.464 (0.55), 6.469 (1.67), 6.474 (2.30), 6.478 (1.59), 6.482 (1.78), 6.492 (1.67), 6.494 (1.73), 6.496 (1.92), 6.499 (2.24), 6.504 (1.62), 6.513 (1.67), 6.518 (1.64), 6.521 (1.55), 6.526 (1.44), 7.366 (1.60), 7.383 (3.24), 7.393 (2.53), 7.411 (3.67), 7.423 (1.62), 7.427 (2.46), 7.432 (3.22), 7.438 (2.60), 7.444 (4.17), 7.448 (5.11), 7.455 (2.37), 7.464 (3.15), 7.473 (1.27), 7.477 (1.51), 7.481 (0.98), 7.487 (0.52), 7.495 (1.25), 7.696 (2.76), 7.699 (2.99), 7.701 (2.80), 7.713 (1.14), 7.715 (1.30), 7.718 (1.21), 7.720 (1.14), 7.727 (1.94), 7.729 (2.17), 7.732 (2.12), 7.734 (1.92).

Intermediate 10

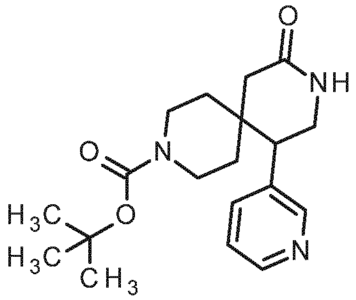
tert-butyl 4-[cyano(pyridin-3-yl)methyl]-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (mixture of stereoisomers)



Using an analogous method as described for Intermediate 3 the title compound was prepared starting from tert-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (10.3 g, 38.1 mmol) and (pyridin-3-yl)acetonitrile (4.50 g, 38.1 mmol) to give the title compound 5.5 g (35 % yield).

Intermediate 11

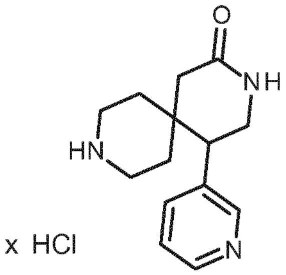
tert-butyl 10-oxo-7-(pyridin-3-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (mixture of stereoisomers)



An autoclave was charged with tert-butyl 4-[cyano(pyridin-3-yl)methyl]-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (5.50 g, 14.2 mmol, Intermediate 10), ammonia (110 ml, 2.0 M, 210 mmol) and Raney-Nickel (2.08 g, 35.5 mmol, 50% wet) and the mixture was stirred under 28 bar hydrogen atmosphere at 85℃ for 50 h. For the work-up, the mixture was filtered through a pad of celite, eluted with ethanol and the combined filtrates were concentrated under reduced pressure. The residue (4.88g, 95%) was used directly without further purification.

Intermediate 12

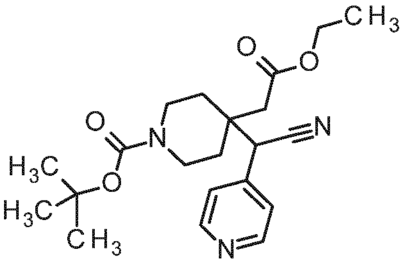
5-(pyridin-3-yl)-3,9-diazaspiro[5.5]undecan-2-one, salt with hydrochloric acid (mixture of stereoisomers)



To tert-butyl 10-oxo-7-(pyridin-3-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.00 g, 2.89 mmol, Intermediate 11) under Argon at 0℃ was added 1M HCl (4M in dioxane, 40ml). The reaction was stirred at RT for 1h and then concentrated to give the title compound (1.2g) which was used directly in the next step.

Intermediate 13

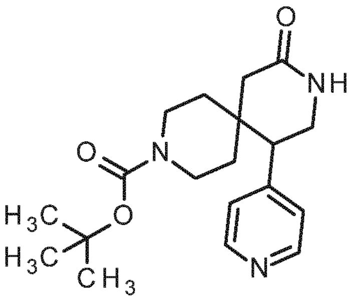
tert-butyl 4-[cyano(pyridin-4-yl)methyl]-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (mixture of stereoisomers)



Using an analogous method as described for Intermediate 3 the title compound was prepared starting from tert-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (11.4 g, 42.3 mmol) and pyridin-4-yl)acetonitrile (5.00 g, 42.3 mmol) to give the title compound 2.2 g (13 % yield).

Intermediate 14

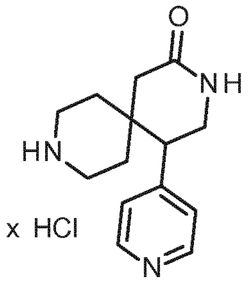
tert-butyl 10-oxo-7-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (mixture of stereoisomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from 4-[cyano(pyridin-4-yl)methyl]-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (2.20 g, 5.68 mmol, Intermediate 13) and gave the title compound 1.67 g (81 %), which was used further without purification.

Intermediate 15

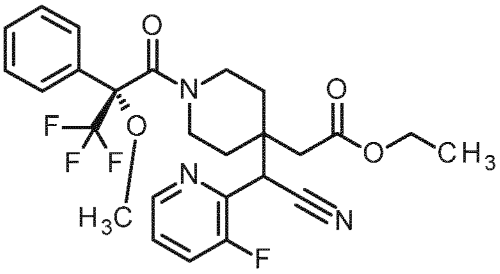
5-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecan-2-one, salt with hydrochloric acid (mixture of stereoisomers)



Using an analogous method as described for Intermediate 12, the title compound was prepared starting from tert-butyl 10-oxo-7-(pyridin-4-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (1.00 g, 2.89 mmol, Intermediate 14) and gave the title compound 1.00 g (quantitative), which was used further without purification.

Intermediate 16

ethyl {4-[cyano(3-fluoropyridin-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereosiomers)

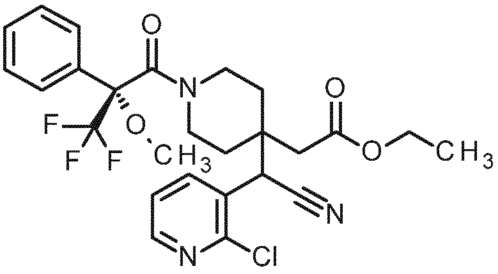


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol) and (3-fluoropyridin-2-yl)acetonitrile (353 mg, 2.59 mmol) gave the title compound 509 mg (68 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.080 (0.84), 1.098 (2.15), 1.106 (1.14), 1.116 (1.13), 1.124 (4.01), 1.134 (4.82), 1.136 (3.01), 1.141 (5.95), 1.151 (9.08), 1.154 (5.31), 1.158 (3.07), 1.169 (4.94), 1.172 (2.65), 1.215 (0.51), 1.777 (0.53), 1.812 (0.50), 1.966 (16.00), 2.497 (2.66), 2.502 (1.84), 2.549 (0.56), 2.555 (0.59), 2.589 (0.74), 2.596 (0.76), 2.745 (0.76), 2.787 (0.73), 2.795 (0.90), 2.837 (0.57), 3.460 (1.15), 3.481 (0.44), 3.515 (1.38), 3.560 (3.98), 3.563 (3.77), 3.937 (0.55), 3.949 (0.56), 3.954 (0.87), 3.961 (0.55), 3.972 (0.61), 3.978 (1.67), 3.992 (1.08), 3.996 (4.08), 4.009 (2.48), 4.014 (4.58), 4.027 (2.39), 4.032 (2.26), 4.044 (0.78), 4.049 (0.40), 4.291 (4.02), 4.295 (4.10), 4.760 (1.89), 4.786 (1.69), 5.021 (1.10), 7.119 (0.46), 7.139 (1.25), 7.158 (1.04), 7.190 (1.27), 7.209 (0.69), 7.245 (0.64), 7.263 (1.22), 7.296 (0.98), 7.314 (1.55), 7.331 (1.02), 7.335 (0.93), 7.349 (0.65), 7.364 (0.58), 7.373 (0.70), 7.408 (0.95), 7.412 (0.91), 7.419 (1.15), 7.425 (1.05), 7.436 (0.54), 7.462 (0.85), 7.474 (0.87), 7.480 (0.80), 7.483 (1.14), 7.494 (1.10), 7.501 (0.57), 7.505 (0.65), 7.512 (0.49), 7.523 (0.51), 7.534 (0.41), 7.563 (0.47), 7.574 (0.58), 7.584 (0.60), 7.595 (0.42), 7.602 (0.53), 7.612 (0.65), 7.622 (0.65), 7.750 (0.63), 7.753 (0.69), 7.771 (1.01), 7.774 (1.55), 7.777 (0.90), 7.782 (0.57), 7.785 (0.61), 7.791 (0.74), 7.795 (1.34), 7.798 (1.15), 7.802 (0.52), 7.807 (0.70), 7.810 (0.68), 7.816 (0.58), 7.819 (0.51), 8.405 (0.61), 8.409 (1.04), 8.412 (0.68), 8.417 (0.66), 8.420 (1.04), 8.424 (0.65), 8.460 (0.93), 8.472 (0.72), 8.491 (0.76), 8.495 (0.48), 8.503 (0.74).

Intermediate 17

ethyl {4-[(2-chloropyridin-3-yl)(cyano)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereosiomers)

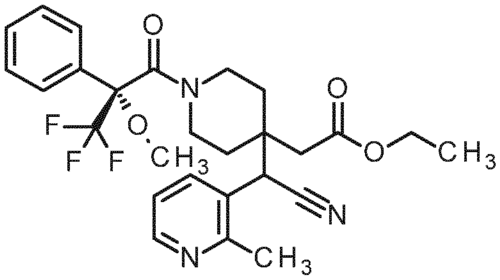


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol) and (2-chloropyridin-3-yl)acetonitrile (396 mg, 2.59 mmol) gave the title compound 465 mg (60 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.322 (0.47), 0.393 (0.50), 0.404 (0.50), 1.039 (0.93), 1.064 (0.70), 1.103 (1.31), 1.122 (2.94), 1.139 (2.13), 1.154 (2.59), 1.162 (6.35), 1.172 (6.67), 1.180 (16.00), 1.190 (5.89), 1.199 (10.58), 1.208 (1.89), 1.217 (4.20), 1.393 (0.44), 1.414 (0.76), 1.425 (0.76), 1.447 (0.50), 1.458 (0.41), 1.694 (0.99), 1.724 (0.70), 1.952 (0.61), 1.987 (8.95), 2.420 (1.14), 2.461 (1.63), 2.518 (8.77), 2.522 (5.33), 2.795 (0.41), 2.921 (0.67), 2.957 (0.82), 2.994 (1.92), 3.034 (1.22), 3.107 (1.22), 3.143 (1.49), 3.174 (0.64), 3.245 (0.61), 3.469 (1.72), 3.573 (9.09), 3.587 (6.56), 3.635 (0.44), 3.971 (0.58), 3.976 (0.64), 3.989 (0.61), 3.994 (0.61), 3.999 (0.70), 4.017 (1.98), 4.024 (0.47), 4.035 (2.27), 4.042 (1.25), 4.051 (2.36), 4.059 (2.33), 4.067 (3.58), 4.072 (3.23), 4.077 (2.04), 4.085 (3.12), 4.089 (2.77), 4.103 (1.02), 4.107 (0.82), 4.144 (1.66), 4.334 (0.50), 4.375 (0.99), 4.411 (0.67), 4.833 (6.47), 4.959 (1.37), 4.979 (1.40), 6.992 (1.14), 7.010 (2.48), 7.030 (1.60), 7.148 (2.68), 7.167 (2.10), 7.227 (1.14), 7.245 (1.87), 7.264 (0.87), 7.283 (1.14), 7.301 (2.54), 7.321 (2.21), 7.339 (2.62), 7.360 (1.89), 7.442 (2.42), 7.447 (2.21), 7.457 (1.43), 7.504 (1.25), 7.517 (1.31), 7.522 (1.49), 7.536 (1.17), 7.549 (0.52), 7.584 (0.58), 7.588 (0.67), 7.603 (1.84), 7.607 (2.86), 7.619 (2.33), 7.626 (1.98), 7.632 (1.72), 7.638 (1.95), 7.652 (0.64), 7.927 (1.31), 7.931 (1.37), 7.947 (1.19), 8.100 (0.64), 8.444 (0.55), 8.449 (0.87), 8.455 (0.82), 8.461 (0.85), 8.466 (0.52), 8.512 (1.49), 8.517 (1.46), 8.524 (1.28), 8.528 (1.34), 8.595 (2.01), 8.599 (2.04), 8.606 (2.04), 8.611 (1.87).

Intermediate 18

ethyl {4-[cyano(2-methylpyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereosiomers)

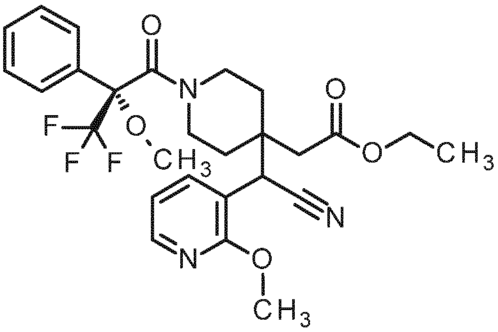


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and (2-methylpyridin-3-yl)acetonitrile (320 µl, 2.6 mmol) gave the title compound 131 mg (18 % yield) after silica chromatography (ethylacetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.000 (0.43), 0.471 (0.45), 0.482 (0.47), 1.043 (0.94), 1.078 (0.73), 1.167 (1.22), 1.185 (2.62), 1.203 (1.36), 1.221 (4.46), 1.229 (2.92), 1.239 (9.59), 1.247 (5.96), 1.257 (7.16), 1.259 (7.77), 1.265 (3.27), 1.277 (3.21), 1.751 (0.54), 1.786 (0.44), 2.000 (0.53), 2.033 (0.55), 2.054 (16.00), 2.262 (5.55), 2.389 (0.52), 2.393 (0.69), 2.398 (0.52), 2.451 (0.88), 2.468 (0.57), 2.496 (9.21), 2.732 (0.53), 2.736 (0.70), 2.740 (0.53), 2.924 (0.51), 2.954 (0.62), 3.038 (0.68), 3.050 (1.19), 3.091 (0.97), 3.141 (0.65), 3.184 (0.87), 3.295 (0.59), 3.369 (1.71), 3.512 (0.91), 3.630 (3.91), 3.650 (5.63), 3.694 (0.43), 4.012 (0.47), 4.020 (0.52), 4.030 (0.51), 4.038 (0.51), 4.061 (0.46), 4.066 (1.42), 4.084 (4.21), 4.102 (5.01), 4.120 (3.38), 4.137 (2.26), 4.149 (0.47), 4.154 (0.58), 4.385 (0.55), 4.423 (0.63), 4.704 (2.11), 4.717 (2.75), 4.833 (1.06), 4.861 (0.54), 7.056 (0.55), 7.075 (1.28), 7.094 (0.85), 7.189 (1.25), 7.208 (0.96), 7.294 (0.50), 7.313 (0.84), 7.334 (1.84), 7.352 (2.41), 7.368 (0.48), 7.391 (0.73), 7.396 (0.81), 7.415 (3.41), 7.434 (3.19), 7.441 (1.90), 7.454 (2.74), 7.462 (0.92), 7.473 (0.62), 7.501 (1.42), 7.508 (1.77), 7.515 (1.15), 7.586 (0.75), 7.604 (1.19), 7.622 (0.50), 7.708 (0.72), 7.724 (0.61), 7.885 (0.52), 8.510 (0.61), 8.522 (0.59), 8.574 (1.11), 8.578 (1.17), 8.586 (1.13), 8.589 (1.06), 8.653 (0.77), 8.657 (0.80), 8.665 (0.81), 8.668 (0.74).

Intermediate 19

ethyl {4-[cyano(2-methoxypyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereosiomers)

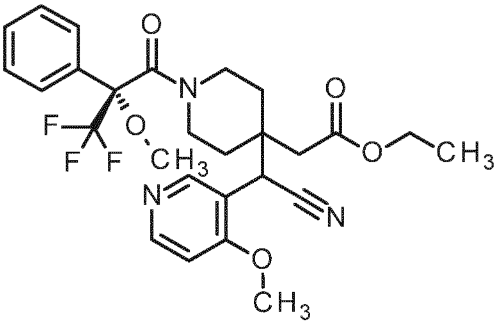


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (1.30 g, 3.37 mmol – Intermediate 2) and (2-methoxypyridin-3-yl)acetonitrile (1.00 g, 6.75 mmol) gave the title compound 1.46 g (73 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.951 (0.56), 0.980 (0.52), 1.116 (1.41), 1.134 (3.25), 1.151 (3.03), 1.154 (4.22), 1.159 (4.56), 1.168 (3.67), 1.172 (8.01), 1.173 (5.07), 1.177 (10.30), 1.187 (2.34), 1.191 (7.41), 1.194 (5.11), 1.210 (2.93), 1.392 (0.57), 1.403 (0.80), 1.424 (0.72), 1.436 (0.58), 1.458 (0.45), 1.711 (0.41), 1.737 (0.92), 1.764 (0.59), 1.987 (10.66), 2.322 (0.56), 2.327 (0.93), 2.331 (0.86), 2.391 (0.50), 2.404 (0.52), 2.432 (0.53), 2.444 (0.44), 2.458 (0.88), 2.518 (3.47), 2.522 (2.71), 2.632 (1.02), 2.664 (0.59), 2.669 (1.01), 2.673 (1.15), 2.798 (0.62), 2.837 (0.46), 2.969 (0.45), 2.979 (0.52), 2.995 (0.66), 3.127 (0.66), 3.158 (0.44), 3.226 (0.45), 3.510 (1.99), 3.525 (1.01), 3.558 (2.00), 3.575 (6.02), 3.588 (4.31), 3.688 (16.00), 3.779 (11.30), 3.839 (4.65), 3.853 (4.96), 3.858 (3.42), 3.979 (0.89), 3.999 (1.23), 4.017 (2.85), 4.022 (1.08), 4.025 (0.91), 4.028 (0.91), 4.035 (3.54), 4.040 (2.86), 4.053 (2.95), 4.058 (2.91), 4.068 (2.14), 4.070 (2.28), 4.075 (1.12), 4.085 (1.70), 4.095 (0.57), 4.103 (0.50), 4.334 (0.47), 4.368 (0.46), 4.583 (1.18), 4.598 (2.02), 4.783 (0.92), 4.807 (0.92), 7.045 (0.44), 7.054 (0.51), 7.057 (0.49), 7.066 (0.59), 7.072 (0.56), 7.076 (0.51), 7.084 (0.50), 7.108 (0.79), 7.117 (1.50), 7.129 (3.33), 7.136 (1.76), 7.142 (1.64), 7.148 (3.03), 7.160 (0.95), 7.196 (2.01), 7.215 (1.24), 7.305 (1.01), 7.325 (1.95), 7.348 (1.34), 7.360 (1.62), 7.367 (1.21), 7.370 (1.11), 7.379 (2.58), 7.399 (1.18), 7.432 (1.60), 7.441 (1.86), 7.448 (2.30), 7.453 (1.67), 7.467 (1.01), 7.472 (0.90), 7.499 (0.67), 7.517 (0.99), 7.585 (1.12), 7.590 (1.16), 7.604 (1.04), 7.608 (0.99), 7.788 (0.60), 7.793 (0.44), 7.807 (0.56), 8.187 (0.51), 8.191 (0.57), 8.195 (0.58), 8.199 (0.98), 8.203 (0.52), 8.207 (0.57), 8.211 (0.49), 8.235 (1.16), 8.240 (1.16), 8.248 (1.21), 8.252 (1.08), 8.297 (1.38), 8.301 (1.43), 8.309 (1.44), 8.313 (1.29).

Intermediate 20

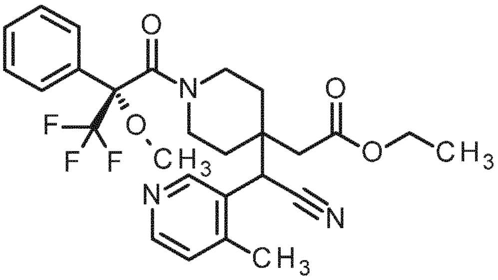
ethyl {4-[cyano(4-methoxypyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereosiomers)



Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and (4-methoxypyridin-3-yl)acetonitrile (384 mg, 2.59 mmol) gave the title compound 540 mg (70 % yield) after silica chromatography (ethyl acetate: hexane).

Intermediate 21

ethyl {4-[cyano(4-methylpyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereosiomers)

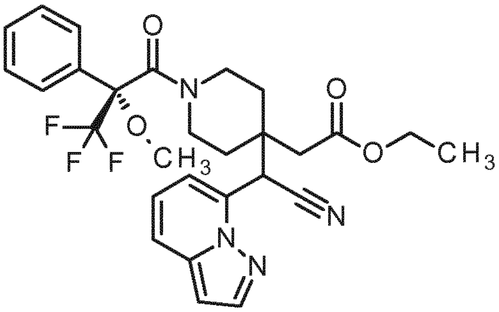


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and 4-methylpyridin-3-yl)acetonitrile (320 µl, 2.6 mmol) gave the title compound 590 mg (66 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.315 (0.49), 0.475 (0.55), 0.486 (0.55), 0.939 (0.58), 0.950 (0.61), 0.984 (1.00), 1.016 (0.73), 1.102 (2.03), 1.120 (3.76), 1.138 (2.00), 1.154 (3.37), 1.159 (6.89), 1.172 (7.10), 1.177 (16.00), 1.180 (7.56), 1.190 (4.13), 1.195 (9.02), 1.198 (11.96), 1.216 (5.31), 1.418 (0.39), 1.439 (0.76), 1.451 (0.76), 1.471 (0.61), 1.483 (0.49), 1.722 (1.00), 1.750 (0.91), 1.904 (0.73), 1.938 (0.67), 1.987 (10.66), 2.025 (10.41), 2.259 (12.17), 2.322 (1.34), 2.326 (1.85), 2.332 (1.49), 2.342 (6.62), 2.404 (1.12), 2.414 (0.82), 2.446 (1.49), 2.454 (1.18), 2.518 (8.56), 2.522 (6.07), 2.664 (1.34), 2.668 (1.79), 2.673 (1.31), 2.783 (0.49), 2.791 (0.46), 2.823 (0.46), 2.855 (0.52), 2.889 (0.91), 2.917 (0.55), 2.938 (0.67), 2.971 (1.03), 3.002 (1.91), 3.043 (1.82), 3.081 (0.97), 3.122 (0.91), 3.154 (0.55), 3.199 (0.43), 3.230 (0.82), 3.261 (0.52), 3.440 (1.70), 3.571 (10.23), 3.577 (9.50), 3.952 (0.76), 3.955 (0.82), 3.970 (0.76), 3.973 (0.76), 4.000 (1.03), 4.017 (3.13), 4.024 (1.85), 4.035 (3.64), 4.041 (5.10), 4.051 (2.91), 4.059 (5.07), 4.069 (2.34), 4.078 (1.88), 4.086 (0.73), 4.095 (0.43), 4.304 (0.76), 4.338 (0.70), 4.376 (0.67), 4.409 (0.64), 4.635 (4.74), 4.677 (3.49), 4.772 (1.46), 4.791 (1.31), 7.028 (1.15), 7.048 (2.70), 7.067 (1.82), 7.152 (2.73), 7.172 (2.00), 7.231 (2.13), 7.250 (2.73), 7.280 (0.67), 7.290 (0.88), 7.309 (2.94), 7.322 (3.55), 7.335 (2.67), 7.347 (3.25), 7.362 (1.12), 7.382 (1.82), 7.401 (3.25), 7.421 (1.94), 7.436 (2.16), 7.440 (2.58), 7.453 (1.49), 7.492 (1.34), 7.510 (1.88), 7.529 (0.67), 8.140 (4.80), 8.377 (3.46), 8.392 (1.12), 8.396 (1.18), 8.404 (0.97), 8.408 (1.09), 8.484 (3.46), 8.497 (3.16), 8.520 (3.43), 8.532 (3.28), 8.547 (2.34).

Intermediate 22

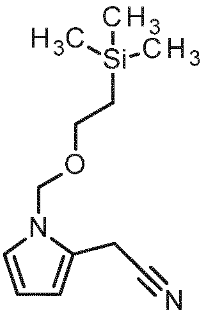
ethyl {4-[cyano(pyrazolo[1,5-a]pyridin-7-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate



Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate ((800 mg, 2.08 mmol – Intermediate 2) and (pyrazolo[1,5-a]pyridin-7-yl)acetonitrile (653 mg, 4.15 mmol; CAS: 1936585-59-9) gave the title compound 615 mg (49 % yield) after silica chromatography (ethyl acetate:hexane).

Intermediate 23

(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-2-yl)acetonitrile

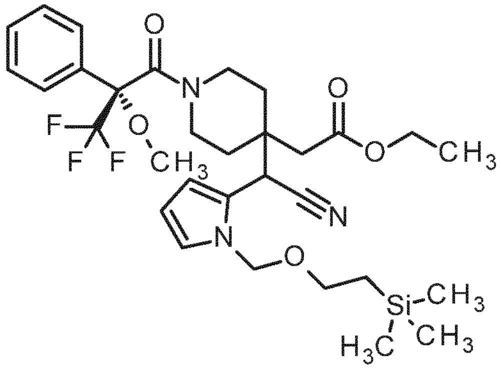


To a suspension of NaH 60% in DMF was added dropwise as a solution (1H-pyrrol-2-yl)acetonitrile (5.00 g, 47.1 mmol) in anhydrous DMF (70 ml) at 0℃. The solution was stirred at 0℃ for 30 minutes and then 2-(chloromethoxy)ethyl](trimethyl)silane (11 ml, 61 mmol) was added dropwise. The solution is stirred at 0℃ for 1.5 h. The mixture was then poured into cold water, and the aqueous phase was extracted with EtOAc. The organic phase was washed with sat. sodium chloride (aq), filtrated and concentrated. The mixture was by silica chromatography (ethyl acetate:hexane) and gave the title compound 6.7 g (60 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.051 (1.81), -0.047 (2.12), -0.041 (16.00), -0.033 (0.61), 0.000 (0.64), 0.820 (0.66), 0.840 (0.67), 0.860 (0.65), 1.160 (1.13), 1.178 (2.21), 1.196 (1.07), 1.993 (4.06), 3.378 (0.72), 3.396 (0.50), 3.399 (0.68), 3.419 (0.64), 4.001 (1.78), 4.006 (0.46), 4.023 (0.99), 4.041 (0.97), 5.247 (2.51), 6.002 (0.57), 6.010 (0.41), 6.908 (0.43), 6.910 (0.44).

Intermediate 24

ethyl {4-[cyano(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate



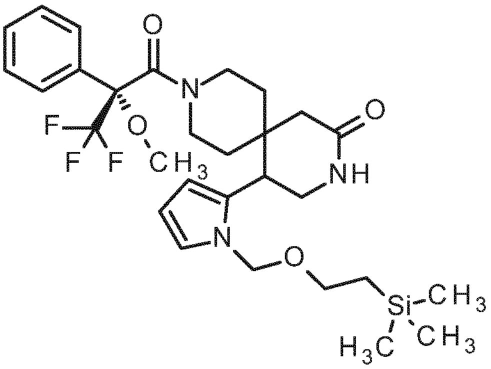
Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-

ylidene}acetate ((800 mg, 2.08 mmol – Intermediate 2) and (1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-2-yl)acetonitrile (7.10 g, 30.0 mmol; Intermediate 23) gave the title compound 5.13 g (55 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.066 (0.72), -0.059 (1.32), -0.050 (15.42), -0.044 (16.00), -0.039 (8.65), -0.037 (9.10), -0.005 (0.52), 0.000 (0.52), 0.764 (0.60), 0.771 (0.52), 0.781 (0.63), 0.793 (0.78), 0.805 (0.49), 1.121 (0.46), 1.139 (1.05), 1.154 (1.16), 1.161 (0.64), 1.168 (0.58), 1.172 (2.34), 1.179 (1.72), 1.186 (0.73), 1.190 (1.18), 1.197 (2.33), 1.216 (0.93), 2.001 (0.72), 2.446 (0.46), 2.469 (0.52), 2.532 (0.76), 2.537 (0.51), 2.845 (0.52), 3.297 (0.43), 3.301 (0.43), 3.321 (0.68), 3.325 (0.66), 3.372 (0.67), 3.579 (0.71), 3.599 (1.69), 3.606 (1.53), 4.008 (0.47), 4.027 (0.71), 4.037 (0.54), 4.045 (1.00), 4.055 (0.50), 4.063 (1.12), 4.081 (0.73), 4.532 (0.81), 4.597 (0.76), 5.046 (0.42), 5.187 (0.47), 5.205 (0.46), 5.252 (0.66), 6.148 (0.45), 6.212 (0.42), 6.996 (0.42), 6.999 (0.44), 7.005 (0.50), 7.009 (0.43), 7.012 (0.42), 7.258 (1.18), 7.270 (1.87), 7.313 (0.41), 7.332 (0.50), 7.375 (0.45), 7.454 (0.78), 7.462 (0.83), 7.467 (0.70), 7.482 (0.67).

Intermediate 25

9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-2-yl)-3,9-diazaspiro[5.5]undecan-2-one

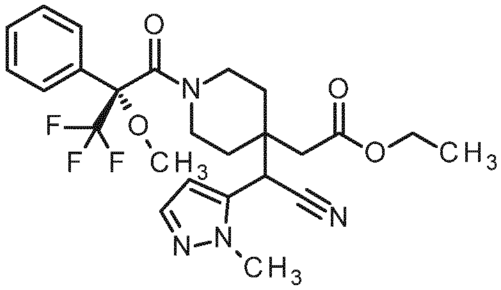


Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (5.13 g, 8.25 mmol, Intermediate 24) and gave the title compound 3.28 g (65 %) after silica chromatography (dichloromethane:ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.079 (0.60), -0.071 (15.28), -0.061 (7.28), -0.058 (16.00), -0.047 (8.03), 0.690 (0.41), 0.733 (0.51), 0.756 (0.80), 0.774 (0.65), 2.519 (1.70), 2.524 (1.11), 2.987 (0.56), 3.237 (0.98), 3.251 (0.47), 3.270 (0.74), 3.351 (0.64), 3.367 (0.48), 3.497 (0.50), 3.562 (1.44), 3.567 (0.92), 3.577 (1.48), 4.949 (0.44), 4.987 (0.43), 5.158 (0.40), 5.274 (0.48), 5.760 (12.27), 5.961 (0.51), 5.978 (0.49), 5.984 (0.42), 6.097 (0.46), 6.105 (0.56), 6.113 (0.49), 6.859 (0.51), 6.864 (0.43), 6.866 (0.42), 7.155 (0.65), 7.170 (1.71), 7.255 (0.43), 7.274 (0.55), 7.420 (0.46), 7.424 (0.54), 7.436 (1.28), 7.441 (1.08), 7.458 (0.49).

Intermediate 26

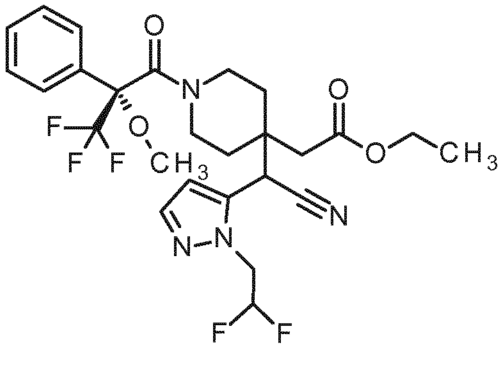
ethyl {4-[cyano(1-methyl-1H-pyrazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate



Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and (1-methyl-1H-pyrazol-5-yl)acetonitrile (280 µl, 2.6 mmol; CAS: 1071814-43-1) gave the title compound 140 mg (20 % yield) after silica chromatography (ethyl acetate:hexane).

Intermediate 27

ethyl (4-{cyano[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]methyl}-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl)acetate

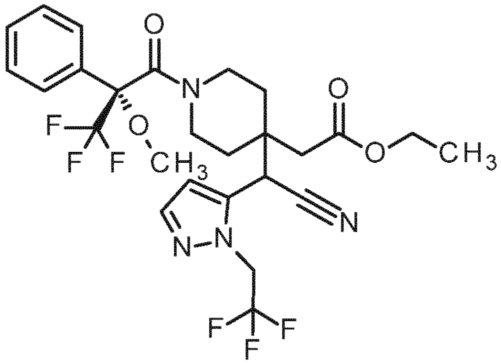


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and [1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]acetonitrile (444 mg, 2.59 mmol; CAS: 1823789-71-4) gave the title compound 223 mg (28 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.108 (0.65), 1.126 (1.54), 1.140 (2.21), 1.154 (4.83), 1.158 (4.46), 1.172 (9.53), 1.176 (2.19), 1.190 (4.72), 1.987 (16.00), 2.518 (1.09), 2.522 (0.92), 2.527 (0.64), 2.602 (0.54), 3.560 (0.85), 3.602 (2.25), 3.956 (0.59), 3.974 (0.75), 3.988 (0.75), 3.993 (0.96), 4.000 (1.20), 4.005 (0.87), 4.011 (0.96), 4.017 (3.45), 4.022 (0.43), 4.029 (0.42), 4.035 (3.42), 4.053 (1.11), 4.691 (1.33), 4.802 (0.49), 6.212 (1.14), 6.216 (1.16), 6.581 (0.46), 6.586 (0.46), 7.300 (0.53), 7.311 (0.42), 7.369 (0.75), 7.387 (1.07), 7.450 (0.98), 7.456 (0.98), 7.464 (0.48), 7.473 (1.12), 7.493 (0.70), 7.504 (0.56), 7.521 (0.49), 7.596 (0.42), 7.601 (0.45), 7.688 (0.97), 7.693 (0.96).

Intermediate 28

ethyl (4-{cyano[1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]methyl}-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl)acetate (mixture of stereoisomers)

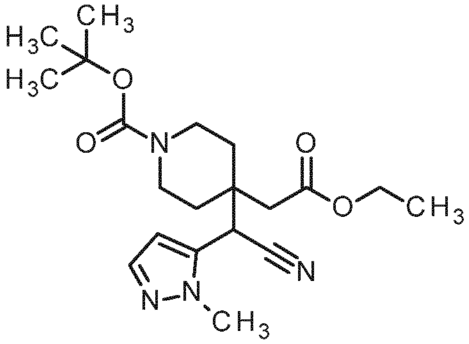


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and [[1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]acetonitrile (491 mg, 2.59 mmol; CAS: 1378831-53-8) gave the title compound 243 mg (29 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.552 (0.46), 0.562 (0.46), 1.019 (0.56), 1.052 (0.51), 1.094 (1.57), 1.102 (1.42), 1.112 (6.58), 1.119 (3.44), 1.123 (3.49), 1.131 (9.97), 1.141 (7.04), 1.149 (4.35), 1.154 (4.96), 1.159 (3.14), 1.172 (9.47), 1.190 (4.51), 1.338 (0.51), 1.349 (0.51), 1.636 (0.46), 1.648 (0.41), 1.669 (0.46), 1.712 (0.51), 1.747 (0.71), 1.779 (0.41), 1.915 (0.56), 1.948 (0.51), 1.987 (16.00), 2.336 (0.76), 2.518 (9.97), 2.522 (6.63), 2.536 (2.13), 2.553 (1.27), 2.575 (0.61), 2.590 (1.11), 2.678 (0.76), 2.896 (0.46), 2.926 (0.91), 2.969 (0.51), 3.176 (0.56), 3.213 (0.66), 3.601 (5.47), 3.610 (8.05), 3.650 (1.97), 3.680 (0.41), 3.899 (0.41), 3.917 (1.72), 3.933 (2.48), 3.938 (2.03), 3.950 (2.78), 3.956 (1.92), 3.962 (1.52), 3.969 (2.08), 3.980 (1.37), 3.987 (1.32), 3.999 (1.37), 4.017 (3.44), 4.035 (3.44), 4.053 (1.16), 4.268 (2.28), 4.401 (0.66), 4.430 (0.56), 4.693 (4.56), 4.805 (1.16), 4.820 (0.96), 4.984 (0.66), 4.991 (0.71), 5.014 (0.66), 5.033 (0.51), 5.055 (0.81), 5.065 (0.81), 5.078 (0.76), 5.086 (0.76), 5.119 (0.41), 5.142 (1.16), 5.152 (0.66), 5.164 (1.32), 5.174 (0.66), 5.187 (0.66), 6.321 (1.87), 6.326 (1.87), 6.352 (2.53), 6.358 (2.58), 6.420 (0.61), 6.424 (0.66), 6.649 (1.06), 6.654 (1.06), 6.667 (0.91), 6.672 (0.86), 7.335 (2.99), 7.347 (5.97), 7.378 (0.86), 7.397 (2.33), 7.418 (2.78), 7.448 (2.03), 7.454 (3.34), 7.457 (2.63), 7.473 (3.04), 7.493 (1.67), 7.498 (1.06), 7.502 (1.42), 7.512 (0.46), 7.519 (1.11), 7.589 (0.71), 7.593 (0.71), 7.639 (1.01), 7.644 (1.01), 7.654 (0.86), 7.658 (0.81), 7.681 (1.77), 7.686 (1.72), 7.712 (2.38), 7.717 (2.28).

Intermediate 29

tert-butyl 4-[cyano(1-methyl-1H-pyrazol-5-yl)methyl]-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (mixture of stereoisomers)

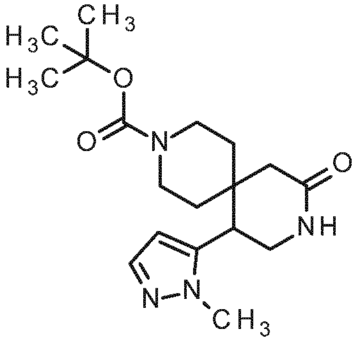


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from tert-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (11.1 g, 41.3 mmol) and (1-methyl-1H-pyrazol-5-yl)acetonitrile (2.2 ml, 21 mmol) to give the title compound 5.38g (67 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.154 (1.25), 1.172 (2.48), 1.189 (2.76), 1.206 (5.04), 1.224 (2.33), 1.361 (16.00), 1.574 (0.48), 1.586 (0.71), 1.596 (0.53), 1.987 (3.85), 2.518 (0.90), 2.523 (0.58), 2.538 (0.74), 2.713 (0.73), 2.753 (0.53), 3.811 (7.82), 4.017 (0.95), 4.035 (0.97), 4.045 (0.57), 4.063 (1.65), 4.080 (1.54), 4.098 (0.47), 4.823 (1.84), 6.427 (1.64), 6.432 (1.63), 7.466 (1.32), 7.471 (1.30).

Intermediate 30

tert-butyl 7-(1-methyl-1H-pyrazol-5-yl)-10-oxo-3,9-diazaspiro[5.5]undecane-3-carboxylate (mixture of stereoisomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from tert-butyl 4-[cyano(1-methyl-1H-pyrazol-5-yl)methyl]-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (6.40 g, 16.4 mmol;, Intermediate 29) and gave the title compound 5.7 g (100 %), which was used further without purification.

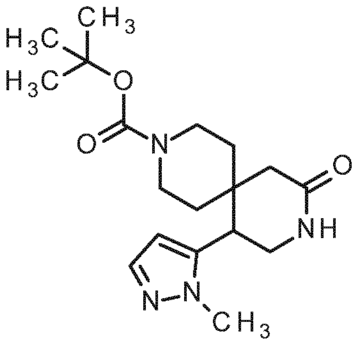
The title compound (5700 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (2410 mg, see Intermediate 31) and stereoisomer 2 (2500 mg, see Intermediate 32).

Preparative chiral HPLC method: Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IC 5µm 250x30mm; Eluent A: CO2, Eluent B: Ethanol; Isocratic: 25%B; Flow: 100.0 ml/min Temperature: 40℃; BPR: 150bar; MWD @ 220nm.

Analytical chiral HPLC method: Instrument: Agilent: 1260, Aurora SFC-Module; Column: Chiralpak IC 5µm 100x4.6mm; Eluent A: CO2, Eluent B: Ethanol; Isocratic: 25%B; Flow: 4.0 ml/min; Temperature: 37.5℃; BPR: 100bar; MWD @ 220 nm.

Intermediate 31

tert-butyl 7-(1-methyl-1H-pyrazol-5-yl)-10-oxo-3,9-diazaspiro[5.5]undecane-3-carboxylate (Stereoisomer 1)



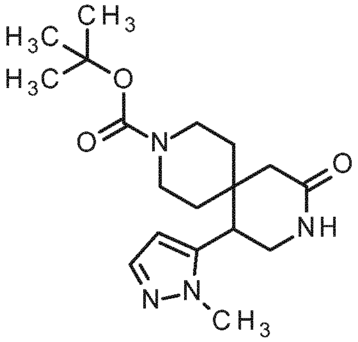
For the preparation of the title compound and the separation into the corresponding stereoisomers, see see Intermediate 30.

Analytical chiral HPLC (method see Intermediate 30): R_t = 3.89 min; ee >99%% Optical rotation (method OR1) = +8.4° +/- 0.23° (me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 1.321 (6.36), 2.551 (0.42), 3.275 (0.44), 3.797 (3.98), 4.195 (1.24), 6.138 (0.74), 6.143 (0.72), 7.353 (0.80), 7.357 (0.76).

Intermediate 32

tert-butyl 7-(1-methyl-1H-pyrazol-5-yl)-10-oxo-3,9-diazaspiro[5.5]undecane-3-carboxylate (Stereoisomer 2)

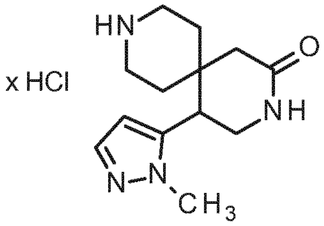


For the preparation of the title compound and the separation into the corresponding stereoisomers, see see Intermediate 30.

Analytical chiral HPLC (method see Intermediate 30): R_t = 5.41 min; ee >99%% Optical rotation (method OR1) = -8.7° +/- 0.40° (me thanol).

Intermediate 33

5-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-2-one, salt with hydrochloric acid (Stereoisomer 2)

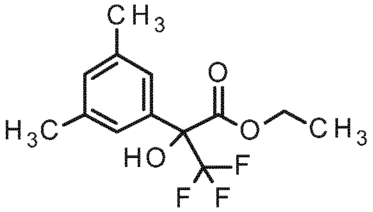


Using an analogous method as described for Intermediate 12, the title compound was prepared starting from 7-(1-methyl-1H-pyrazol-5-yl)-10-oxo-3,9-diazaspiro[5.5]undecane-3-carboxylate (1000 mg, 2.87 mmol, Intermediate 32) and gave the title compound 1.00 g, which was used further without purification.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.231 (0.59), 1.243 (0.56), 1.481 (0.47), 1.513 (0.61), 1.602 (0.59), 1.637 (0.50), 1.710 (0.46), 1.720 (0.46), 2.305 (0.87), 2.327 (0.44), 2.349 (1.09), 2.518 (1.65), 2.523 (1.09), 2.649 (1.50), 2.669 (0.46), 2.693 (1.22), 2.972 (0.61), 2.986 (0.64), 3.024 (0.74), 3.093 (0.55), 3.162 (16.00), 3.209 (0.67), 3.218 (0.80), 3.226 (0.45), 3.310 (0.46), 3.327 (1.39), 3.336 (2.43), 3.564 (2.51), 4.748 (3.47), 6.207 (2.51), 6.212 (2.56), 7.425 (2.64), 7.429 (2.56), 7.745 (1.23), 7.751 (1.21).

Intermediate 34

(rac)-ethyl 2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-hydroxypropanoate

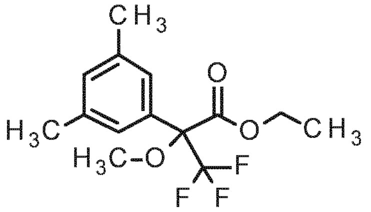


To a solution of 1-bromo-3,5-dimethylbenzene (CAS-RN: 556-96-7) (89.0 g, 481 mmol, 65.4 mL) and magnesium (17.7 g, 731 mmol) in THF (500 mL) was added iodine (4.88 g, 19.2 mmol) at 50℃ under an atmosphere of nitrogen. To a solution of ethyl 3,3,3-trifluoro-2-oxopropanoate (CAS-RN: 13081-18-0) (120 g, 705 mmol, 93.7 mL) in THF (400 mL) was added into the above solution drop-wise at -78℃ under an atmosphere of nitrogen. The mixture was stirred at -78℃ for 12 hours. The mixture was poured into water (1 L), extracted with ethyl acetate twice (1 L). The combined organic layer was washed with brine (1 L), dried with sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel to give the title compound (56.0 g, 202 mmol, 42.1% yield) as a white solid.

^{1}H-NMR: (400MHz, $CDCl_3$) δ [ppm] = 7.39 (s, 2H), 7.06 (s, 1H), 4.40-4.48 (m, 2H), 4.25 (s, 1H), 2.36 (s, 6H), 1.37-1.42 (m, 3H).

Intermediate 35

(rac)-ethyl 2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoate

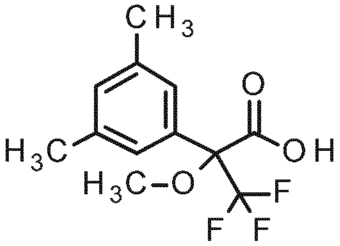


To a solution of Intermediate 34 (56.0 g, 202 mmol) in acetone (550 mL) was added dimethyl sulfate (CAS-RN: 77-78-1) (127 g, 1.01 mol) and potassium carbonate (140 g, 1.01 mol) at 15℃. The mixture was stirred at 60℃ for 12 hours . The mixture was filtered and the filtrate was concentrated. The residue was diluted with ethyl acetate (300 mL) and washed three times with 10% aqueous ammonium hydroxide solution. The organic layer was washed with brine twice (200 mL), dried with sodium sulfate, filtered and concentrated. The title compound (72.0 g, crude) was obtained as colorless oil.

^{1}H-NMR: (400MHz, $CDCl_3$) δ [ppm] = 7.12 (s, 2 H) 7.04 (s, 1 H), 4.37-4.43 (m, 2H), 3.97 (s, 3H), 3.56 (m, 3H), 2.34 (s, 6H), 1.33-1.38 (t, J=7.15 Hz, 3 H).

Intermediate 36

(rac)-2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoic acid



To a solution of Intermediate 35 (77.0 g, 265 mmol) in ethanol (700 mL) was added potassium hydroxide (35.8 g, 639 mmol) at 15℃. The mixture was stirred at 50℃ for 2 hours. The mixture was concentrated. Then the residue diluted with water (300 mL), extracted twice with ethyl acetate (200 mL). The aqueous layer was adjust to a pH=3 with 1M HCl, extracted twice with ethyl acetate (200 mL). The combined organic layer was washed with brine (300 mL), dried with sodium sulfate, filtered and concentrated to give the title compound (53.0 g, 192 mmol, 72.3% yield, 95% purity) as a white solid.

^{1}H-NMR: (400MHz, $CDCl_3$) δ [ppm] = 9.75 (s, 1 H) 7.17 (s, 2 H) 7.09 (s, 1 H) 3.56 (s, 3 H) 2.36 (s, 6 H)

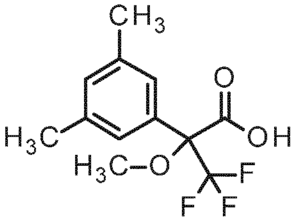
Intermediate 37 and Intermediate 38

ethyl (2R)-2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoate

ethyl (2S)-2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoate

Intermediate 37

2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoic acid (Enantiomer 1)



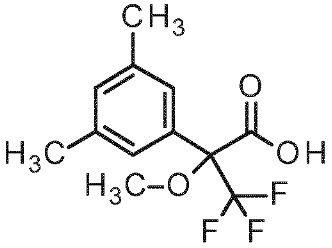
To a solution of Intermediate 36 (15 g, 55.2 mmol) in acetonitrile (150 mL) was added (1S)-1-(1-naphthyl) ethanamine (CAS-RN: 10420-89-0) (8.51 g, 49.7 mmol) at 15℃. The mixture was stirred at 80℃ for 5 hours. Then the mixture was cooled to 15℃ and stirred for 12 hours. The mixture was filtered. And the solid residue was diluted with ethyl acetate (50 mL), washed three times with 1M HCl (30 mL) and brine (80 mL), dried with sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica and the title compound was obtained as a white solid (5.7 g, 21.7 mmol, 39.4% yield).

^{1}H-NMR: (400MHz, $CDCl_3$) δ [ppm] = 7.16 (s, 2 H) 7.08 (s, 1 H) 3.54 (s, 3 H) 2.35 (s, 6 H).

Optical rotation (method OR1): +57.9° (methanol).

Intermediate 38

2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoic acid (Enantiomer 2)



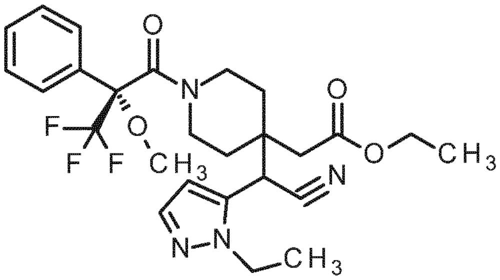
To a solution of Intermediate 36 (25 g, 95.3 mmol) in acetonitrile (250 mL) was added (R)-(6-methoxy-4-quinolyl)-[(2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol (CAS-RN: 130-95-0) (15.4 g, 47.6 mmol) at 15℃. The mixture was stirred at 80° C for 5 hours. Then the mixture was cooled to 15℃ and stirred for 12 hours. The mixtur e was filtered. And the solid residue was diluted with ethyl acetate (100 mL), washed three times with 1M HCl (80 mL) and brine (100 mL), dried with sodium sulfate, filtered and concentrated to get the crude product, then purified by column chromatography on silica gel to get the title compound (5.04 g, 19.2 mmol, 20.1% yield, 100% purity) as a white solid.

^{1}H-NMR: (400MHz, $CDCl_3$) δ [ppm] = 8.67 (s, 1 H) 7.16 (s, 2 H) 7.08 (s, 1 H) 3.55 (s, 3 H) 2.36 (s, 6 H)

Optical rotation (method OR1): -60.4°(methanol).

Intermediate 39

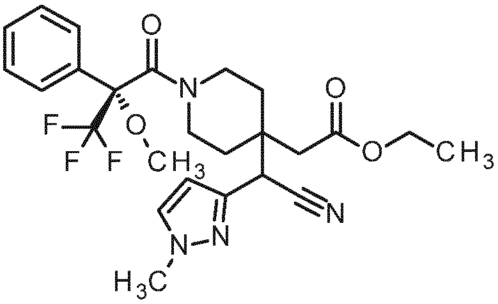
ethyl {4-[cyano(1-ethyl-1H-pyrazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)



Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and (1-ethyl-1H-pyrazol-5-yl)acetonitrile (351 mg, 2.59 mmol; Vendor: Fluorochem) to give the title compound 451 mg (60 % yield) after silica chromatography (ethyl acetate:hexane).

Intermediate 40

ethyl {4-[cyano(1-methyl-1H-pyrazol-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)

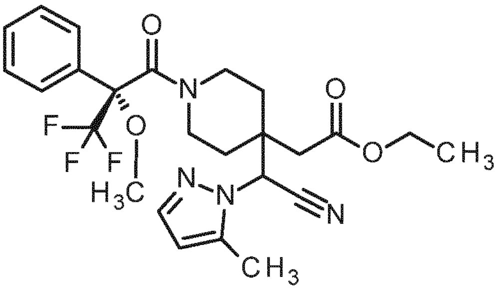


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and (1-methyl-1H-pyrazol-3-yl)acetonitrile (290 µl, 2.6 mmol; Vendor: Zelinsky) to give the title compound 195 mg (27 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.124 (1.39), 1.129 (1.54), 1.142 (3.19), 1.147 (4.35), 1.150 (2.96), 1.154 (4.91), 1.159 (1.95), 1.166 (6.69), 1.168 (5.81), 1.172 (8.85), 1.184 (2.86), 1.186 (2.68), 1.190 (4.45), 1.391 (0.80), 1.597 (0.46), 1.624 (0.44), 1.631 (0.46), 1.641 (0.75), 1.743 (0.44), 1.988 (16.00), 2.274 (0.54), 2.285 (0.49), 2.332 (1.05), 2.336 (0.46), 2.389 (0.67), 2.408 (0.59), 2.426 (0.46), 2.430 (0.41), 2.442 (0.51), 2.518 (6.43), 2.523 (4.12), 2.555 (1.05), 2.558 (1.03), 2.565 (0.82), 2.595 (0.46), 2.606 (0.46), 2.673 (1.08), 2.678 (0.46), 3.470 (0.54), 3.597 (5.27), 3.611 (1.90), 3.789 (4.73), 3.800 (4.32), 3.808 (4.40), 3.818 (8.03), 3.821 (7.49), 3.923 (2.01), 3.991 (0.72), 4.000 (1.52), 4.008 (1.36), 4.017 (4.55), 4.025 (1.54), 4.035 (5.71), 4.042 (1.13), 4.052 (3.47), 4.070 (0.80), 4.386 (1.85), 4.393 (2.08), 4.708 (1.03), 4.723 (1.16), 6.041 (1.49), 6.046 (1.54), 6.055 (1.41), 6.061 (1.39), 6.180 (0.54), 6.186 (0.57), 6.222 (1.03), 6.227 (1.03), 6.235 (0.90), 6.240 (0.90), 7.341 (2.96), 7.359 (1.52), 7.371 (1.23), 7.380 (0.82), 7.385 (0.59), 7.398 (1.44), 7.403 (1.23), 7.416 (1.75), 7.426 (1.70), 7.431 (1.65), 7.437 (1.49), 7.445 (1.77), 7.452 (1.44), 7.463 (0.90), 7.467 (0.80), 7.485 (0.62), 7.664 (0.49), 7.670 (0.51), 7.675 (0.85), 7.680 (0.82), 7.697 (0.75), 7.703 (0.75), 7.713 (1.26), 7.719 (1.47), 7.727 (1.08).

Intermediate 41

ethyl {4-[cyano(5-methyl-1H-pyrazol-1-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)

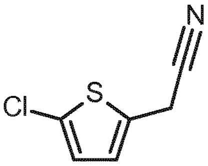


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and 5-methyl-1H-pyrazol-1-yl)acetonitrile (290 µl, 2.6 mmol; CAS: 218921-02-9) to give the title compound 210 mg (29 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.179 (0.45), 0.189 (0.43), 0.852 (0.52), 0.984 (0.52), 0.996 (0.52), 1.030 (0.62), 1.054 (0.71), 1.064 (0.75), 1.096 (2.12), 1.114 (4.16), 1.124 (4.73), 1.127 (3.26), 1.131 (5.64), 1.142 (8.81), 1.145 (5.44), 1.149 (8.94), 1.154 (5.51), 1.159 (4.74), 1.163 (2.93), 1.166 (4.46), 1.172 (8.94), 1.190 (4.28), 1.237 (1.00), 1.259 (0.43), 1.298 (0.62), 1.329 (0.55), 1.836 (0.84), 1.870 (0.68), 1.889 (0.46), 1.902 (0.43), 1.987 (16.00), 2.032 (0.73), 2.096 (8.38), 2.209 (8.72), 2.278 (7.13), 2.322 (0.78), 2.326 (1.03), 2.332 (0.77), 2.518 (4.73), 2.522 (3.16), 2.544 (0.77), 2.552 (0.84), 2.569 (0.62), 2.611 (2.00), 2.627 (5.73), 2.642 (0.84), 2.665 (1.14), 2.669 (1.52), 2.902 (0.66), 2.935 (0.46), 2.993 (0.61), 3.026 (0.52), 3.152 (0.57), 3.234 (0.57), 3.457 (2.14), 3.528 (0.62), 3.590 (9.08), 3.955 (0.52), 3.973 (1.78), 3.980 (1.32), 3.993 (3.00), 3.998 (4.28), 4.010 (3.57), 4.017 (6.15), 4.028 (2.07), 4.035 (4.35), 4.045 (0.55), 4.053 (1.18), 4.310 (0.48), 4.345 (0.45), 4.377 (0.43), 4.412 (0.41), 5.693 (3.57), 5.701 (3.35), 5.868 (2.84), 6.129 (5.01), 7.287 (0.77), 7.305 (2.66), 7.311 (2.62), 7.329 (2.37), 7.350 (2.44), 7.370 (2.78), 7.375 (2.39), 7.386 (1.20), 7.393 (1.57), 7.409 (0.46), 7.439 (2.23), 7.448 (2.48), 7.454 (2.53), 7.463 (1.77), 7.469 (2.41), 7.475 (2.84), 7.495 (3.46), 7.506 (2.48), 7.510 (2.66), 7.543 (2.23), 7.547 (2.27).

Intermediate 42

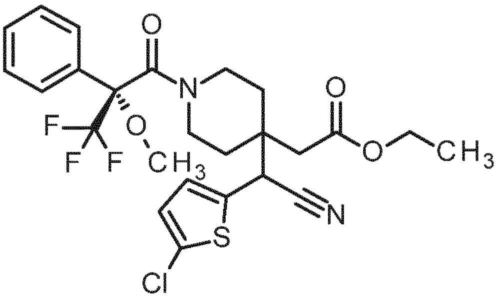
(5-chlorothiophen-2-yl)acetonitrile



A mixture of 2-chloro-5-(chloromethyl)thiophene (850 mg, 5.09 mmol), sodium cyanide (1.50 g, 30.5 mmol) and sodium iodide (153 mg, 1.02 mmol) in DMF:water (5:1; 24 ml) was stirred at RT for 2h. The reaction was diluted with water and sat. sodium bicarbonate (aq) and extracted with ethyl acetate. The organics were combined and washed with sat. sodium bicarbonate (aq), filtered through an hydrophobic filter and concentrated under reduced pressure. The title compound was used directly in the next step with further purification.

Intermediate 43

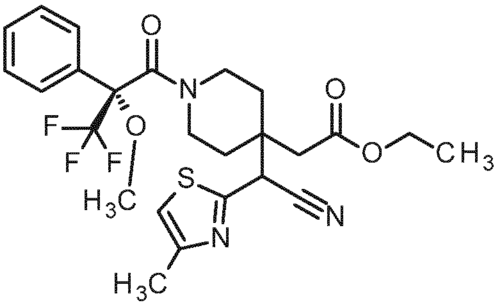
ethyl {4-[(5-chlorothiophen-2-yl)(cyano)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)



Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (400 mg, 1.04 mmol – Intermediate 2) and (5-chlorothiophen-2-yl)acetonitrile (327 mg, 2.08 mmol; Intermediate 42) to give the title compound 570 mg (100 % yield) after silica chromatography (ethyl acetate:hexane).

Intermediate 44

ethyl {4-[cyano(4-methyl-1,3-thiazol-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (mixture of stereoisomers)

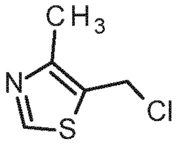


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (500 mg, 1.30 mmol – Intermediate 2) and 4-methyl-1,3-thiazol-2-yl)acetonitrile (310 µl, 2.6 mmol) to give the title compound 590 mg (69 % yield) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.126 (0.50), 1.129 (0.51), 1.144 (1.28), 1.147 (1.76), 1.151 (0.97), 1.154 (1.18), 1.165 (2.10), 1.169 (1.90), 1.172 (2.08), 1.183 (0.80), 1.187 (0.84), 1.190 (0.99), 1.988 (3.46), 2.332 (0.64), 2.338 (1.00), 2.340 (1.01), 2.353 (14.44), 2.356 (14.87), 2.364 (1.79), 2.367 (1.83), 2.373 (1.64), 2.375 (1.63), 2.518 (2.87), 2.523 (1.90), 3.307 (0.54), 3.604 (1.37), 3.621 (0.51), 3.634 (0.51), 4.000 (0.41), 4.011 (0.63), 4.017 (0.99), 4.029 (1.05), 4.035 (1.00), 4.040 (0.74), 4.042 (0.85), 4.044 (0.82), 4.047 (1.07), 4.504 (16.00), 4.912 (0.68), 4.952 (0.71), 5.248 (0.68), 7.280 (1.13), 7.283 (3.30), 7.285 (3.20), 7.288 (1.17), 7.358 (1.01), 7.369 (1.27), 7.376 (1.03), 7.399 (0.69), 7.419 (0.60), 7.434 (0.63), 7.439 (0.58), 7.449 (0.79), 7.453 (0.50).

Intermediate 45

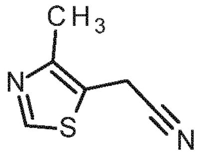
5-(chloromethyl)-4-methyl-1,3-thiazole



To a solution of (4-methyl-1,3-thiazol-5-yl)methanol (800 mg, 6.19 mmol) in anhydrous THF (50 ml) was added thionyl chloride (1.4 ml, 19 mmol) and the reaction was stirred at RT for 1h. The rewaction was carefully poured onto sat. sodium bicarbonate (aq) and extracted with ethyl acetate. The organics were combined and washed with sat. sodium chloridel (aq), filtered through an hydrophobic filter and concentrated under reduced pressure. The title compound (530 mg, 58%) was used directly in the next step with further purification.

Intermediate 46

(4-methyl-1,3-thiazol-5-yl)acetonitrile



Using an analogous method as described for Intermediate 42 the title compound was prepared starting from 5-(chloromethyl)-4-methyl-1,3-thiazole (530 mg, 80 % purity, 2.87 mmol – Intermediate 45) to give the title compound 370 mg (93 % yield) which was used without further purification.

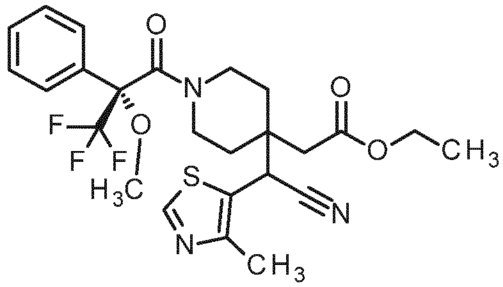
Intermediate 47 and Intermediate 48

ethyl {4-[(R)-cyano(4-methyl-1,3-thiazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate

ethyl {4-[(S)-cyano(4-methyl-1,3-thiazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate

Intermediate 47

ethyl {4-[cyano(4-methyl-1,3-thiazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (Stereoisomer 1)

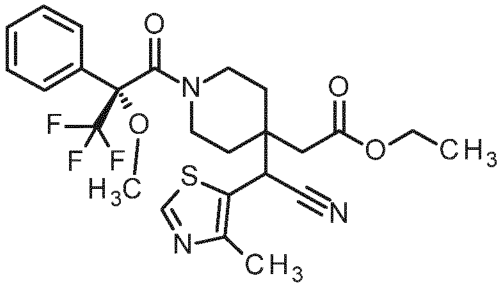


Using an analogous method as described for Intermediate 3 the title compound was prepared starting from ethyl {1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-ylidene}acetate (400 mg, 1.04 mmol – Intermediate 2) and Intermediate 46 (287 mg, 2.08 mmol) to give the title compound (162 mg , 30 % yield) and its diastereosiomer (141 mg, 26 %) after silica chromatography (ethyl acetate:hexane).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.032 (0.55), 0.042 (0.55), 0.729 (0.42), 0.964 (0.79), 0.968 (0.70), 0.991 (0.64), 1.018 (0.80), 1.060 (1.57), 1.076 (6.86), 1.089 (1.51), 1.094 (13.71), 1.106 (2.28), 1.111 (5.84), 1.124 (1.07), 1.193 (1.09), 1.488 (0.44), 1.510 (0.79), 1.521 (0.80), 1.542 (0.54), 1.554 (0.45), 1.714 (0.74), 1.743 (0.57), 1.921 (3.23), 2.066 (16.00), 2.196 (0.59), 2.265 (0.74), 2.293 (4.44), 2.452 (4.02), 2.457 (2.81), 2.476 (1.02), 2.517 (1.57), 2.608 (0.77), 2.627 (1.72), 2.669 (1.07), 2.894 (0.44), 2.920 (0.69), 2.953 (0.44), 3.085 (0.70), 3.116 (0.42), 3.507 (0.84), 3.526 (6.90), 3.562 (1.71), 3.905 (0.42), 3.923 (1.36), 3.934 (1.37), 3.941 (1.36), 3.952 (3.75), 3.958 (0.59), 3.968 (3.43), 3.987 (1.09), 4.322 (0.54), 4.356 (0.52), 4.762 (3.72), 4.937 (1.04), 5.693 (0.45), 7.167 (0.89), 7.187 (2.61), 7.205 (2.63), 7.226 (2.93), 7.244 (1.32), 7.279 (0.75), 7.283 (1.10), 7.288 (0.57), 7.301 (1.81), 7.315 (0.85), 7.318 (1.02), 7.322 (0.77), 7.335 (0.64), 7.344 (0.40), 7.380 (1.61), 7.385 (1.31), 7.393 (0.69), 7.398 (0.67), 9.006 (1.26), 9.053 (4.49).

Intermediate 48

ethyl {4-[cyano(4-methyl-1,3-thiazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (Stereoisomer 2)

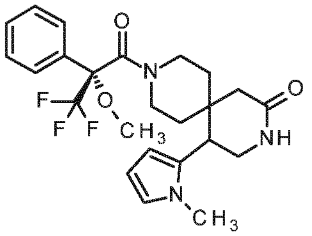


For the preparation of the diastereoisomeric title compound and the separation into the corresponding diastereoisomers, see Intermediate 47.

EXPERIMENTAL SECTION – EXAMPLES

Example 1

5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



An autoclave was charged with ethyl {4-[cyano(1-methyl-1H-pyrrol-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (200 mg, 396 µmol, Intermediate 3), ammonia (3 ml, 2.0 M in ethanol) and Raney-Nickel (100 mg, 50% wet) and the mixture was stirred under 28 bar hydrogen atmosphere at 85°C for 50 h. For the work-up, the mixture was filtered through a pad of celite, eluted with ethanol and the combined filtrates were concentrated under reduced pressure. The residue was purified by preparative HPLC (Method 5) to give the title compound 170 mg (93 % yield).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.144 (0.71), -0.133 (0.72), -0.111 (0.41), 0.535 (0.49), 0.545 (0.50), 0.567 (0.43), 0.577 (0.41), 0.601 (1.14), 0.607 (1.14), 0.633 (0.88), 0.871 (0.65), 0.884 (0.67), 0.905 (0.43), 1.353 (0.57), 1.388 (1.14), 1.395 (1.16), 1.433 (0.67), 1.448 (0.59), 1.456 (0.64), 1.481 (0.73), 1.489 (0.74), 1.995 (1.05), 2.013 (0.47), 2.038 (1.20), 2.056 (0.52), 2.155 (0.49), 2.165 (1.01), 2.209 (1.19), 2.327 (0.53), 2.332 (0.60), 2.337 (0.64), 2.444 (0.57), 2.478 (1.23), 2.518 (2.29), 2.523 (1.72), 2.534 (1.71), 2.577 (1.29), 2.623 (1.65), 2.666 (1.69), 2.768 (1.10), 2.802 (1.68), 2.835 (1.37), 2.848 (1.02), 2.863 (0.81), 2.877 (0.89), 2.953 (4.18), 2.970 (1.82), 2.975 (1.57), 2.984 (0.90), 2.989 (0.81), 2.998 (0.94), 3.006 (0.96), 3.024 (0.54), 3.039 (0.80), 3.051 (1.46), 3.057 (1.38), 3.066 (0.91), 3.076 (1.00), 3.093 (1.11), 3.112 (0.86), 3.119 (0.80), 3.124 (0.87), 3.199 (16.00), 3.218 (2.58), 3.242 (1.06), 3.257 (0.63), 3.273 (1.65), 3.303 (0.90), 3.417 (0.68), 3.463 (2.89), 3.471 (14.60), 3.526 (6.00), 3.541 (5.06), 3.559 (8.08), 3.573 (7.30), 3.618 (0.54), 4.215 (0.56), 4.248 (0.53), 4.355 (0.62), 4.389 (0.58), 5.395 (1.37), 5.399 (1.54), 5.404 (1.56), 5.408 (1.42), 5.853 (1.49), 5.857 (1.66), 5.862 (1.76), 5.866 (1.66), 5.877 (0.49), 5.881 (0.56), 5.886 (0.98), 5.890 (1.03), 5.897 (1.68), 5.903 (1.87), 5.909 (1.08), 5.918 (0.48), 6.033 (1.94), 6.035 (2.30), 6.041 (3.84), 6.048 (2.10), 6.050 (1.91), 6.636 (0.58), 6.641 (0.94), 6.647 (1.25), 6.655 (2.31), 6.659 (2.51), 6.666 (1.59), 6.742 (1.77), 6.747 (2.24), 6.749 (2.20), 6.753 (1.72), 7.141 (8.30), 7.153 (4.62), 7.176 (0.48), 7.244 (2.02), 7.263 (2.53), 7.330 (1.21), 7.338 (1.99), 7.344 (2.08), 7.352 (1.87), 7.360 (1.41), 7.365 (1.21), 7.373 (0.47), 7.411 (1.52), 7.429 (4.63), 7.434 (4.06), 7.442 (2.84), 7.449 (3.07), 7.485 (2.74), 7.488

(2.30), 7.498 (0.76), 7.504 (1.82), 7.522 (0.57), 7.542 (0.60), 7.559 (1.50), 7.565 (1.49), 7.583 (0.67).

The title compound (159 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (60 mg, see Example 2) and stereoisomer 2 (55 mg, see Example 3).

Preparative chiral HPLC method: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000, column: Cellulose SB 5µ 250x30mm; eluent A: methyl *tert*-butyl ether; + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; isocratic: 90%A+10%B; flow 50.0 mL/min; UV 220 nm.

Analytical chiral HPLC method: Instrument: Agilent HPLC 1260; column: Cellulose SB 3µ 100x4,6mm; eluent A: methyl tert-butyl ether + 0.1 Vol-% diethylamine (99%); Eluent B: ethanol; isocratic: 90%A+10%B; flow 1.4 mL/min; temperature: 25 ℃; DAD 254 nm.

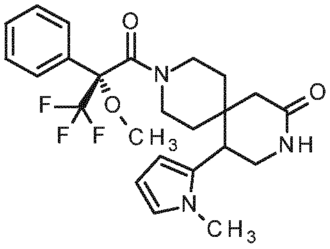
Example 2 and Example 3

(5S)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 2

5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 1)



For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 1.

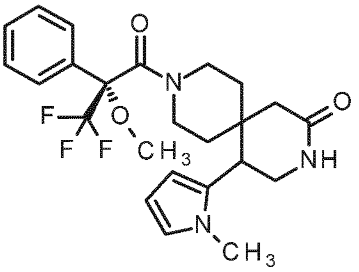
Analytical chiral HPLC (method see Example 1): R_t = 3.5 min; ee > 99.9% Optical rotation (method OR1) = 21.2°+/- 0.98°(me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.166 (0.42), -0.145 (0.74), -0.133 (0.75), -0.111 (0.44), 0.599 (0.81), 0.628 (0.74), 1.137 (0.65), 1.233 (0.45), 1.352 (0.58), 1.382 (0.94), 1.455 (0.68), 1.481 (0.79), 1.488 (0.80), 1.994 (1.09), 2.037 (1.23), 2.153 (0.42), 2.443 (0.62), 2.518 (1.16), 2.522 (0.76), 2.539 (1.28), 2.622 (1.70), 2.665 (1.64), 2.768 (0.61), 2.776 (0.53), 2.802 (0.97), 2.809 (0.87), 2.835 (1.09), 2.847 (1.04), 2.863 (0.84), 2.877 (0.91), 2.945 (0.52), 2.953

(0.64), 2.958 (0.58), 2.967 (0.72), 2.975 (1.17), 2.984 (0.82), 2.998 (0.70), 3.005 (0.95), 3.039 (0.53), 3.094 (0.49), 3.112 (0.70), 3.124 (0.41), 3.198 (16.00), 3.242 (1.02), 3.272 (1.47), 3.303 (0.77), 3.417 (0.73), 3.460 (2.63), 3.541 (5.04), 3.559 (8.08), 4.355 (0.65), 4.388 (0.62), 5.853 (1.56), 5.857 (1.75), 5.862 (1.85), 5.865 (1.67), 5.897 (1.65), 5.900 (1.23), 5.903 (1.15), 6.034 (1.74), 6.042 (2.30), 6.050 (1.59), 6.636 (0.57), 6.641 (0.89), 6.647 (0.54), 6.742 (1.85), 6.746 (2.31), 6.748 (2.31), 6.752 (1.75), 7.140 (8.39), 7.153 (4.70), 7.175 (0.50), 7.330 (0.69), 7.338 (1.33), 7.344 (1.53), 7.352 (1.72), 7.360 (1.40), 7.364 (1.19), 7.373 (0.47), 7.435 (1.98), 7.441 (1.52), 7.450 (0.86), 7.452 (0.90), 7.540 (0.65), 7.558 (1.57), 7.564 (1.53).

Example 3

5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 2)



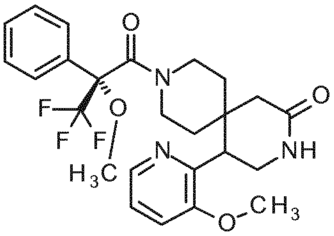
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 1.

Analytical chiral HPLC (method see Example 1): R_t = 4.3 min; ee > 99.9%
Optical rotation (method OR1) = 25.9° +/- 1.57° (methanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.535 (0.56), 0.545 (0.56), 0.567 (0.47), 0.578 (0.41), 0.611 (0.97), 0.640 (0.47), 0.798 (0.81), 0.814 (0.90), 0.821 (0.92), 0.840 (0.85), 0.851 (0.56), 0.872 (0.82), 0.886 (0.99), 0.904 (1.37), 0.923 (0.58), 1.061 (0.47), 1.138 (0.79), 1.170 (0.42), 1.232 (0.53), 1.400 (1.13), 1.429 (0.73), 2.013 (0.47), 2.057 (0.56), 2.166 (1.11), 2.209 (1.45), 2.477 (1.38), 2.518 (1.38), 2.522 (1.18), 2.534 (1.92), 2.539 (1.76), 2.577 (1.49), 2.768 (0.67), 2.795 (0.94), 2.801 (0.99), 2.829 (0.51), 2.953 (4.16), 2.970 (1.39), 2.995 (0.44), 3.025 (0.43), 3.031 (0.48), 3.036 (0.46), 3.051 (1.52), 3.057 (1.55), 3.066 (1.00), 3.076 (1.11), 3.084 (0.87), 3.118 (0.52), 3.124 (0.59), 3.198 (0.57), 3.218 (2.78), 3.257 (0.59), 3.297 (0.42), 3.305 (0.49), 3.471 (16.00), 3.526 (6.80), 3.573 (8.06), 3.618 (0.61), 4.215 (0.65), 4.248 (0.62), 5.395 (1.62), 5.399 (1.80), 5.404 (1.80), 5.408 (1.62), 5.877 (0.50), 5.881 (0.60), 5.886 (0.98), 5.890 (0.91), 5.902 (1.03), 5.909 (1.09), 5.918 (0.52), 6.032 (1.84), 6.039 (2.34), 6.048 (1.76), 6.647 (0.96), 6.654 (2.71), 6.659 (2.90), 6.665 (1.78), 7.244 (2.32), 7.263 (2.88), 7.324 (0.61), 7.329 (0.72), 7.338 (0.92), 7.346 (0.88), 7.411 (1.75), 7.429 (5.01), 7.433 (3.41), 7.443 (2.10), 7.448 (2.62), 7.485 (3.18), 7.488 (2.58), 7.497 (0.93), 7.503 (2.09), 7.509 (0.49), 7.521 (0.60), 7.584 (0.70).

Example 4

5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Example 1 the title compound was prepared, 310 mg (50 % yield), starting from Intermediate 5.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.170 (0.64), -0.158 (0.64), 0.686 (1.36), 0.721 (0.77), 0.994 (0.42), 1.016 (0.60), 1.027 (0.68), 1.387 (0.59), 1.418 (0.73), 1.494 (0.66), 1.530 (0.46), 1.675 (0.55), 1.686 (0.62), 1.710 (0.40), 1.720 (0.44), 1.838 (0.42), 1.881 (0.46), 1.936 (1.01), 1.979 (1.12), 1.995 (0.42), 2.093 (0.88), 2.137 (1.03), 2.465 (0.59), 2.518 (1.52), 2.522 (0.95), 2.539 (2.14), 2.553 (0.71), 2.565 (1.36), 2.608 (1.21), 2.686 (1.54), 2.730 (1.37), 2.796 (0.44), 2.823 (0.79), 2.829 (0.77), 2.857 (0.46), 2.896 (0.48), 2.910 (1.04), 2.917 (1.10), 2.927 (0.66), 2.936 (0.64), 2.941 (0.77), 2.949 (0.75), 3.007 (0.59), 3.041 (1.10), 3.054 (1.04), 3.069 (1.12), 3.089 (0.68), 3.276 (0.92), 3.292 (2.68), 3.304 (1.26), 3.317 (1.03), 3.372 (0.73), 3.396 (2.86), 3.406 (1.67), 3.424 (2.25), 3.448 (0.79), 3.468 (0.62), 3.499 (0.64), 3.555 (7.99), 3.563 (6.78), 3.583 (0.55), 3.607 (16.00), 3.663 (0.77), 3.692 (1.21), 3.722 (0.62), 3.756 (11.84), 3.808 (5.77), 3.813 (5.11), 4.124 (0.46), 4.158 (0.44), 4.284 (0.57), 4.318 (0.55), 6.994 (1.14), 7.014 (2.66), 7.033 (1.87), 7.100 (2.49), 7.119 (1.72), 7.210 (1.52), 7.228 (2.46), 7.239 (1.12), 7.248 (0.70), 7.251 (0.68), 7.260 (1.14), 7.272 (0.75), 7.276 (1.12), 7.288 (1.81), 7.297 (1.69), 7.308 (4.53), 7.327 (3.13), 7.348 (2.11), 7.355 (1.32), 7.364 (1.36), 7.370 (1.63), 7.376 (1.76), 7.379 (2.11), 7.391 (2.80), 7.397 (1.48), 7.402 (2.90), 7.407 (0.97), 7.410 (1.14), 7.415 (0.86), 7.424 (2.24), 7.429 (4.60), 7.433 (4.95), 7.441 (3.21), 7.450 (2.24), 7.469 (1.23), 7.471 (1.47), 7.490 (1.50), 7.509 (0.82), 7.517 (1.41), 7.523 (1.39), 8.064 (0.60), 8.068 (0.68), 8.073 (1.56), 8.076 (2.00), 8.084 (1.52), 8.087 (1.36), 8.092 (0.75), 8.096 (0.70), 8.104 (0.66), 8.107 (0.60), 8.181 (1.83), 8.184 (1.83), 8.192 (1.87), 8.196 (1.69).

The title compound (299 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (125 mg, see Example 5) and stereoisomer 2 (115 mg, see Example 6).

Preparative chiral HPLC method: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000, column: Chiralpak ID 5µ 250x30mm; eluent A: methyl *tert*-butyl ether + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; isocratic: 90% A+10% B; flow 50.0 mL/min; UV 220 nm.

Analytical chiral HPLC method: Instrument: Agilent HPLC 1260; column: Chiralpak ID 3µ 100x4,6mm; eluent A: methyl *tert*-butyl ether + 0.1 Vol-% diethylamine (99%); eluent B: ethanol; isocratic: 90% A + 10% B; flow 1.4 mL/min; temperature: 25 ℃; DAD 254 nm.

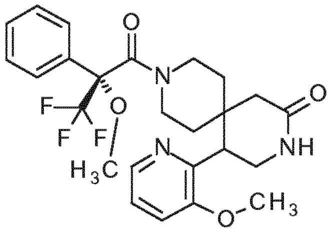
Example 5 and Example 6

(5R)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5S)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 5

5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 1)



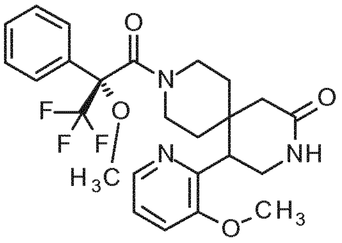
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 4.

Analytical chiral HPLC (method see Example 4): R_t = 2.91 min; ee > 99.9% Optical rotation (method OR1) = 15.9° +/- 0.88° (me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.160 (2.05), 0.693 (2.09), 0.724 (2.28), 0.812 (0.98), 0.902 (0.60), 0.929 (0.78), 0.964 (0.75), 1.137 (0.90), 1.166 (0.86), 1.229 (0.63), 1.323 (0.62), 1.388 (1.91), 1.420 (2.52), 1.684 (2.06), 1.765 (0.88), 1.937 (2.26), 1.979 (2.84), 2.687 (2.61), 2.730 (2.50), 2.796 (1.44), 2.827 (2.40), 2.857 (1.76), 2.938 (2.51), 3.004 (1.91), 3.038 (2.65), 3.069 (1.82), 3.172 (0.93), 3.424 (7.18), 3.554 (14.25), 3.606 (16.00), 3.661 (2.84), 3.693 (3.14), 3.721 (2.08), 3.812 (4.35), 3.993 (0.68), 4.290 (1.95), 4.319 (2.15), 7.013 (5.54), 7.029 (5.20), 7.102 (5.93), 7.116 (5.89), 7.256 (1.20), 7.306 (3.39), 7.367 (3.67), 7.390 (5.05), 7.400 (5.11), 7.428 (7.73), 7.520 (4.32), 8.076 (1.12), 8.191 (3.77).

Example 6

5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 2)



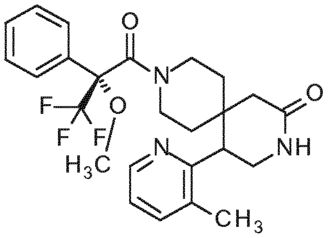
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 4.

Analytical chiral HPLC (method see Example 4): R_t = 3.68 min; ee = 99.5% Optical rotation (method OR1) = 26.1°+/- 1.60°(methanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.678 (3.42), 0.797 (0.74), 0.818 (0.84), 0.837 (0.51), 0.903 (0.55), 0.995 (1.35), 1.027 (2.18), 1.050 (1.20), 1.138 (1.14), 1.161 (0.88), 1.230 (0.59), 1.323 (0.79), 1.344 (0.76), 1.496 (1.70), 1.530 (1.52), 1.696 (0.45), 1.721 (0.66), 1.838 (0.95), 1.882 (1.02), 2.094 (1.99), 2.114 (0.64), 2.137 (2.31), 2.409 (0.45), 2.566 (3.29), 2.609 (2.60), 2.884 (1.00), 2.916 (1.79), 2.946 (1.01), 3.056 (2.95), 3.064 (2.91), 3.090 (2.22), 3.118 (1.11), 3.190 (0.72), 3.216 (0.84), 3.250 (1.01), 3.294 (6.26), 3.396 (6.11), 3.466 (2.21), 3.498 (2.00), 3.565 (13.61), 3.756 (16.00), 3.808 (7.33), 4.015 (0.67), 4.048 (0.63), 4.125 (1.49), 4.158 (1.41), 7.211 (4.08), 7.230 (5.54), 7.250 (1.56), 7.259 (1.54), 7.275 (2.26), 7.289 (2.36), 7.297 (3.19), 7.309 (5.34), 7.328 (5.82), 7.347 (4.71), 7.377 (4.00), 7.399 (2.98), 7.435 (7.94), 7.469 (3.59), 7.489 (2.95), 7.506 (1.41), 8.076 (3.19), 8.086 (3.45), 8.104 (1.64).

Example 7

5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Example 1 the title compound was prepared 310 mg (50 % yield) starting from Intermediate 5.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.237 (0.51), -0.216 (0.91), -0.204 (0.93), -0.183 (0.53), -0.172 (0.44), 0.694 (1.53), 0.725 (1.65), 0.896 (0.58), 0.907 (0.70), 0.929 (1.23), 0.941 (1.21), 0.962 (0.70), 0.973 (0.67), 1.418 (1.09), 1.453 (1.16), 1.509 (0.91), 1.542 (0.84), 1.985 (0.44), 2.010 (1.16), 2.052 (16.00), 2.084 (1.56), 2.117 (0.65), 2.161 (0.63), 2.194 (1.14), 2.237 (1.49), 2.276 (11.10), 2.323 (5.69), 2.343 (4.99), 2.374 (0.44), 2.518 (4.41), 2.522 (2.88), 2.539 (3.67), 2.570 (0.74), 2.612 (0.65), 2.637 (0.81), 2.664 (2.32), 2.673 (0.95), 2.678 (0.98), 2.712 (2.35), 2.756 (1.83), 2.780 (0.88), 2.814 (2.02), 2.842 (1.53), 2.847 (1.58), 2.876 (0.51), 2.926 (0.56), 2.939 (0.79), 2.947 (0.79), 2.956 (0.72), 2.969 (0.84), 2.977 (0.70), 3.008 (0.60), 3.021 (0.53), 3.041 (1.63), 3.051 (0.95), 3.074 (1.97), 3.089 (1.76), 3.103 (1.63), 3.117 (1.39), 3.139 (3.13), 3.177 (1.00), 3.191 (0.98), 3.201 (1.14), 3.214 (0.88), 3.281 (0.46), 3.296 (0.65), 3.307 (0.77), 3.379 (0.84), 3.409 (1.79), 3.427 (3.44), 3.444 (1.04), 3.553 (10.59), 3.566 (8.62), 3.630 (1.04), 3.659 (1.67), 3.688 (0.84), 4.184 (0.63), 4.217 (0.77), 4.318 (0.79), 4.353 (0.74), 6.934 (1.63), 6.953 (3.65), 6.972 (2.37), 7.091 (3.32), 7.110 (2.62), 7.131 (1.21), 7.143 (1.23), 7.150 (1.30), 7.163 (1.79), 7.167 (1.53), 7.184 (3.11), 7.195 (1.65), 7.203 (2.46), 7.214 (3.60), 7.234 (2.86), 7.279 (1.81), 7.291 (1.93), 7.298 (2.11), 7.310 (2.62), 7.331 (2.95), 7.350 (4.04), 7.370 (1.95), 7.423 (2.46), 7.434 (3.79), 7.440 (4.67), 7.447 (2.74), 7.491 (1.23), 7.509 (2.42), 7.531 (2.62), 7.557 (1.51), 7.560 (1.56), 7.581 (3.16), 7.602 (2.18), 8.309 (1.37), 8.313 (1.42), 8.325 (1.79), 8.337 (0.65), 8.349 (0.67), 8.361 (0.65), 8.455 (1.81), 8.458 (1.88), 8.467 (1.86), 8.470 (1.70).

The title compound (229 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (90 mg, see Example 8) and stereoisomer 2 (70 mg, see Example 9).

<u>Preparative chiral HPLC method</u>: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000, column: Cellulose SB 5µ 250x30mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: 2-propanol; isocratic: 70%A+30%B; flow 50.0 mL/min; UV 220 nm.

<u>Analytical chiral HPLC method</u>: Instrument: Agilent HPLC 1260; column: Cellulose SB 3µ 100x4,6mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: 2-propanol; isokratic: 70%A+30%B; flow 1.4 mL/min; temperatur: 25 ℃; DAD 254 nm.

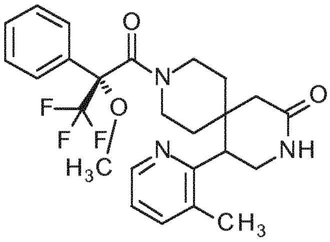
Example 8 and Example 9

(5S)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 8

5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 1)



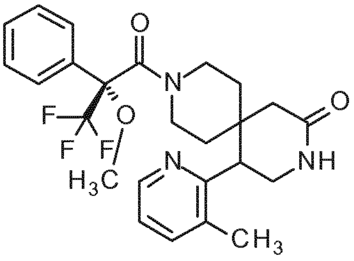
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 7.

Analytical chiral HPLC (method see Example 7): R_t = 3.42 min; ee > 99.9%
Optical rotation (method OR1) = +47.0°+/- 0.55°(m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.248 (0.42), -0.237 (0.53), -0.215 (0.94), -0.204 (0.95), -0.182 (0.55), -0.171 (0.45), 0.695 (1.00), 0.725 (0.93), 1.026 (1.25), 1.042 (1.40), 1.418 (0.92), 1.450 (1.00), 1.986 (0.62), 2.008 (0.80), 2.019 (0.83), 2.052 (16.00), 2.085 (1.58), 2.119 (0.49), 2.161 (0.55), 2.342 (5.02), 2.522 (0.68), 2.539 (1.84), 2.570 (0.71), 2.613 (0.62), 2.713 (2.08), 2.757 (1.88), 2.780 (0.82), 2.813 (1.44), 2.846 (0.71), 2.927 (0.55), 2.935 (0.73), 2.940 (0.79), 2.948 (0.80), 2.957 (0.73), 2.966 (0.78), 2.970 (0.84), 2.978 (0.70), 3.008 (0.60), 3.038 (1.09), 3.076 (1.60), 3.089 (1.05), 3.103 (1.42), 3.117 (1.23), 3.426 (3.40), 3.450 (1.02), 3.536 (0.55), 3.553 (10.22), 3.632 (1.05), 3.661 (1.71), 3.690 (0.85), 4.319 (0.80), 4.351 (0.86), 6.934 (1.66), 6.952 (3.74), 6.971 (2.44), 7.091 (3.42), 7.110 (2.71), 7.130 (0.70), 7.141 (0.69), 7.149 (0.73), 7.163 (1.14), 7.167 (1.47), 7.185 (2.37), 7.203 (1.05), 7.279 (1.87), 7.291 (1.93), 7.298 (2.11), 7.310 (2.07), 7.343 (0.72), 7.353 (0.86), 7.362 (0.92), 7.434 (2.29), 7.439 (1.96), 7.447 (1.13), 7.451 (1.05), 7.509 (0.72), 7.535 (1.93), 7.542 (1.94), 7.568 (0.68), 7.570 (0.71), 7.586 (2.49), 7.602 (1.74), 7.605 (1.65), 8.325 (0.60), 8.328 (0.62), 8.337 (0.62), 8.455 (1.87), 8.458 (1.95), 8.466 (1.94), 8.469 (1.78).

Example 9

5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 2)



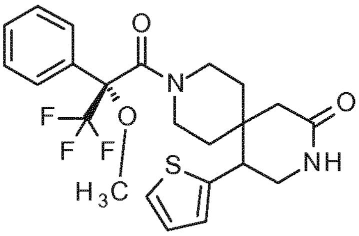
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 7.

Analytical chiral HPLC (method see Example 7): R_t = 4.44 min; ee > 99.9% Optical rotation (method OR1) = +3.4° +/- 0.36° (me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.694 (0.85), 0.725 (1.10), 0.898 (0.81), 0.908 (0.98), 0.931 (1.72), 0.942 (1.68), 0.964 (0.99), 0.975 (0.81), 1.026 (4.03), 1.041 (3.92), 1.058 (0.45), 1.069 (0.57), 1.088 (0.57), 1.202 (0.54), 1.232 (0.62), 1.424 (0.47), 1.458 (0.48), 1.515 (1.05), 1.543 (0.94), 2.013 (0.71), 2.055 (0.83), 2.195 (1.59), 2.238 (1.83), 2.276 (16.00), 2.323 (7.56), 2.383 (0.47), 2.518 (1.55), 2.522 (0.99), 2.539 (4.16), 2.637 (1.12), 2.665 (2.61), 2.680 (1.12), 2.708 (2.05), 2.815 (0.93), 2.843 (1.23), 2.848 (1.30), 2.876 (0.66), 2.995 (0.41), 3.022 (0.56), 3.029 (0.70), 3.035 (0.79), 3.043 (0.86), 3.053 (1.16), 3.061 (1.36), 3.074 (0.86), 3.090 (1.11), 3.095 (1.08), 3.123 (0.79), 3.140 (4.15), 3.160 (0.49), 3.168 (0.54), 3.178 (1.40), 3.191 (1.39), 3.201 (1.68), 3.215 (1.26), 3.230 (0.47), 3.266 (0.43), 3.282 (0.62), 3.296 (0.56), 3.307 (0.83), 3.379 (1.32), 3.408 (1.27), 3.434 (0.78), 3.540 (1.42), 3.567 (11.36), 4.185 (0.90), 4.219 (1.09), 4.243 (0.43), 4.350 (0.48), 4.361 (0.46), 5.757 (0.46), 7.131 (0.91), 7.143 (0.98), 7.150 (0.99), 7.162 (1.01), 7.183 (2.02), 7.194 (2.08), 7.202 (2.32), 7.214 (4.96), 7.235 (4.10), 7.316 (1.06), 7.330 (4.03), 7.349 (4.89), 7.369 (2.64), 7.413 (0.52), 7.423 (3.23), 7.430 (2.97), 7.439 (3.94), 7.490 (1.65), 7.509 (2.61), 7.527 (2.03), 7.556 (1.99), 7.559 (2.09), 7.578 (2.61), 7.597 (0.87), 7.600 (0.84), 8.309 (1.94), 8.312 (2.04), 8.321 (2.02), 8.324 (1.87), 8.349 (0.91), 8.353 (0.96), 8.361 (0.93), 8.364 (0.86).

Example 10

5-(thiophen-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro-[5.5]undecan-2-one (mixture of stereoisomers)

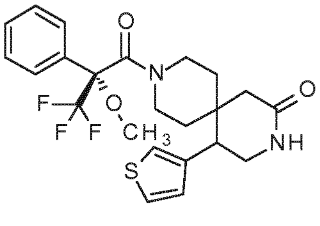


Using an analogous method as described for Example 1 the title compound was prepared 114 mg (26 % yield) starting from Intermediate 6.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.185 (0.47), 0.207 (0.78), 0.216 (0.78), 0.238 (0.56), 0.366 (0.44), 0.389 (0.81), 0.400 (0.81), 0.421 (0.56), 0.644 (1.21), 0.867 (0.59), 1.163 (0.53), 1.185 (1.09), 1.196 (1.21), 1.218 (1.25), 1.319 (0.65), 1.354 (0.68), 1.404 (2.12), 1.439 (2.43), 1.850 (1.00), 1.893 (1.12), 1.940 (0.59), 1.984 (1.06), 2.000 (1.49), 2.043 (1.68), 2.070 (2.40), 2.145 (1.53), 2.173 (1.03), 2.188 (2.05), 2.216 (0.75), 2.242 (1.40), 2.286 (1.15), 2.323 (1.84), 2.403 (2.43), 2.447 (2.27), 2.570 (1.84), 2.665 (1.99), 2.669 (1.59), 2.729 (0.56), 2.755 (0.40), 2.896 (1.12), 2.924 (1.93), 2.958 (1.00), 3.080 (2.46), 3.115 (4.42), 3.127 (2.09), 3.148 (2.09), 3.187 (1.74), 3.199 (1.77), 3.223 (1.40), 3.240 (1.77), 3.269 (2.40), 3.296 (1.84), 3.429 (1.96), 3.448 (7.75), 3.552 (3.95), 3.578 (16.00), 3.911 (0.62), 4.179 (0.87), 4.212 (0.81), 4.281 (0.81), 4.315 (0.75), 6.644 (2.40), 6.650 (2.49), 6.816 (2.21), 6.823 (2.37), 6.961 (2.80), 6.972 (2.21), 6.976 (2.15), 6.990 (1.71), 7.003 (1.68), 7.011 (1.03), 7.029 (2.15), 7.038 (2.21), 7.042 (2.43), 7.051 (2.30), 7.056 (2.12), 7.065 (2.02), 7.069 (2.30), 7.078 (1.90), 7.131 (1.37), 7.151 (3.55), 7.169 (3.08), 7.208 (3.80), 7.228 (2.24), 7.274 (3.89), 7.293 (5.29), 7.374 (4.64), 7.383 (4.11), 7.393 (7.47), 7.414 (3.36), 7.421 (2.96), 7.443 (7.07), 7.448 (4.26), 7.455 (4.33), 7.476 (1.81), 7.495 (4.61), 7.509 (2.68), 7.587 (2.43), 7.621 (3.49).

Example 11

5-(thiophen-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro-[5.5]undecan-2-one (mixture of stereoisomers)

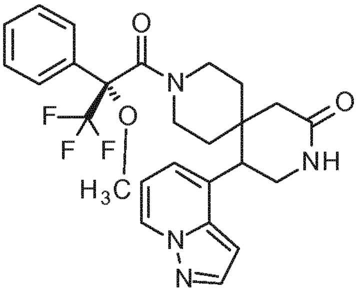


Using an analogous method as described for Example 1 the title compound was prepared 34 mg (16 % yield) starting from Intermediate 7.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.518 (2.47), 2.523 (1.63), 3.482 (0.59), 3.574 (2.47), 4.193 (1.66), 6.989 (0.54), 6.992 (0.47), 6.996 (0.43), 7.002 (0.40), 7.162 (0.67), 7.179 (1.22), 7.185 (1.16), 7.193 (0.54), 7.196 (0.50), 7.234 (0.45), 7.254 (0.59), 7.301 (0.52), 7.305 (0.58), 7.309 (0.53), 7.362 (0.68), 7.381 (0.97), 7.401 (0.45), 7.426 (0.54), 7.431 (0.54), 7.440 (1.03), 7.447 (0.72), 7.454 (0.40), 7.457 (0.42), 7.500 (0.52), 7.540 (0.59), 7.543 (0.58), 7.547 (0.71), 7.552 (0.82), 7.559 (0.57), 7.599 (0.66).

Example 12

5-(pyrazolo[1,5-a]pyridin-4-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



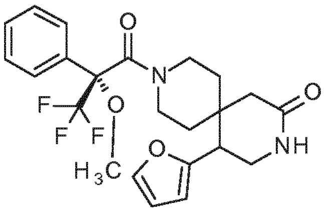
Using an analogous method as described for Example 1 the title compound was prepared 133 mg (68 % yield) starting from Intermediate 8.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.459 (0.47), -0.437 (0.86), -0.427 (0.86), -0.404 (0.47), 0.420 (0.47), 0.653 (1.37), 0.686 (1.20), 0.798 (1.89), 0.802 (0.82), 0.814 (1.97), 0.821 (2.02), 0.840 (0.90), 0.886 (1.29), 0.904 (2.62), 0.922 (1.46), 1.035 (7.85), 1.052 (16.00), 1.070 (8.88), 1.142 (0.47), 1.159 (0.43), 1.231 (0.51), 1.255 (0.43), 1.383 (0.43), 1.394 (0.43), 1.417 (0.94), 1.451 (0.69), 1.493 (1.33), 1.517 (1.07), 1.545 (1.07), 2.176 (1.33), 2.219 (1.50), 2.318 (0.69), 2.365 (0.90), 2.389 (0.47), 2.394 (0.64), 2.407 (1.42), 2.431 (0.64), 2.444 (0.51), 2.518 (8.11), 2.523 (5.10), 2.558 (1.16), 2.660 (0.69), 2.698 (2.36), 2.741 (2.06), 2.782 (0.56), 2.808 (1.46), 2.840 (1.59), 2.866 (0.73), 2.969 (0.60), 3.002 (1.16), 3.034 (1.46), 3.064 (1.29), 3.095 (0.82), 3.114 (1.50), 3.157 (1.24), 3.169 (1.29), 3.187 (1.63), 3.199 (1.33), 3.259 (0.99), 3.269 (1.03), 3.295 (1.07), 3.387 (1.07), 3.404 (1.54), 3.417 (1.29), 3.422 (3.09), 3.435 (3.86), 3.439 (3.86), 3.452 (3.05), 3.457 (1.29), 3.469 (1.16), 3.529 (11.50), 3.561 (7.29), 3.604 (1.93), 3.634 (0.73), 4.175 (0.56), 4.209 (0.64), 4.345 (1.84), 4.357 (3.86), 4.370 (1.93), 4.392 (0.86), 5.758 (0.56), 6.533 (2.75), 6.538 (2.79), 6.611 (0.94), 6.628 (1.07), 6.657 (1.29), 6.674 (2.40), 6.682 (3.09), 6.701 (3.09), 6.717 (1.20), 6.767 (1.42), 6.807 (0.39), 6.824 (0.77), 6.836 (0.47), 6.842 (0.43), 6.853 (0.82), 6.871 (0.47), 6.899 (0.51), 6.913 (1.20), 6.930 (3.43), 6.947 (3.47), 6.963 (1.63), 6.994 (3.47), 7.013 (2.83), 7.060 (2.27), 7.077 (1.72), 7.119 (0.69), 7.136 (0.60), 7.233 (1.50), 7.253 (1.89), 7.298 (0.60), 7.308 (0.64), 7.335 (0.64), 7.344 (0.69), 7.355 (1.12), 7.375 (1.80), 7.395 (0.94), 7.412 (1.16), 7.425 (2.49), 7.429 (2.23), 7.440 (1.07), 7.539 (0.60), 7.558 (0.94), 7.576 (0.43), 7.630 (1.42), 7.666 (2.45), 7.672 (2.53), 7.708 (0.47), 7.894 (3.47), 7.899

(3.43), 7.983 (1.16), 7.989 (4.50), 7.995 (3.82), 8.560 (0.51), 8.578 (0.86), 8.602 (1.54), 8.620 (1.46), 8.748 (3.30), 8.765 (3.22).

Example 13

5-(furan-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro-[5.5]undecan-2-one (mixture of stereoisomers)

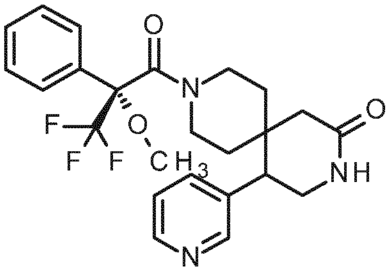


Using an analogous method as described for Example 1 the title compound was prepared 264 mg (81 % yield) starting from Intermediate 9.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.176 (0.45), 0.197 (0.75), 0.209 (0.75), 0.230 (0.51), 0.241 (0.42), 0.360 (0.66), 0.394 (0.42), 0.690 (0.84), 0.720 (1.71), 0.753 (1.02), 0.884 (0.54), 0.902 (0.99), 1.052 (0.60), 1.071 (0.63), 1.089 (0.51), 1.101 (0.45), 1.123 (0.78), 1.134 (0.96), 1.154 (0.99), 1.172 (1.14), 1.189 (0.63), 1.243 (0.66), 1.292 (0.72), 1.334 (0.96), 1.361 (2.10), 1.396 (1.65), 1.822 (0.84), 1.866 (0.93), 1.909 (0.69), 1.952 (0.96), 1.981 (1.50), 1.987 (1.74), 2.024 (1.71), 2.065 (0.96), 2.088 (1.29), 2.131 (1.59), 2.144 (1.23), 2.187 (0.87), 2.228 (1.14), 2.272 (1.05), 2.322 (1.02), 2.327 (1.41), 2.331 (1.02), 2.437 (2.28), 2.522 (4.08), 2.548 (2.07), 2.665 (1.26), 2.669 (1.68), 2.673 (1.38), 2.719 (0.48), 2.844 (0.81), 2.859 (1.08), 2.870 (1.14), 2.884 (1.08), 2.907 (1.05), 2.931 (2.22), 2.955 (1.35), 2.969 (1.89), 3.081 (1.05), 3.112 (2.67), 3.137 (2.70), 3.170 (1.29), 3.201 (1.38), 3.214 (1.23), 3.235 (2.10), 3.269 (2.40), 3.300 (1.89), 3.355 (1.44), 3.372 (0.75), 3.397 (1.17), 3.434 (0.96), 3.457 (4.23), 3.509 (0.84), 3.535 (4.14), 3.583 (16.00), 4.137 (0.72), 4.171 (0.69), 4.253 (0.75), 4.286 (0.72), 5.758 (3.12), 5.950 (2.58), 5.957 (2.67), 6.160 (2.79), 6.167 (3.00), 6.229 (1.32), 6.238 (1.62), 6.241 (1.59), 6.249 (1.59), 6.370 (1.14), 6.375 (1.26), 6.378 (1.11), 6.383 (1.05), 6.401 (1.26), 6.405 (1.32), 6.409 (1.23), 6.414 (1.14), 6.468 (2.28), 6.476 (4.35), 6.480 (4.41), 6.488 (2.10), 7.240 (1.29), 7.263 (7.77), 7.281 (5.43), 7.301 (1.47), 7.366 (1.83), 7.378 (4.23), 7.383 (4.05), 7.396 (6.51), 7.417 (2.43), 7.432 (3.21), 7.437 (3.24), 7.447 (4.62), 7.451 (3.84), 7.460 (1.95), 7.465 (2.07), 7.469 (1.95), 7.487 (2.16), 7.505 (0.78), 7.526 (1.92), 7.545 (2.04), 7.548 (2.40), 7.555 (1.89), 7.580 (3.69), 7.588 (4.29), 7.593 (3.96), 7.599 (3.54), 7.602 (3.39).

Example 14

5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Intermediate 1 the title compound was prepared starting from Intermediate 12 (70.0 mg, 248 µmol) and ((2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (75.6 mg, 323 µmol) to give the title compound 4 mg (3 % yield) after purification be preparative HPLC (Method 5).

Additional the titled compound was synthesized via a different method:

An autoclave was charged with ethyl rel-{4-[(2-chloropyridin-3-yl)(cyano)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate, Intermediate 17), ammonia (077 ml, 2.0 M in ethanol) and Raney-Nickel (18 mg, 50% wet) and the mixture was stirred under 28 bar hydrogen atmosphere at 85℃ for 50 h. For the w ork-up, the mixture was filtered through a pad of celite, eluted with ethanol and the combined filtrates were concentrated under reduced pressure to give the title compound 55 mg (>100 % yield) which was used directly for chiral HPLC separation.

The title compound (55 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (16 mg, see Example 15) and stereoisomer 2 (16 mg, see Example 16).

Preparative chiral HPLC method: Instrument: Sepiatec: Prep SFC100, column: Reprosil Chiral NR 8µm 250x30mm; eluent A: CO2; eluent B: methanol; isocratic: 33%B; flow 100.0 mL/min; pressure: 150 bar; UV 220 nm.

Analytical chiral HPLC method: Instrument: 1260, Aurora SFC-Module; column: Reprosil Chiral NR 5µm 100x4.6mm; eluent A: CO2; eluent B: methanol; isocratic: 33%B; flow: 4 mL/min; pressure: 100 bar; UV 220 nm.

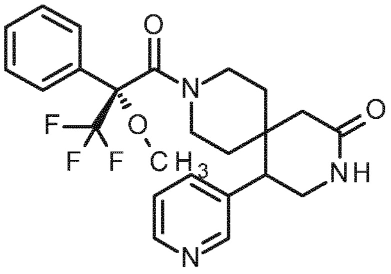
Example 15 and Example 16

(5S)-5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 15

5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 1)



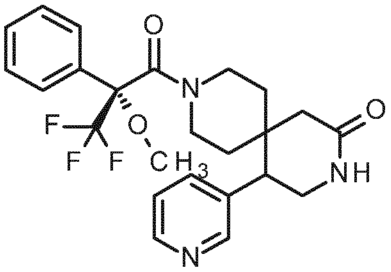
For the preparation of the title compound and the separation into the corresponding diastereoisomers, see Example 14.

Analytical chiral HPLC (method see Example 14): R_t = 2.27 min; ee 98.6.%

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.156 (0.46), -0.147 (0.46), 0.670 (0.56), 0.703 (0.52), 1.106 (16.00), 1.208 (0.43), 1.239 (0.73), 1.273 (0.43), 1.437 (0.64), 1.470 (0.60), 1.993 (0.74), 2.036 (0.87), 2.572 (1.02), 2.616 (0.75), 2.789 (0.52), 2.803 (0.53), 2.815 (0.47), 2.884 (0.64), 3.090 (1.14), 3.119 (1.08), 3.420 (0.94), 3.478 (1.78), 3.502 (0.60), 3.532 (0.81), 3.562 (5.91), 4.194 (1.64), 4.320 (0.51), 4.354 (0.49), 6.978 (0.78), 6.997 (1.70), 7.015 (1.13), 7.128 (1.82), 7.147 (1.42), 7.192 (0.61), 7.211 (0.96), 7.229 (0.47), 7.349 (0.61), 7.369 (0.68), 7.386 (0.56), 7.420 (1.59), 7.542 (0.75), 7.561 (0.61), 7.674 (1.34), 8.252 (1.14), 8.456 (0.63), 8.581 (0.87), 8.591 (0.85).

Example 16

5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 2)



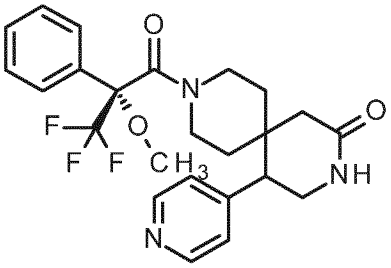
For the preparation of the title compound and the separation into the corresponding diastereoisomers, see Example 14.

Analytical chiral HPLC (method see Example 14): R_t = 2.98 min; ee 97.4%

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.672 (0.43), 0.966 (0.45), 1.107 (16.00), 1.144 (0.43), 1.284 (0.44), 1.440 (0.45), 1.471 (0.43), 2.138 (0.55), 2.181 (0.75), 2.202 (0.48), 2.322 (0.43), 2.327 (0.52), 2.332 (0.43), 2.669 (0.45), 2.847 (0.48), 2.872 (0.92), 2.885 (0.56), 3.086 (0.85), 3.117 (0.78), 3.153 (0.64), 3.178 (0.49), 3.185 (0.51), 3.572 (4.11), 4.194 (1.90), 7.211 (1.19), 7.230 (1.55), 7.311 (0.64), 7.331 (1.79), 7.350 (2.29), 7.370 (1.68), 7.390 (0.82), 7.402 (0.82), 7.409 (0.66), 7.422 (0.70), 7.440 (1.45), 7.446 (1.18), 7.456 (0.79), 7.493 (0.59), 7.512 (0.86), 7.530 (0.43), 7.632 (0.83), 7.661 (0.41), 7.688 (0.63), 8.197 (0.88), 8.464 (0.76), 8.520 (0.69), 8.530 (0.66).

Example 17

5-(pyridin-4-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)

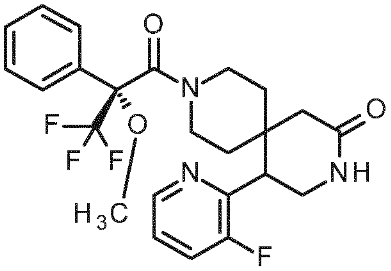


Using an analogous method as described for Intermediate 1 the title compound was prepared starting from Intermediate 12 (70.0 mg, 248 µmol) and ((2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (75.6 mg, 323 µmol) to give the title compound 20 mg (17 % yield) after purification be preparative HPLC (Method 5).

LC-MS (method 2): R_t = 0.96 min; MS (ESIpos): m/z = 462.6 $[M+H]^+$

Example 18

5-(3-fluoropyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers



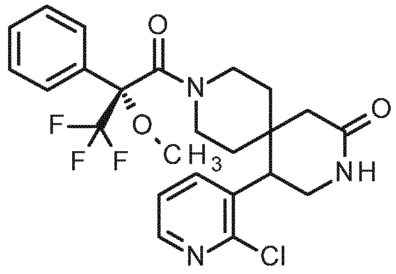
Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(3-fluoropyridin-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-

methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (500 mg, 959 µmol, Intermediate 16) and gave the title compound 300 mg (62 %) after purification by preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.203 (0.44), -0.180 (0.83), -0.171 (0.83), -0.147 (0.47), 0.532 (0.69), 0.543 (0.69), 0.566 (0.47), 0.576 (0.40), 0.707 (1.16), 0.719 (1.16), 0.752 (1.05), 0.961 (0.40), 0.982 (0.91), 0.991 (0.80), 1.013 (0.65), 1.131 (0.73), 1.165 (0.40), 1.434 (0.80), 1.466 (1.12), 1.507 (1.12), 1.540 (0.98), 1.583 (0.47), 1.596 (0.58), 1.616 (1.02), 1.628 (1.12), 1.648 (0.73), 1.662 (0.62), 1.949 (0.65), 1.992 (0.73), 2.033 (1.49), 2.047 (0.58), 2.076 (1.67), 2.090 (0.65), 2.174 (1.34), 2.217 (1.63), 2.322 (0.40), 2.327 (0.58), 2.331 (0.44), 2.427 (0.73), 2.471 (0.98), 2.518 (3.05), 2.522 (2.76), 2.539 (3.56), 2.547 (0.47), 2.587 (2.32), 2.631 (1.85), 2.664 (0.47), 2.669 (0.65), 2.673 (0.54), 2.687 (2.36), 2.730 (2.07), 2.820 (0.65), 2.848 (1.52), 2.854 (1.67), 2.882 (1.56), 2.888 (1.52), 2.915 (0.58), 2.982 (0.40), 3.014 (1.09), 3.022 (0.91), 3.027 (0.94), 3.036 (1.27), 3.045 (1.56), 3.058 (1.05), 3.067 (0.94), 3.082 (2.00), 3.096 (0.94), 3.104 (1.05), 3.114 (2.18), 3.137 (1.31), 3.153 (1.23), 3.169 (1.02), 3.180 (0.80), 3.236 (0.76), 3.262 (1.34), 3.282 (3.92), 3.300 (0.91), 3.312 (0.76), 3.374 (0.58), 3.383 (0.65), 3.391 (0.47), 3.417 (3.08), 3.447 (1.45), 3.469 (1.23), 3.494 (1.56), 3.527 (1.27), 3.539 (1.34), 3.564 (16.00), 3.679 (1.05), 3.707 (1.63), 3.737 (0.91), 4.058 (0.58), 4.191 (0.76), 4.225 (0.73), 4.303 (0.83), 4.337 (0.80), 6.997 (1.74), 7.017 (4.03), 7.036 (2.76), 7.122 (3.66), 7.141 (2.72), 7.193 (2.29), 7.212 (3.77), 7.250 (1.60), 7.261 (3.27), 7.266 (2.50), 7.268 (3.01), 7.279 (4.39), 7.300 (2.07), 7.345 (1.38), 7.353 (1.78), 7.363 (2.25), 7.373 (1.02), 7.378 (0.91), 7.384 (0.80), 7.388 (0.91), 7.399 (0.87), 7.410 (0.54), 7.419 (1.38), 7.426 (2.83), 7.431 (3.77), 7.436 (3.81), 7.441 (4.43), 7.452 (3.30), 7.462 (2.54), 7.481 (2.36), 7.497 (1.78), 7.500 (1.63), 7.508 (3.52), 7.518 (3.12), 7.529 (2.50), 7.540 (2.61), 7.585 (2.00), 7.590 (2.03), 7.669 (1.52), 7.672 (2.29), 7.694 (3.45), 7.698 (3.81), 7.720 (2.29), 7.743 (0.44), 7.747 (0.40), 8.385 (2.50), 8.389 (1.89), 8.394 (1.78), 8.397 (2.21), 8.408 (1.02), 8.419 (0.91), 8.484 (2.54), 8.488 (1.52), 8.496 (2.47).

Example 19

5-(2-chloropyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)

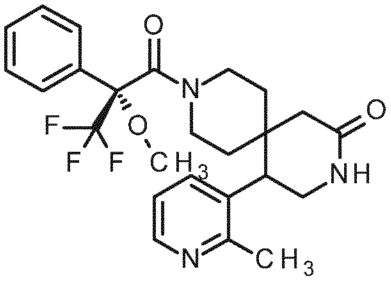


To a solution of ethyl {4-(2-chloropyridin-3-yl)(cyano)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (400 mg, 744 µmol, Intermediate 17) and cobalt(II) chloride hexahydrate (354 mg, 1.49 mmol) in methanol (18 ml) under Argon was added portionwise sodium borohydride (281 mg, 7.44 mmol). The reaction was strred at RT for 1h and 3M HCl (aq) was added until pH 7. The reaction was diluted with water and the methanol was removed in vacuo. The aqueous solution was extracted with ethylacetate, filtered through an hydrophobic filter and concentrated. The residue was purified by silica chromatography (dichloromethane:methanol) to to give the title compound 124 mg (32 % yield.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.338 (0.52), -0.325 (0.69), -0.304 (1.17), -0.292 (1.17), -0.270 (0.67), -0.259 (0.56), 0.689 (0.49), 0.717 (0.40), 0.798 (1.84), 0.802 (1.66), 0.814 (1.79), 0.821 (1.46), 0.840 (1.64), 0.886 (0.69), 0.904 (1.55), 0.922 (0.78), 0.969 (0.49), 0.981 (0.49), 1.035 (6.08), 1.052 (16.00), 1.070 (7.05), 1.108 (0.41), 1.123 (0.49), 1.159 (0.52), 1.233 (0.72), 1.241 (0.63), 1.265 (0.94), 1.275 (0.97), 1.297 (0.61), 1.448 (0.45), 1.492 (1.32), 1.525 (0.99), 1.629 (0.49), 1.664 (0.54), 2.055 (1.68), 2.099 (2.15), 2.226 (0.52), 2.269 (0.69), 2.313 (0.97), 2.388 (0.47), 2.401 (0.76), 2.412 (0.52), 2.445 (0.54), 2.454 (0.51), 2.518 (3.59), 2.523 (2.38), 2.530 (1.05), 2.673 (0.83), 2.679 (0.47), 2.690 (2.80), 2.734 (2.47), 2.822 (1.10), 2.855 (2.20), 2.888 (1.19), 3.007 (0.69), 3.021 (1.21), 3.029 (1.66), 3.038 (1.10), 3.060 (2.09), 3.093 (1.08), 3.124 (0.56), 3.157 (0.63), 3.168 (0.49), 3.175 (0.63), 3.234 (1.48), 3.242 (1.44), 3.255 (1.39), 3.271 (2.00), 3.283 (1.88), 3.301 (1.24), 3.405 (0.52), 3.417 (0.76), 3.422 (1.46), 3.435 (2.36), 3.441 (3.57), 3.452 (1.86), 3.479 (2.11), 3.495 (2.06), 3.526 (2.81), 3.562 (12.95), 3.575 (5.29), 4.259 (0.47), 4.287 (0.47), 4.357 (2.00), 4.387 (0.97), 6.935 (2.11), 6.954 (4.58), 6.974 (2.94), 7.129 (4.22), 7.148 (3.48), 7.162 (1.50), 7.165 (2.07), 7.181 (2.15), 7.184 (3.26), 7.199 (0.99), 7.202 (1.48), 7.254 (1.17), 7.273 (2.00), 7.314 (1.77), 7.333 (3.03), 7.354 (1.82), 7.387 (0.67), 7.393 (0.74), 7.398 (1.12), 7.407 (0.79), 7.412 (1.39), 7.418 (1.64), 7.432 (3.48), 7.438 (2.42), 7.445 (1.68), 7.449 (1.82), 7.461 (1.48), 7.473 (1.46), 7.480 (1.24), 7.484 (0.99), 7.487 (0.74), 7.492 (3.25), 7.504 (3.30), 7.512 (2.83), 7.524 (2.94), 7.667 (1.03), 7.703 (2.92), 7.852 (2.34), 7.856 (2.49), 7.872 (2.22), 7.876 (2.11), 7.895 (0.79), 7.914 (0.70), 8.306 (0.72), 8.311 (0.74), 8.317 (0.97), 8.321 (0.88), 8.328 (0.49), 8.333 (0.41), 8.352 (1.30), 8.357 (1.41), 8.364 (1.23), 8.368 (1.21), 8.454 (3.54), 8.459 (3.63), 8.466 (3.50), 8.470 (3.12).

Example 20

5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-cyano(2-methylpyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (347 mg, 670 µmol, Intermediate 18) and gave the title compound 347 mg (76 %) after purification by preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.346 (0.45), -0.324 (0.78), -0.313 (0.82), -0.291 (0.45), 0.308 (0.67), 0.318 (0.67), 0.340 (0.41), 0.681 (0.86), 0.717 (1.45), 0.757 (0.78), 0.859 (0.48), 0.879 (0.86), 0.891 (0.86), 0.913 (0.56), 1.296 (0.60), 1.328 (0.86), 1.352 (0.48), 1.513 (2.01), 1.546 (1.60), 2.087 (1.19), 2.109 (0.48), 2.131 (1.30), 2.152 (0.60), 2.231 (15.52), 2.268 (1.23), 2.313 (1.90), 2.462 (16.00), 2.518 (10.16), 2.523 (8.00), 2.525 (7.59), 2.539 (3.80), 2.546 (4.17), 2.581 (1.60), 2.690 (1.86), 2.734 (1.71), 2.796 (0.89), 2.810 (0.82), 2.829 (1.23), 2.838 (1.12), 2.856 (0.63), 2.871 (0.60), 2.942 (0.41), 2.955 (0.67), 2.964 (0.67), 2.972 (0.60), 2.986 (0.78), 2.995 (0.82), 3.032 (1.53), 3.059 (1.64), 3.072 (1.93), 3.082 (1.15), 3.116 (3.65), 3.148 (1.79), 3.159 (1.56), 3.224 (1.04), 3.252 (1.23), 3.276 (1.00), 3.398 (1.67), 3.429 (0.93), 3.458 (1.00), 3.478 (1.12), 3.507 (1.53), 3.537 (0.89), 3.554 (8.97), 3.566 (3.01), 3.574 (8.86), 3.599 (0.82), 3.635 (0.63), 4.231 (0.71), 4.264 (0.67), 4.352 (0.74), 4.387 (0.67), 5.759 (12.09), 6.869 (1.41), 6.887 (3.13), 6.906 (1.93), 7.074 (2.90), 7.094 (3.68), 7.117 (2.57), 7.138 (2.31), 7.157 (1.15), 7.160 (1.12), 7.173 (0.78), 7.181 (0.56), 7.193 (0.52), 7.229 (2.90), 7.239 (2.42), 7.251 (3.72), 7.265 (1.53), 7.277 (1.34), 7.285 (1.45), 7.297 (1.45), 7.332 (3.50), 7.351 (4.50), 7.371 (2.16), 7.425 (2.08), 7.432 (2.12), 7.437 (2.46), 7.441 (2.34), 7.453 (0.89), 7.511 (1.38), 7.529 (2.16), 7.547 (0.86), 7.605 (2.49), 7.629 (1.67), 7.646 (2.38), 7.683 (0.93), 8.311 (1.08), 8.319 (1.08), 8.364 (1.97), 8.368 (2.08), 8.375 (1.93), 8.379 (1.90), 8.463 (1.97), 8.467 (2.08), 8.475 (2.01), 8.479 (1.86).

The title compound (415 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (223 mg, see Example 21) and stereoisomer 2 (16 mg, see Example 22).

<u>Preparative chiral HPLC method</u>: Instrument: Sepiatec: Prep SFC100, column: Reprosil Chiral NR 8µm 250x30mm; eluent A: CO2; eluent B: methanol; isocratic: 33%B; flow 100.0 mL/min; pressure: 150 bar; UV 220 nm.

<u>Analytical chiral HPLC method</u>: Instrument: 1260, Aurora SFC-Module; column: Reprosil Chiral NR 5µm 100x4.6mm; eluent A: CO2; eluent B: methanol; isocratic: 33%B; flow: 4 mL/min; pressure: 100 bar; UV 220 nm.

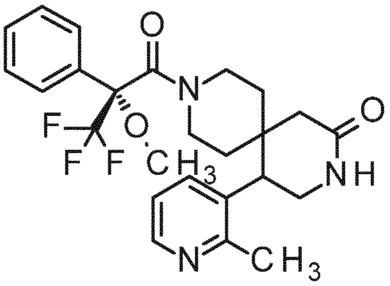
Example 21 and Example 22

(5S)-5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 21

5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 1)



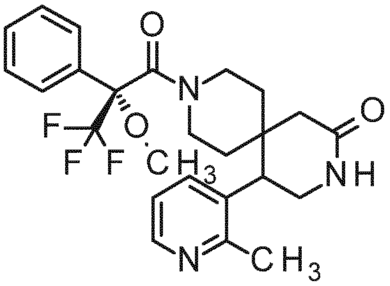
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 20.

Analytical chiral HPLC (method see Example 20): R_t = 2.23 min; ee 99.3% Optical rotation (method OR1) = -11.9° +/- 0.39° (m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.231 (4.38), 2.518 (0.70), 2.522 (0.42), 2.546 (0.95), 2.690 (0.54), 2.734 (0.49), 3.031 (0.45), 3.398 (0.48), 3.507 (0.42), 3.553 (2.56), 4.191 (1.53), 6.868 (0.41), 6.887 (0.89), 6.906 (0.55), 7.074 (0.83), 7.093 (0.69), 7.138 (0.63), 7.284 (0.40), 7.436 (0.42), 7.608 (0.46), 7.626 (0.45), 7.629 (0.45), 7.647 (0.53), 7.655 (0.51), 8.463 (0.56), 8.467 (0.57), 8.475 (0.57), 8.479 (0.52).

Example 22

5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (stereoisomer 2)



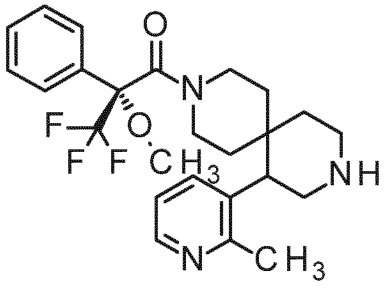
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 20.

Analytical chiral HPLC (method see Example 20): R_t = 4.33 min; ee 96.8% Optical rotation (method OR1) = +43.8° +/- 0.32° (m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.462 (2.55), 2.518 (0.49), 2.525 (1.00), 2.538 (0.41), 3.115 (0.59), 3.574 (1.46), 4.191 (1.52), 7.229 (0.49), 7.252 (0.62), 7.332 (0.52), 7.351 (0.67).

Example 23

(2R)-3,3,3-trifluoro-2-methoxy-1-[7-(2-methylpyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-phenylpropan-1-one (stereoisomer 2)



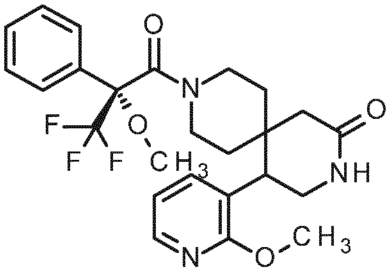
To a solution of Example 22 ((40.0 mg, 84.1 µmol) in THF (2.2. ml) under Argon was added borane dimethylsulfide (290µl, 2M in THF) and heated at 70℃ for 3h. To the reaction mixture was added ethanol (1ml) and 3 drops of 3M HCl (aq) and heated at 70℃ for 2h. The reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method 5) and gave the title compound (27.9mg, 68%).

Optical rotation (method OR1) = +23.9° +/- 1.49° (m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.943 (0.41), 1.107 (16.00), 1.198 (0.53), 1.232 (0.64), 2.106 (0.44), 2.140 (0.64), 2.383 (0.50), 2.402 (0.52), 2.472 (7.59), 2.480 (4.45), 2.518 (4.96), 2.522 (3.22), 2.539 (0.91), 2.601 (0.47), 2.713 (0.75), 2.741 (1.16), 2.760 (1.98), 2.850 (0.64), 3.045 (0.47), 3.102 (1.08), 3.506 (0.41), 3.556 (4.14), 4.194 (1.36), 4.217 (0.41), 6.927 (0.55), 6.944 (0.66), 7.133 (1.08), 7.144 (1.31), 7.160 (1.94), 7.184 (1.45), 7.202 (1.75), 7.223 (0.76), 7.421 (0.94), 7.428 (0.78), 7.437 (0.62), 7.468 (0.56), 7.487 (0.94), 7.504 (0.44), 8.333 (0.84), 8.337 (0.87), 8.345 (0.86), 8.349 (0.81).

Example 24

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(2-methoxypyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (1.46 g, 2.73 mmol, Intermediate 19) and gave the title compound 1.11 g (78 %) after purification by silica chromatography (dichloromethane:ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.035 (7.42), 1.052 (16.00), 1.070 (8.25), 1.951 (0.70), 1.996 (0.59), 2.166 (0.40), 2.210 (0.59), 2.375 (0.43), 2.518 (1.72), 2.522 (1.17), 2.634 (0.81), 2.678 (0.86), 2.848 (0.40), 2.854 (0.40), 2.937 (0.43), 3.030 (0.49), 3.103 (0.57), 3.132 (0.63), 3.209 (0.66), 3.404 (1.27), 3.417 (1.50), 3.422 (3.40), 3.435 (3.41), 3.440 (3.10), 3.452 (3.88), 3.457 (1.85), 3.469 (1.22), 3.504 (0.62), 3.536 (0.45), 3.556 (3.88), 3.571 (2.92), 3.671 (3.99), 3.777 (2.66), 3.855 (3.52), 4.344 (2.22), 4.357 (4.27), 4.369 (1.99), 6.962 (0.83), 6.980 (1.51), 6.998 (0.92), 7.010 (0.50), 7.022 (0.51), 7.028 (0.58), 7.040 (0.87), 7.052 (0.51), 7.057 (0.50), 7.070 (0.45), 7.104 (1.18), 7.123 (0.91), 7.223 (0.72), 7.242 (1.10), 7.261 (0.71), 7.268 (1.02), 7.342 (0.69), 7.361 (1.25), 7.380 (0.45), 7.425 (0.71), 7.430 (0.63), 7.438 (1.16), 7.444 (0.79), 7.454 (0.43), 7.511 (0.43), 7.599 (0.99), 7.623 (1.16), 7.642 (0.67), 8.067 (0.44), 8.093 (0.62), 8.098 (0.62), 8.105 (0.62), 8.110 (0.56), 8.205 (0.95), 8.210 (0.96), 8.217 (0.93), 8.222 (0.85).

The title compound (1080 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (223 mg, see Example 25) and stereoisomer 2 (465 mg, see Example 26).

Preparative chiral HPLC method: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000, Column: Cellulose SC 5µ 250x30mm; Eluent A: Hexane + 0.1 Vol-% Diethylamine (99%); Eluent B: 2-Propanol; Isocratic: 50%A+50%B; Flow: 40.0 ml/min; UV 280 nm.

Analytical chiral HPLC method: Instrument: Agilent HPLC 1260; Column: Cellulose SC 3µ 100x4,6mm; Eluent A: Hexane + 0.1 Vol-% Diethylamine (99%); Eluent B: 2-Propanol; Isocratic: 50%A+50%B; Flow 1.4 ml/min; Temperature: 25 ℃; DAD 280 nm.

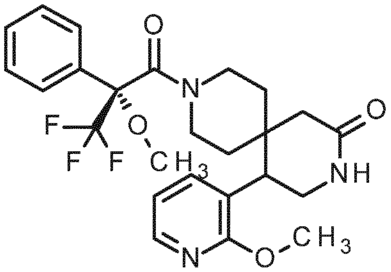
Example 25 and Example 26

(5S)-5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 25

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



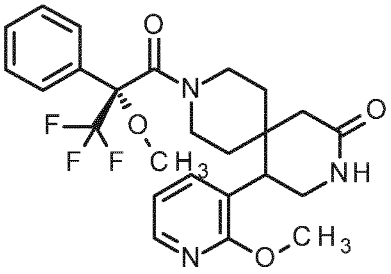
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 24.

Analytical chiral HPLC (method see Example 24): R_t = 3.21 min; ee > 99.9%
Optical rotation (method OR1) = +57.4°+/- 0.44°(m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.313 (0.59), 0.345 (1.05), 0.367 (0.67), 0.618 (1.26), 0.651 (1.01), 0.961 (0.71), 0.984 (1.22), 0.995 (1.26), 1.017 (0.80), 1.084 (0.76), 1.136 (0.55), 1.232 (0.50), 1.301 (1.30), 1.506 (1.34), 1.539 (1.18), 1.906 (0.97), 1.949 (1.22), 2.074 (1.85), 2.166 (2.18), 2.210 (3.19), 2.268 (0.80), 2.322 (1.85), 2.326 (2.44), 2.331 (1.81), 2.374 (2.31), 2.418 (1.60), 2.522 (8.19), 2.539 (3.40), 2.568 (0.80), 2.594 (0.46), 2.664 (1.85), 2.669 (2.48), 2.673 (1.85), 2.875 (0.97), 2.907 (1.68), 2.935 (0.97), 3.051 (0.63), 3.073 (1.26), 3.103 (1.93), 3.138 (2.14), 3.185 (1.26), 3.209 (3.70), 3.255 (0.80), 3.370 (1.60), 3.500 (1.39), 3.536 (1.26), 3.572 (16.00), 3.777 (14.74), 3.854 (11.04), 4.071 (0.42), 4.104 (0.42), 4.171 (1.34), 4.203 (1.26), 6.963 (1.13), 6.975 (1.26), 6.981 (1.22), 6.993 (1.22), 7.010 (2.31), 7.022 (2.56), 7.029 (2.90), 7.041 (2.69), 7.201 (1.97), 7.219 (1.72), 7.248 (4.03), 7.268 (5.63), 7.343 (3.19), 7.360 (6.09), 7.380 (2.52), 7.438 (4.54), 7.445 (3.65), 7.455 (2.31), 7.493 (1.60), 7.512 (2.39), 7.530 (1.01), 7.601 (3.74), 7.621 (1.30), 7.624 (1.30), 7.643 (2.02), 8.067 (1.39), 8.071 (1.47), 8.080 (1.47), 8.083 (1.43), 8.094 (3.23), 8.097 (3.40), 8.106 (3.32), 8.109 (3.02).

Example 26

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 2)



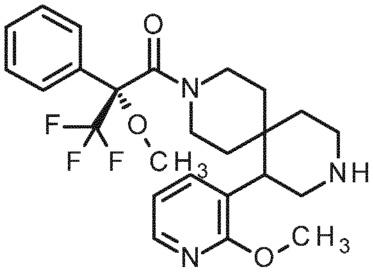
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 24.

Analytical chiral HPLC (method see Example 24): R_t = 3.99 min; ee 99.8%
Optical rotation (method OR1) = -25.6° +/- 0.23° (m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.276 (0.66), -0.253 (1.12), -0.243 (1.12), -0.220 (0.68), 0.666 (1.42), 0.698 (1.31), 1.026 (0.49), 1.042 (0.46), 1.199 (0.55), 1.231 (1.37), 1.258 (0.98), 1.423 (1.53), 1.454 (1.12), 1.750 (0.44), 1.952 (2.16), 1.996 (2.41), 2.052 (0.57), 2.263 (0.52), 2.322 (1.20), 2.326 (1.61), 2.331 (1.20), 2.517 (9.27), 2.522 (5.80), 2.634 (3.25), 2.664 (1.37), 2.668 (1.97), 2.677 (3.50), 2.820 (0.96), 2.848 (1.64), 2.853 (1.67), 2.881 (0.93), 2.924 (0.79), 2.936 (1.18), 2.945 (1.15), 2.955 (1.12), 2.967 (1.37), 2.998 (1.20), 3.029 (1.86), 3.060 (1.01), 3.102 (1.12), 3.115 (1.09), 3.131 (1.34), 3.143 (1.12), 3.385 (0.90), 3.414 (1.61), 3.453 (4.16), 3.475 (1.18), 3.505 (1.75), 3.537 (1.04), 3.556 (15.48), 3.671 (16.00), 3.777 (0.71), 3.854 (6.21), 4.319 (1.23), 4.353 (1.20), 6.932 (0.71), 6.944 (0.85), 6.951 (1.04), 6.959 (2.57), 6.978 (5.55), 6.997 (3.66), 7.039 (1.75), 7.052 (2.02), 7.058 (2.08), 7.070 (1.81), 7.103 (4.87), 7.122 (3.75), 7.223 (2.02), 7.241 (3.39), 7.260 (1.59), 7.346 (0.88), 7.364 (1.23), 7.425 (2.57), 7.431 (2.16), 7.438 (1.39), 7.442 (1.29), 7.596 (2.05), 7.623 (4.02), 8.051 (0.77), 8.056 (0.82), 8.064 (0.79), 8.068 (0.79), 8.206 (3.45), 8.210 (3.64), 8.218 (3.58), 8.222 (3.31).

Example 27

(2R)-3,3,3-trifluoro-2-methoxy-1-[7-(2-methoxypyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-phenylpropan-1-one (Stereoisomer 1)

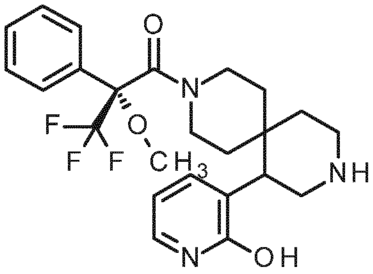


Using an analogous method as described for Intermediate 23, the title compound was prepared starting from Example 25 (55 mg, 112 µmol) and gave the title compound 22 mg (53 %) after purification Biotage NH-column chromatography (hexane:ethyl acetate, then ethyl acetate:ethanol). A by-product was also isolated and identified as the demethylated analog (23 mg, 42%) see Example 28).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.023 (0.64), 0.033 (0.64), 0.741 (0.95), 0.746 (0.45), 0.759 (0.97), 0.765 (0.99), 0.784 (0.52), 0.830 (0.57), 0.848 (1.33), 0.866 (0.80), 0.873 (0.78), 0.884 (0.76), 0.906 (0.50), 0.918 (0.45), 1.015 (0.52), 1.053 (1.09), 1.087 (1.11), 1.098 (3.72), 1.116 (7.24), 1.133 (3.41), 1.149 (0.80), 1.176 (0.47), 1.296 (0.95), 1.325 (0.71), 1.359 (0.50), 1.366 (1.23), 1.373 (0.50), 1.843 (0.40), 1.931 (10.67), 1.967 (0.45), 1.993 (0.85), 2.028 (0.83), 2.154 (0.43), 2.304 (1.02), 2.313 (1.07), 2.338 (1.33), 2.357 (0.69), 2.462 (5.75), 2.466 (3.98), 2.493 (0.64), 2.525 (0.78), 2.554 (0.50), 2.618 (1.30), 2.622 (1.14), 2.634 (1.49), 2.645 (1.63), 2.675 (1.51), 2.706 (0.88), 2.766 (0.66), 2.799 (0.97), 2.838 (1.09), 2.847 (1.11), 2.867 (0.92), 2.875 (0.73), 2.893 (0.45), 2.922 (0.45), 2.938 (0.99), 2.975 (0.97), 3.006 (0.59), 3.106 (2.18), 3.175 (0.69), 3.410 (0.76), 3.446 (0.73), 3.497 (8.45), 3.516 (0.80), 3.721 (0.59), 3.762 (0.97), 3.775 (7.31), 3.781 (16.00), 3.799 (0.59), 3.943 (0.78), 3.960 (2.37), 3.978 (2.22), 3.997 (0.76), 4.081 (0.73), 4.113 (0.73), 4.316 (0.45), 6.856 (0.47), 6.869 (0.57), 6.875 (0.62), 6.889 (1.04), 6.902 (1.02), 6.908 (1.82), 6.920 (1.89), 6.942 (1.33), 6.955 (0.66), 7.082 (1.63), 7.101 (3.36), 7.123 (2.53), 7.142 (3.08), 7.162 (1.30), 7.273 (0.99), 7.367 (2.01), 7.375 (1.78), 7.384 (2.04), 7.387 (1.49), 7.405 (1.66), 7.423 (0.73), 7.541 (0.40), 7.938 (0.54), 7.941 (0.57), 7.950 (0.57), 7.953 (0.52), 8.019 (1.49), 8.024 (1.47), 8.031 (1.47), 8.036 (1.49).

Example 28

(2R)-3,3,3-trifluoro-1-[7-(2-hydroxypyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-methoxy-2-phenylpropan-1-one (Stereoisomer 1)

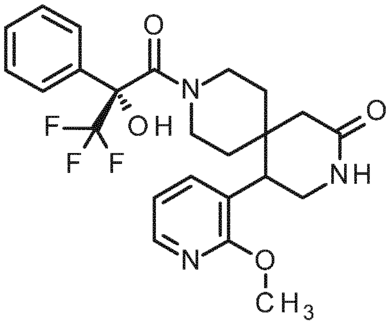


For the preparation of the title compound and the separation into the corresponding diastereoisomers, see Example 27.

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.129 (0.69), 0.150 (1.20), 0.160 (1.20), 0.183 (0.69), 0.798 (5.28), 0.803 (2.16), 0.814 (5.36), 0.821 (5.40), 0.840 (2.54), 0.886 (3.08), 0.904 (6.82), 0.923 (3.24), 0.949 (0.66), 0.989 (1.31), 1.035 (5.78), 1.052 (11.99), 1.070 (5.82), 1.090 (1.62), 1.109 (1.39), 1.124 (1.62), 1.142 (2.27), 1.154 (1.50), 1.161 (1.93), 1.172 (2.24), 1.190 (1.00), 1.204 (0.93), 1.223 (1.16), 1.236 (1.54), 1.241 (1.31), 1.256 (1.39), 1.275 (2.04), 1.314 (1.43), 1.682 (0.46), 1.718 (0.42), 1.764 (0.81), 1.800 (0.89), 1.816 (0.66), 1.835 (0.73), 1.987 (0.93), 2.025 (1.50), 2.059 (1.43), 2.084 (0.42), 2.171 (0.69), 2.190 (0.66), 2.211 (1.12), 2.231 (1.00), 2.268 (1.12), 2.297 (1.27), 2.318 (1.08), 2.323 (1.93), 2.327 (2.62), 2.331 (1.89), 2.337 (1.00), 2.359 (0.96), 2.373 (1.04), 2.388 (1.27), 2.394 (1.35), 2.399 (0.81), 2.407 (1.27), 2.413 (1.58), 2.425 (0.58), 2.431 (0.66), 2.518 (9.45), 2.523 (7.17), 2.531 (3.08), 2.563 (2.16), 2.593 (0.73), 2.660 (3.43), 2.665 (4.36), 2.669 (4.55), 2.673 (3.28), 2.694 (1.39), 2.807 (1.08), 2.840 (1.89), 2.867 (1.39), 2.896 (0.81), 2.947 (1.31), 2.972 (1.12), 2.990 (1.20), 3.025 (1.81), 3.060 (1.35), 3.215 (0.81), 3.266 (1.77), 3.423 (1.08), 3.434 (1.08), 3.440 (1.08), 3.450 (1.08), 3.495 (1.39), 3.530 (1.27), 3.566 (16.00), 3.837 (0.69), 4.053 (0.54), 4.115 (1.23), 4.148 (1.12), 4.360 (0.54), 6.099 (0.85), 6.116 (1.58), 6.133 (1.00), 6.146 (2.51), 6.162 (4.74), 6.179 (2.70), 6.606 (1.27), 6.621 (1.23), 7.193 (0.93), 7.205 (0.96), 7.226 (2.74), 7.245 (8.02), 7.255 (8.06), 7.273 (8.48), 7.294 (2.97), 7.347 (2.12), 7.356 (2.31), 7.364 (2.58), 7.421 (1.50), 7.430 (6.01), 7.438 (5.67), 7.443 (3.82), 7.447 (3.51), 7.457 (4.01), 7.474 (1.66).

Example 29

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-hydroxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



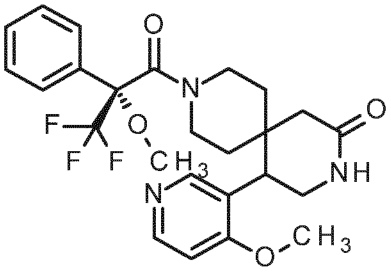
To a solution of Example 25 (140 mg, 285 µmol) in dichloromethane (9.7 ml) under Argon at -78℃ was added dropwise boron tribromide (1.1 ml, 1 M in dichloromethane). The reaction was stirred at -78℃ for 4h, then was allowed to warm t o RT and stirred at RT for 16h. The reaction was quenched by the addition of water. The organics were extracted with dichloromethane, the dichloromethane layers were combined and washed with sat. sodium chloride (aq) and filtered through an hydrophobic filter and concentrated under reduced pressure to give the title compound (131 mg, 92%).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.233 (0.67), 1.981 (0.43), 2.084 (1.29), 2.123 (0.61), 2.166 (0.89), 2.314 (0.69), 2.322 (0.54), 2.327 (0.57), 2.332 (0.41), 2.358 (0.45), 2.518 (2.41), 2.523 (1.58), 2.669 (0.50), 2.743 (0.46), 2.891 (0.46), 2.921 (0.57), 3.168 (0.72), 3.186 (0.87), 3.764 (4.08), 3.848 (5.16), 5.758 (16.00), 6.981 (0.46), 6.994 (0.95), 6.999 (0.68), 7.007 (0.84), 7.013 (1.07), 7.026 (0.77), 7.183 (0.52), 7.200 (0.44), 7.300 (0.95), 7.319 (1.77), 7.350 (0.82), 7.368 (1.22), 7.387 (0.95), 7.407 (1.86), 7.420 (1.93), 7.466 (0.45), 7.485 (0.62), 7.604 (1.22), 7.630 (0.64), 7.968 (1.38), 8.014 (3.03), 8.083 (1.70), 8.087 (1.73), 8.095 (1.70), 8.099 (1.55).

Optical rotation (method OR1) = +63.9°+/- 0.61°(m ethanol).

Example 30

5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-cyano(4-methoxypyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (540 mg, 1.01 mmol, Intermediate 20) and gave the title compound 240 mg (46 %) after purification by preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.637 (0.64), 0.669 (0.57), 1.231 (0.42), 1.443 (0.50), 1.476 (0.52), 1.517 (0.40), 1.961 (0.84), 2.005 (0.82), 2.322 (0.47), 2.327 (0.59), 2.331 (0.43), 2.449 (0.49), 2.522 (1.73), 2.539 (0.55), 2.631 (1.09), 2.674 (1.33), 2.853 (0.64), 2.886 (0.46), 2.943 (0.41), 2.951 (0.43), 2.960 (0.41), 2.974 (0.45), 2.982 (0.44), 3.031 (0.59), 3.063 (0.41), 3.147 (0.53), 3.178 (0.46), 3.278 (0.56), 3.319 (0.90), 3.435 (1.80), 3.473 (0.70), 3.561 (6.11), 3.600 (0.66), 3.642 (4.94), 3.781 (1.89), 3.847 (1.97), 4.327 (0.40), 5.758 (16.00), 6.966 (0.68), 6.985 (1.51), 7.004 (1.00), 7.025 (0.84), 7.039 (0.85), 7.084 (1.48), 7.099 (1.60), 7.114 (1.57), 7.134 (1.22), 7.212 (0.57), 7.232 (0.73), 7.318 (0.45), 7.337 (0.85), 7.356 (0.87), 7.365 (0.83), 7.386 (0.59), 7.427 (0.96), 7.433 (0.85), 7.440 (0.91), 7.445 (0.77), 7.624 (0.49), 7.641 (0.95), 7.935 (0.61), 8.271 (1.54), 8.317 (0.54), 8.337 (0.61), 8.351 (0.57), 8.409 (0.66), 8.424 (0.63), 8.483 (1.51), 8.497 (1.42).

The title compound (203 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (134 mg, see Example 31) and stereoisomer 2 (44,5 mg, see Example 32).

Preparative chiral HPLC method: Instrument: Sepiatec: Prep SFC100, column: Reprosil Chiral NR 8µm 250x30mm; eluent A: CO2; eluent B: methanol; isocratic: 33%B; flow 100.0 mL/min; pressure: 150 bar; UV 220 nm.

Analytical chiral HPLC method: Instrument: 1260, Aurora SFC-Module; column: Reprosil Chiral NR 5µm 100x4.6mm; eluent A: CO2; eluent B: methanol; isocratic: 33%B; flow: 4 mL/min; pressure: 100 bar; UV 220 nm.

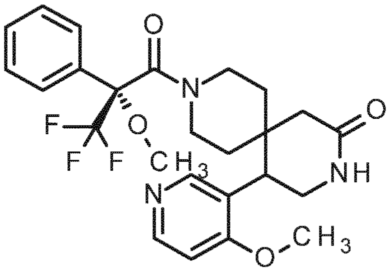
Example 31 and Example 32

(5S)-5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 31

5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



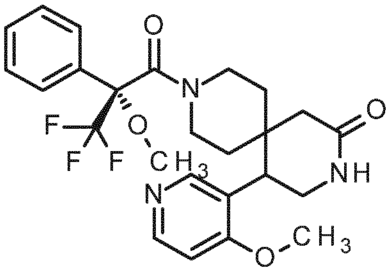
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 30.

Analytical chiral HPLC (method see Example 30: R_t = 2.53 min Optical rotation (method OR1) = -13.2° +/- 0.64° (m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.518 (1.67), 2.523 (1.21), 2.539 (1.49), 2.673 (0.59), 3.436 (0.43), 3.560 (1.38), 3.642 (1.28), 4.192 (1.45).

Example 32

5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 2)



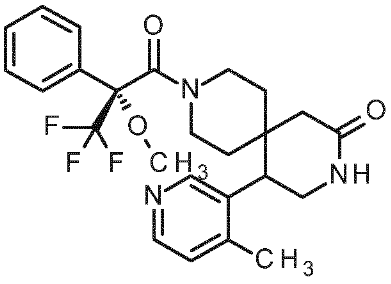
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 30.

Analytical chiral HPLC (method see Example 24): R_t = 3.48 min Optical rotation (method OR1) = +25.1° +/- 0.77° (m ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.331 (0.74), 2.406 (0.40), 2.518 (3.98), 2.523 (2.76), 2.539 (0.92), 2.673 (0.85), 3.278 (0.72), 3.566 (2.63), 3.642 (0.52), 3.781 (2.36), 3.847 (1.15), 4.191 (1.37), 7.027 (0.63), 7.041 (0.65), 7.212 (0.68), 7.231 (0.88), 7.368 (0.59), 7.386 (0.70), 7.405 (0.41), 7.439 (0.70), 7.446 (0.58), 7.622 (0.49), 7.935 (0.67), 8.410 (0.67), 8.424 (0.63).

Example 33

5-(4-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers)

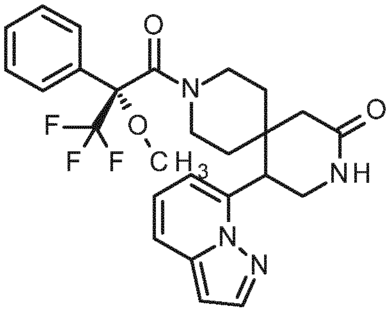


Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(4-methylpyridin-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (210 mg, 406 µmol, Intermediate 21) and gave the title compound 175 mg (86 %).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.429 (0.43), -0.417 (0.58), -0.396 (1.01), -0.384 (0.98), -0.363 (0.58), -0.352 (0.47), 0.446 (0.61), 0.651 (1.12), 0.683 (1.05), 0.750 (0.87), 0.783 (0.72), 0.861 (0.54), 0.873 (0.47), 0.895 (0.79), 0.907 (0.83), 0.929 (0.54), 0.941 (0.51), 0.967 (0.54), 1.035 (0.76), 1.052 (1.34), 1.070 (0.65), 1.107 (0.69), 1.232 (1.05), 1.280 (0.58), 1.315 (0.90), 1.349 (0.94), 1.372 (0.61), 1.491 (1.12), 1.528 (1.37), 1.557 (1.52), 1.587 (0.98), 2.025 (16.00), 2.085 (1.52), 2.112 (0.51), 2.128 (1.66), 2.154 (0.51), 2.281 (11.92), 2.311 (1.99), 2.323 (2.31), 2.331 (5.49), 2.350 (3.83), 2.522 (7.19), 2.550 (1.16), 2.564 (2.17), 2.608 (1.55), 2.665 (1.66), 2.669 (2.20), 2.673 (1.70), 2.693 (2.28), 2.737 (2.13), 2.767 (0.51), 2.791 (0.87), 2.819 (1.37), 2.848 (1.44), 2.876 (0.76), 2.967 (0.90), 2.976 (0.90), 2.984 (0.79), 2.998 (1.37), 3.006 (1.44), 3.039 (2.42), 3.053 (1.19), 3.069 (2.49), 3.081 (1.88), 3.112 (0.90), 3.129 (3.03), 3.145 (1.30), 3.159 (1.30), 3.170 (1.48), 3.183 (1.12), 3.380 (2.42), 3.422 (0.47), 3.452 (1.30), 3.485 (0.98), 3.558 (12.86), 3.567 (9.86), 3.596 (2.06), 3.625 (2.02), 3.654 (0.87), 4.219 (0.69), 4.252 (0.69), 4.346 (0.47), 4.358 (0.76), 4.371 (1.08), 4.406 (0.90), 5.759 (2.53), 6.874 (1.73), 6.894 (3.76), 6.913 (2.28), 7.082 (3.61), 7.101 (3.00), 7.183 (1.77), 7.202 (3.47), 7.214 (3.68), 7.223 (4.30), 7.236 (2.82), 7.248 (3.00), 7.260 (2.93), 7.331 (1.01), 7.346 (0.76), 7.355 (0.69), 7.383 (1.63), 7.402 (3.54), 7.422 (3.00), 7.433 (1.91), 7.439 (2.60), 7.470 (1.41), 7.488 (1.81), 7.506 (0.58), 7.615 (1.66), 7.664 (2.60), 7.709 (0.61), 7.966 (3.68), 8.277 (0.87), 8.287 (1.30), 8.299 (0.90), 8.365 (3.03), 8.377 (3.00), 8.392 (4.80), 8.432 (3.86), 8.445 (4.55).

Example 34

5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(pyrazolo[1,5-a]pyridin-7-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (615 mg, 1.13 mmol, Intermediate 22) and gave the title compound 490 mg (82 %) after silica chromatography (dichloromethane:ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.035 (8.14), 1.052 (16.00), 1.070 (8.96), 1.494 (0.61), 2.106 (0.43), 2.150 (0.49), 2.332 (0.48), 2.335 (0.47), 2.518 (1.55), 2.523 (1.05), 2.565 (0.45), 2.727 (0.57), 2.771 (0.51), 3.215 (0.72), 3.308 (0.51), 3.405 (1.01), 3.418 (1.15), 3.422 (3.24), 3.435 (3.39), 3.440 (3.19), 3.452 (3.43), 3.457 (1.36), 3.469 (1.67), 3.531 (3.04), 3.558 (2.16), 4.344 (2.44), 4.357 (4.27), 4.369 (2.09), 6.658 (0.45), 6.661 (1.19), 6.667 (1.02), 6.677 (0.47), 6.683 (0.46), 6.708 (1.67), 6.713 (1.65), 6.827 (1.32), 6.846 (1.80), 6.866 (0.56), 7.038 (0.83), 7.055 (0.77), 7.211 (0.58), 7.229 (0.74), 7.239 (0.43), 7.256 (0.79), 7.261 (0.47), 7.273 (0.57), 7.278 (0.82), 7.295 (0.49), 7.336 (0.87), 7.355 (0.86), 7.375 (0.45), 7.409 (0.63), 7.416 (0.61), 7.422 (0.73), 7.430 (0.59), 7.438 (0.49), 7.524 (0.41), 7.635 (0.40), 7.660 (0.59), 7.663 (0.60), 7.683 (0.95), 7.721 (0.57), 7.775 (0.75), 7.794 (0.68), 7.867 (1.23), 7.872 (1.19), 7.986 (0.80), 7.992 (0.78), 8.020 (0.61), 8.025 (0.56).

The title compound (470 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (294 mg, see Example 35) and stereoisomer 2 (275 mg, see Example 36).

Preparative chiral HPLC method: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000, Column: Cellulose SC 5µ 250x30mm; Eluent A: Hexane + 0.1 Vol-% TFA (99%); Eluent B: 2-Propanol; Isocratic: 55%A+45%B; Flow: 40.0 ml/min; UV 220 nm.

Analytical chiral HPLC method: Instrument: Waters Alliance 2695Agilent HPLC 1260; Column: Cellulose SC 3µ 100x4,6mm; Eluent A: Hexane + 0.1 Vol-% TFA (99%); Eluent B: 2-Propanol; Gradient: 20-50%B; Flow: 1.4 ml/min; Temperature: 25 ℃; DAD 220 nm.

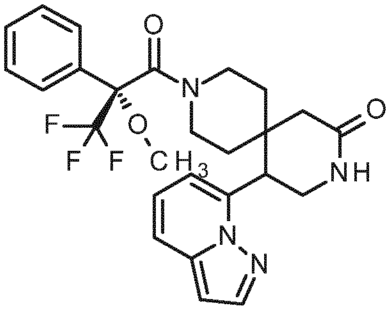
Example 35 and Example 36

(5S)-5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 35

5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



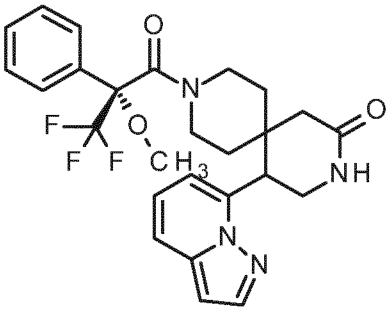
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 34.

Analytical chiral HPLC (method see Example 34): R_t = 5.37 min ee >99% Optical rotation (method OR1) +114.5° +/- 0.80° (me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.518 (0.71), 2.523 (0.47), 3.216 (0.48), 6.661 (0.61), 6.667 (0.60), 7.228 (0.49), 7.335 (0.44), 7.355 (0.54), 7.685 (0.60), 7.986 (0.49), 7.992 (0.47).

Example 36

5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 2)

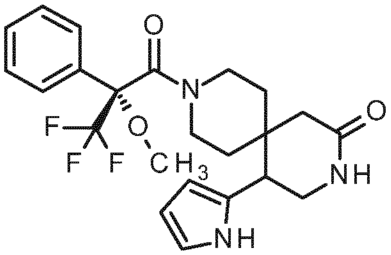


For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 34.

Analytical chiral HPLC (method see Example 34): R_t = 6.95 min ee >99% Optical rotation (method OR1) -95.8°+/- 0.70°(met hanol).

Example 37

5-(1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers)

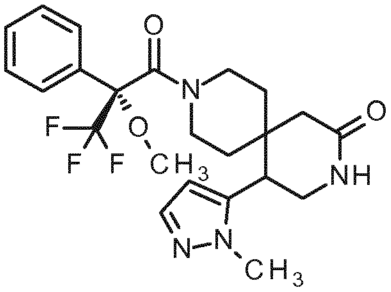


To a solution of 9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-2-yl)-3,9-diazaspiro[5.5]undecan-2-one (770 mg, 1.33 mmol, Intermediate 25) in THF (1.7ml) was added ethylenediamine (35 µl, 520 µmol) and TBAF (7.97 ml, 7.97 mmol) and the reaction was heated at 80℃ for 24h. The reaction was concentrated and purified by preparative HPLC (Method 5) to give the title compound (506 mg, 85%).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.000 (0.52), 0.906 (2.03), 0.925 (5.27), 0.942 (2.53), 1.098 (16.00), 1.251 (0.42), 1.269 (0.89), 1.287 (1.60), 1.306 (1.49), 1.323 (0.95), 1.535 (0.53), 1.555 (0.67), 1.876 (0.44), 1.921 (0.62), 1.971 (0.44), 2.313 (0.55), 2.317 (0.75), 2.322 (0.58), 2.330 (0.48), 2.509 (3.33), 2.513 (2.11), 2.530 (0.69), 2.542 (0.66), 2.564 (0.66), 2.608 (0.53), 2.655 (0.81), 2.660 (0.86), 2.664 (0.76), 2.816 (0.44), 2.858 (0.53), 2.892 (0.42), 3.063 (1.19), 3.080 (0.84), 3.099 (0.52), 3.129 (0.88), 3.149 (0.85), 3.170 (0.94), 3.248 (0.85), 3.269 (1.23), 3.300 (3.16), 3.475 (1.31), 3.561 (5.50), 5.454 (0.58), 5.743 (0.61), 5.806 (0.46), 5.810 (0.48), 5.931 (0.46), 5.938 (0.42), 6.015 (0.66), 6.022 (0.65), 6.046 (0.64), 6.053 (0.64), 6.619 (0.48), 6.622 (0.47), 6.645 (0.72), 6.652 (1.41), 6.655 (1.39), 7.172 (0.44), 7.189 (2.22), 7.197 (1.97), 7.207 (1.22), 7.215 (1.41), 7.236 (0.44), 7.323 (0.48), 7.341 (1.17), 7.359 (1.51), 7.379 (1.33), 7.399 (0.81), 7.419 (1.25), 7.427 (1.96), 7.434 (1.58), 7.444 (0.81), 7.461 (0.76), 7.464 (0.76), 7.469 (0.74), 7.479 (0.84), 7.527 (0.89), 10.403 (0.42), 10.501 (0.41).

Example 38

5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(1-methyl-1H-pyrazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (140 mg, 276 µmol, Intermediate 26) and gave the title compound 79.5 mg (59 %) after preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.237 (0.62), -0.225 (0.63), 0.382 (0.42), 0.393 (0.42), 0.620 (0.56), 0.654 (0.46), 0.673 (0.74), 0.706 (0.68), 0.852 (0.52), 0.863 (0.52), 1.401 (1.09), 1.414 (1.38), 1.477 (0.70), 1.510 (0.81), 2.059 (1.04), 2.073 (2.22), 2.102 (1.18), 2.115 (0.43), 2.242 (0.75), 2.285 (0.99), 2.434 (0.89), 2.478 (0.92), 2.518 (0.99), 2.523 (0.67), 2.539 (0.78), 2.543 (1.04), 2.644 (1.48), 2.687 (1.30), 2.794 (0.70), 2.808 (0.68), 2.822 (1.00), 2.827 (1.22), 2.840 (0.69), 2.855 (0.69), 2.860 (0.57), 3.008 (1.32), 3.015 (1.28), 3.030 (1.95), 3.037 (1.82), 3.045 (1.77), 3.059 (0.90), 3.066 (0.82), 3.100 (1.30), 3.112 (1.54), 3.119 (1.02), 3.128 (1.10), 3.242 (1.39), 3.275 (0.90), 3.290 (1.91), 3.317 (1.34), 3.414 (0.59), 3.458 (16.00), 3.481 (1.76), 3.561 (6.93), 3.577 (5.53), 3.630 (0.47), 3.706 (12.49), 3.788 (4.84), 3.796 (4.16), 4.244 (0.53), 4.277 (0.51), 4.350 (0.58), 4.381 (0.53), 5.629 (2.45), 5.633 (2.37), 6.147 (0.93), 6.152 (0.97), 6.167 (3.04), 6.172 (3.02), 6.179 (0.90), 6.185 (0.85), 7.136 (6.84), 7.147 (6.14), 7.267 (1.58), 7.286 (2.10), 7.301 (0.62), 7.311 (0.98), 7.322 (1.30), 7.332 (1.82), 7.335 (1.90), 7.338 (1.96), 7.343 (2.03), 7.355 (1.07), 7.405 (1.25), 7.423 (2.82), 7.433 (2.27), 7.435 (2.56), 7.442 (3.30), 7.450 (1.62), 7.458 (2.77), 7.463 (2.56), 7.486 (3.52), 7.490 (4.05), 7.504 (0.50), 7.509 (1.40), 7.527 (0.46), 7.570 (1.30), 7.609 (0.45), 7.644 (1.82).

The title compound (60 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (22 mg, see Example 39) and stereoisomer 2 (25 mg, see Example 40).

Preparative chiral HPLC method: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000, Column: Chiralpak IE 5µ 250x30mm; Eluent A: Hexane + 0.1 Vol-% Diethylamine (99%); Eluent B: Ethanol; Isocratic: 60%A+40%B; Flow: 50.0 ml/min; UV 220 nm.

Analytical chiral HPLC method: Instrument: Agilent HPLC 1260; Column: Chiralpak IE 3µ 100x4,6mm; Eluent A: Hexane + 0.1 Vol-% Diethylamine (99%); Eluent B: Ethanol; Isocratic: 60%A+40%B; Flow: 1.4 ml/min; Temperature: 25 ℃; DAD 220 nm.

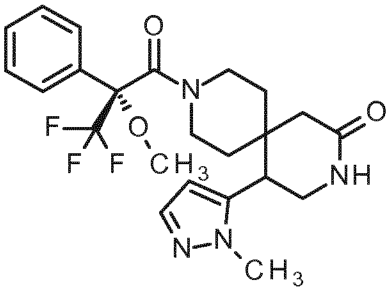
Example 39 and Example 40

(5S)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 39

5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



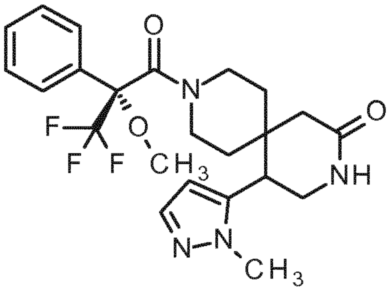
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 38.

Analytical chiral HPLC (method see Example 38): R_t = 3.94 min ee > 99.9% Optical rotation (method OR1) +13.8°+/-0.54°(meth anol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.259 (0.40), -0.237 (0.67), -0.226 (0.69), 0.673 (0.79), 0.706 (0.74), 0.974 (0.42), 0.992 (0.67), 1.053 (0.55), 1.413 (1.54), 2.057 (1.09), 2.100 (1.24), 2.322 (1.04), 2.327 (1.49), 2.332 (1.19), 2.433 (0.47), 2.522 (11.14), 2.642 (1.61), 2.664 (1.12), 2.669 (1.54), 2.673 (1.22), 2.678 (0.74), 2.685 (1.46), 2.808 (0.60), 2.841 (0.60), 2.853 (0.40), 3.005 (0.94), 3.013 (0.89), 3.027 (1.96), 3.034 (1.84), 3.043 (1.54), 3.057 (0.84), 3.065 (0.64), 3.159 (0.62), 3.171 (0.60), 3.274 (0.92), 3.282 (0.97), 3.411 (0.72), 3.457 (16.00), 3.480 (2.03), 3.560 (7.27), 3.795 (4.17), 4.343 (0.69), 4.379 (0.60), 6.167 (3.03), 6.172 (3.20), 6.179 (1.07), 6.185 (0.97), 7.135 (7.22), 7.146 (6.08), 7.301 (0.55), 7.310 (0.87), 7.322 (1.22), 7.331 (1.54), 7.335 (1.71), 7.344 (0.89), 7.354 (0.67), 7.363 (0.62), 7.437 (1.51), 7.443 (1.22), 7.453 (0.77), 7.486 (3.15), 7.490 (3.15), 7.609 (0.45), 7.636 (1.49).

Example 40

5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 2)



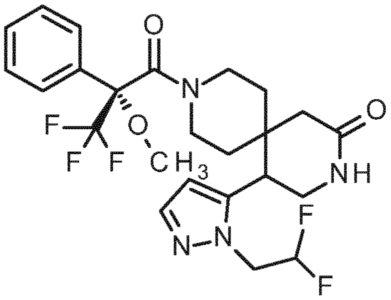
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 38.

Analytical chiral HPLC (method see Example 38): R_t = 4.73 min ee 95.5%
Optical rotation (method OR1) +21.9°+/-0.51°(meth anol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.382 (0.58), 0.393 (0.58), 0.620 (0.79), 0.651 (0.62), 0.815 (0.48), 0.828 (0.48), 0.850 (0.83), 0.861 (0.83), 0.882 (0.48), 0.971 (0.55), 0.988 (1.14), 1.006 (0.72), 1.035 (0.62), 1.052 (0.93), 1.070 (0.55), 1.205 (0.48), 1.233 (0.79), 1.259 (0.58), 1.476 (0.89), 1.509 (0.89), 2.114 (0.52), 2.240 (0.96), 2.283 (1.31), 2.322 (1.41), 2.326 (1.96), 2.332 (1.48), 2.432 (0.72), 2.522 (16.00), 2.541 (5.68), 2.664 (1.48), 2.669 (2.06), 2.673 (1.55), 2.794 (0.55), 2.827 (1.03), 2.860 (0.55), 3.011 (0.93), 3.042 (0.79), 3.068 (0.48), 3.098 (1.75), 3.110 (2.24), 3.128 (1.51), 3.159 (0.76), 3.171 (0.65), 3.240 (1.89), 3.292 (2.44), 3.457 (0.65), 3.578 (7.23), 3.629 (0.62), 3.706 (15.52), 3.787 (5.88), 4.245 (0.72), 4.275 (0.72), 5.628 (2.99), 5.633 (3.06), 6.147 (1.17), 6.152 (1.14), 7.265 (2.10), 7.284 (2.79), 7.338 (1.86), 7.343 (1.89), 7.355 (0.83), 7.405 (1.62), 7.423 (3.54), 7.434 (2.31), 7.442 (3.41), 7.450 (1.62), 7.458 (3.54), 7.463 (3.37), 7.491 (1.51), 7.509 (1.82), 7.528 (0.65), 7.566 (1.75), 7.640 (0.76).

Example 41

5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2- one (mixture of stereosiomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl (4-{cyano[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]methyl}-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl)acetate (442 mg, 794 µmol, Intermediate 27) and gave the title compound 195 mg (45 %) after preparative HPLC (Method 5).

The title compound (311 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (159 mg, see Example 42) and stereoisomer 2 (135 mg, see Example 43).

Preparative chiral HPLC method: Instrument: Sepiatec: Prep SFC100; Column: Reprosil Chiral NR 8µm 250x30mm; Eluent A: CO2, Eluent B: Ethanol; Isocratic: 26%B; Flow: 100.0 ml/min Temperatur: 40℃; BPR: 150bar; MWD @ 220nm.

Analytical chiral HPLC method: Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Reprosil Chiral NR 5µm 100x4.6mm; Eluent A: CO2, Eluent B: Ethanol; Isocratic: 26%B; Flow: 4.0 ml/min; Temperature: 37.5℃; BPR: 100bar; MWD @ 220nm.

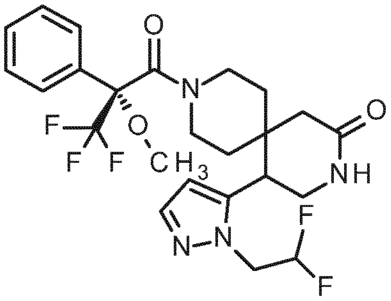
Example 42 and Example 43

(5S)-5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 42

5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



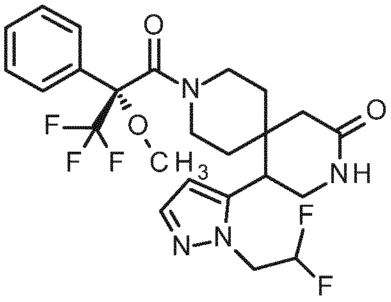
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 41.

Analytical chiral HPLC (method see Example 41): R_t = 1.79 min ee 99%
Optical rotation (method OR1) +38.8° +/- 0.51° (met hanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 1.429 (0.67), 2.122 (0.47), 2.166 (0.55), 2.518 (1.23), 2.523 (0.75), 2.642 (0.68), 2.685 (0.59), 3.134 (0.47), 3.295 (0.43), 3.497 (0.94), 3.557 (3.30), 4.191 (1.82), 6.271 (1.40), 6.276 (1.76), 7.127 (1.76), 7.133 (1.53), 7.141 (3.89), 7.318 (0.42), 7.326 (0.46), 7.333 (0.44), 7.341 (0.51), 7.436 (0.83), 7.443 (0.63), 7.453 (0.40), 7.476 (0.46), 7.481 (0.44), 7.637 (1.54), 7.642 (1.78), 7.652 (0.67).

Example 43

5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 2)



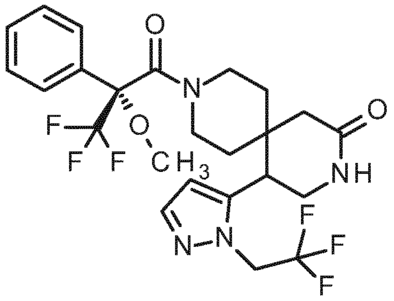
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 41.

Analytical chiral HPLC (method see Example 41): R_t = 2.84 min ee 99%
Optical rotation (method OR1) +8.5° +/- 0.54° (meth anol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.327 (0.41), 2.332 (0.61), 2.518 (0.97), 2.523 (0.62), 2.544 (0.68), 2.587 (0.48), 2.802 (0.43), 3.021 (0.62), 3.040 (0.70), 3.242 (0.54), 3.293 (1.14), 3.576 (2.81), 4.191 (1.55), 5.673 (1.16), 5.678 (1.16), 6.248 (0.47), 6.252 (0.47), 7.259 (0.85), 7.277 (1.08), 7.415 (0.67), 7.433 (2.05), 7.449 (0.87), 7.453 (0.96), 7.486 (0.52), 7.490 (0.50), 7.506 (0.54), 7.524 (0.73), 7.570 (0.74), 7.630 (1.24), 7.634 (1.25).

Example 44

5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



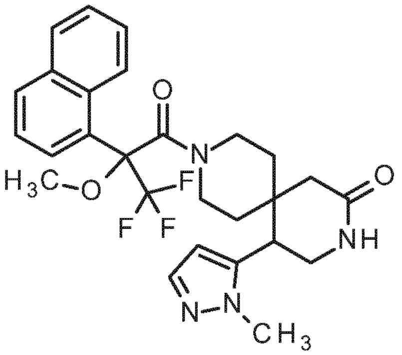
Using an analogous method as described for Intermediate 11, the title compound was prepared starting from (4-{cyano[1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]methyl}-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl)acetate (245 mg, 426 µmol, Intermediate 28) and gave the title compound 195 mg (45 %) after silica chromatography (dichloromethane:ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.411 (0.62), -0.400 (0.81), -0.379 (1.38), -0.367 (1.42), -0.346 (0.81), -0.335 (0.66), 0.373 (0.52), 0.396 (1.00), 0.406 (1.00), 0.429 (0.62), 0.676 (0.57), 0.688 (0.81), 0.710 (2.66), 0.720 (1.95), 0.743 (3.47), 0.776 (1.57), 0.798 (1.47), 0.802 (0.71), 0.815 (1.52), 0.822 (1.52), 0.840 (0.95), 0.851 (0.43), 0.872 (0.57), 0.886 (1.19), 0.905 (2.09), 0.922 (0.95), 0.936 (0.52), 0.946 (0.47), 1.035 (5.03), 1.052 (9.50), 1.070 (5.51), 1.124 (0.62), 1.159 (0.85), 1.289 (0.62), 1.321 (0.47), 1.380 (0.52), 1.414 (1.52), 1.442 (3.18), 1.489 (1.80), 1.523 (2.04), 1.567 (0.85), 1.602 (0.52), 1.987 (0.43), 2.130 (2.23), 2.174 (2.85), 2.223 (0.95), 2.278 (0.66), 2.302 (2.14), 2.322 (3.04), 2.326 (3.23), 2.332 (2.61), 2.337 (2.18), 2.345 (3.23), 2.372 (0.76), 2.430 (1.33), 2.456 (1.66), 2.518 (10.35), 2.523 (6.84), 2.581 (3.13), 2.623 (2.42), 2.657 (3.47), 2.664 (2.47), 2.669 (2.94), 2.673 (2.14), 2.700 (2.85), 2.756 (0.71), 2.774 (1.14), 2.801 (2.09), 2.807 (2.09), 2.835 (1.85), 2.857 (0.76), 2.870 (0.71), 2.898 (1.23), 2.907 (1.09), 2.917 (1.19), 2.929 (1.33), 2.939 (1.28), 2.962 (0.81), 2.972 (1.23), 2.993 (1.71), 3.029 (2.94), 3.058 (2.71), 3.088 (1.85), 3.135 (1.99), 3.149 (1.80), 3.164 (2.28), 3.178 (1.61), 3.228 (0.47), 3.254 (1.09), 3.282 (6.55), 3.301 (3.23), 3.307 (3.28), 3.360 (2.04), 3.383 (1.95), 3.404 (1.57), 3.417 (1.99), 3.422 (3.13), 3.435 (2.14), 3.440 (1.90), 3.452 (1.85), 3.457 (0.76), 3.469 (0.90), 3.505 (4.89), 3.557 (16.00), 3.577 (13.77), 3.619 (1.19), 3.656 (1.00), 4.167

(0.47), 4.202 (1.52), 4.237 (1.09), 4.294 (0.47), 4.344 (1.52), 4.357 (3.47), 4.369 (1.76), 4.393 (1.23), 4.705 (0.90), 4.728 (1.04), 4.744 (1.52), 4.766 (1.28), 4.854 (0.38), 4.875 (1.28), 4.896 (1.38), 4.915 (1.09), 4.936 (0.81), 5.031 (0.81), 5.054 (1.09), 5.071 (1.52), 5.093 (1.42), 5.118 (0.81), 5.144 (0.71), 5.174 (1.23), 5.196 (1.23), 5.214 (1.04), 5.235 (0.95), 5.252 (0.71), 5.283 (0.52), 5.300 (0.47), 5.710 (5.74), 5.715 (5.65), 5.758 (0.95), 6.316 (2.37), 6.320 (2.47), 6.332 (6.74), 6.337 (6.84), 6.345 (2.52), 7.099 (1.61), 7.120 (6.31), 7.138 (12.53), 7.159 (1.99), 7.255 (4.13), 7.274 (5.18), 7.303 (1.38), 7.308 (2.04), 7.313 (1.14), 7.320 (2.75), 7.324 (3.99), 7.336 (3.18), 7.341 (3.89), 7.346 (3.04), 7.361 (1.61), 7.419 (3.61), 7.437 (12.39), 7.449 (4.80), 7.454 (4.46), 7.457 (4.70), 7.518 (2.66), 7.524 (2.85), 7.528 (2.99), 7.532 (3.89), 7.537 (5.98), 7.555 (1.28), 7.579 (2.90), 7.626 (1.23), 7.665 (4.32), 7.686 (7.22), 7.691 (11.35), 7.696 (6.31).

Example 45

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Intermediate 1 the title compound was prepared starting from Intermediate 33 (900 mg, 3.16 mmol) and 3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoic acid (898 mg, 3.16 mmol; CAS: 1058658-57-3; Org. Lett., 2008, 10, 1768) to give the title compound 600 mg (37 % yield) after purification by silica chromatography (dichloromethane:ethanol).

The title compound (750 mg) was separated into the stereoisomers by preparative chiral HPLC to give stereoisomer 1 (310 mg, see Example 46) and stereoisomer 2 (320 mg, see Example 47).

Preparative chiral HPLC method: Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 50%A+50%B; flow: 140 mL/min; temperature: 25°C; UV: 220 nm.

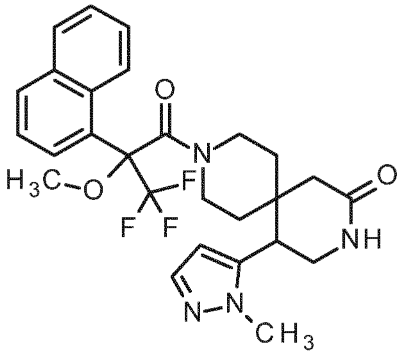
Analytical chiral HPLC method: Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 50%A+50%B; flow: 1.4 ml/min; temperature: 25°C; UV: 220 nm.

Example 46 and Example 47

(5S)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2S)-3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one
(5R)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one
Or
(5S)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one
(5R)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2S)-3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 46

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



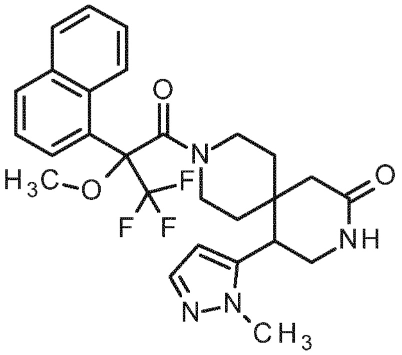
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 45.

Analytical chiral HPLC (method see Example 45): R_t = 3.34 min ee > 99%
Optical rotation (method OR1): -29.6° +/- 1.45° (me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.776 (2.08), 0.795 (4.51), 0.798 (3.76), 0.803 (1.93), 0.814 (4.80), 0.822 (3.97), 0.836 (2.04), 0.840 (2.47), 0.852 (1.22), 0.862 (2.04), 0.880 (1.07), 0.886 (2.15), 0.905 (3.76), 0.922 (2.36), 0.929 (1.00), 0.948 (0.86), 0.984 (0.68), 1.006 (3.69), 1.035 (2.18), 1.068 (0.54), 1.084 (5.12), 1.100 (0.86), 1.109 (0.57), 1.125 (0.64), 1.137 (1.00), 1.142 (1.00), 1.161 (0.93), 1.205 (0.61), 1.237 (1.97), 1.259 (5.80), 1.285 (0.72), 1.304 (0.72), 1.352 (0.79), 1.374 (0.61), 1.392 (0.82), 1.405 (0.82), 1.422 (1.25), 1.440 (1.32), 1.444 (1.40), 1.463 (1.61), 1.489 (1.47), 1.593 (0.39), 1.788 (0.50), 1.801 (0.50), 1.816 (0.47), 2.062 (0.43), 2.075 (1.57), 2.084 (1.22), 2.116 (0.47), 2.170 (0.54), 2.190 (0.54), 2.210 (0.79), 2.231 (1.32), 2.273 (2.11), 2.359 (0.68), 2.374 (0.75), 2.389 (0.86), 2.394 (0.86), 2.406 (0.82), 2.413 (1.07), 2.425 (0.43), 2.431 (0.43), 2.518 (9.09), 2.523 (5.94), 2.850 (1.40), 2.879 (2.08), 2.912 (1.36), 3.096 (1.50), 3.119 (1.25), 3.200 (4.40), 3.228 (0.97), 3.256 (0.72), 3.289 (0.57), 3.371 (6.41), 3.420 (1.75), 3.452 (1.43), 3.658 (16.00), 3.760 (12.60), 4.277 (0.47), 4.307 (0.47), 4.356 (1.15), 4.388 (1.15), 6.130 (2.36), 6.135 (2.33), 7.245 (0.43), 7.338 (3.44), 7.342 (3.26), 7.392 (0.86), 7.501 (3.79), 7.512 (2.47), 7.518 (2.00), 7.521 (2.22), 7.529 (3.19), 7.539 (2.47), 7.544 (2.18), 7.552 (2.51), 7.570 (3.62), 7.589 (3.47), 7.978 (1.29), 8.002 (1.47), 8.013 (3.51), 8.032 (3.51), 8.048 (1.83), 8.070 (4.15), 8.091 (3.76), 10.516 (0.75), 10.636 (0.47), 10.852 (1.07).

Example 47

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 2)



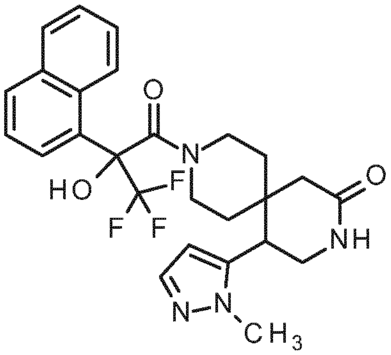
For the preparation of the racemic title compound and the separation into the corresponding diastereoisomers, see Example 45.

Analytical chiral HPLC (method see Example 45): R_t = 4.09 min ee > 99%
Optical rotation (method OR1): -28.8° +/- 1.39° (me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.327 (0.71), 2.331 (0.53), 2.518 (2.80), 2.522 (1.70), 2.669 (0.73), 2.673 (0.54), 3.400 (0.44), 3.547 (0.86), 3.645 (2.02), 3.780 (2.19), 4.190 (1.40), 7.322 (0.54), 7.327 (0.54), 7.524 (0.41), 7.535 (0.46), 7.549 (0.62).

Example 48

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-hydroxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



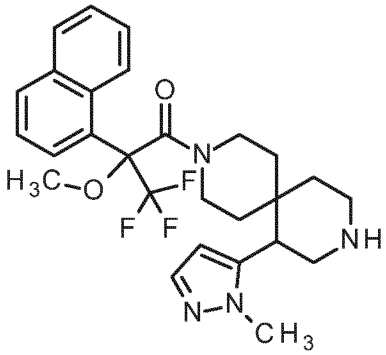
To a solution of Example 46 (80.0 mg, 155 µmol µmol) in dichloromethane (5.3 ml) under Argon at -78℃ was added dropwise boron tribromide (0.311 ml, 1M in dichloromethane). The reaction was stirred at -78℃ for 1h, then was allowed to warm to RT and stirred at RT for 16h. The reaction was quenched by the addition of water. The organics were extracted with dichloromethane, the dichloromethane layers were combined and washed with sat. sodium chloride (aq) and filtered through an hydrophobic filter and concentrated under reduced pressure. The title compound (45 mg, 55%) was obtained after preparative HPLC (Method 5).

Optical rotation (method OR1): -16.5° +/- 1.04° (methanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.065 (0.58), 0.301 (0.87), 0.333 (0.87), 0.808 (0.87), 0.831 (0.58), 0.981 (0.87), 1.263 (0.58), 1.296 (0.87), 1.411 (0.58), 1.442 (2.04), 1.475 (1.45), 1.886 (0.87), 1.929 (1.16), 1.986 (0.29), 2.140 (0.87), 2.181 (0.58), 2.214 (2.33), 2.230 (4.07), 2.274 (0.87), 2.318 (1.45), 2.323 (2.91), 2.327 (4.36), 2.332 (3.20), 2.336 (1.45), 2.518 (16.00), 2.523 (11.35), 2.539 (16.00), 2.660 (2.62), 2.665 (4.07), 2.669 (5.53), 2.673 (4.07), 2.679 (2.33), 2.691 (2.62), 2.718 (1.45), 2.739 (0.87), 2.774 (1.45), 2.807 (0.87), 2.825 (0.87), 2.852 (0.87), 3.110 (1.75), 3.116 (1.75), 3.129 (1.75), 3.141 (1.16), 3.166 (0.87), 3.191 (1.16), 3.225 (1.16), 3.248 (0.29), 3.296 (1.16), 3.378 (1.75), 3.382 (1.75), 3.388 (0.87), 3.392 (0.87), 3.432 (4.95), 3.546 (0.58), 3.580 (1.16), 3.616 (1.16), 3.723 (11.05), 4.225 (0.58), 4.258 (0.58), 4.325 (1.16), 4.358 (1.16), 5.371 (1.16), 6.097 (3.20), 6.102 (3.20), 7.262 (2.62), 7.369 (4.07), 7.374 (4.07), 7.385 (1.45), 7.402 (2.33), 7.421 (1.75), 7.467 (0.58), 7.483 (1.45), 7.507 (6.11), 7.523 (2.04), 7.526 (2.04), 7.539 (3.78), 7.559 (5.82), 7.579 (6.11), 7.599 (1.75), 7.799 (0.58), 7.963 (1.45), 7.983 (1.75), 7.998 (3.78), 8.019 (3.49), 8.038 (3.78), 8.059 (3.49), 8.290 (0.87), 8.320 (7.27).

Example 49

3,3,3-trifluoro-2-methoxy-1-[7-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-(naphthalen-1-yl)propan-1-one (Stereoisomer 1)



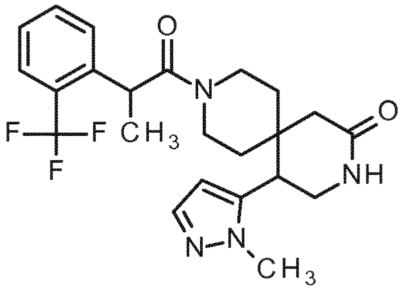
To a solution of Example 46 (100 mg, 194 µmol) in THF (3.2. ml) under Argon was added borane dimethylsulfide (680 µl, 2M in THF) and heated at 70℃ for 3h. To the reaction mixture was added methanol (1ml) and 2M HCl (aq, 100µl) and heated at 70℃ for 2h and then at RT for 16h. The reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method 5) and gave the title compound (40 mg, 39%).

Optical rotation (method OR1): -26.4° +/- 0.87° (me thanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.967 (0.45), 1.107 (16.00), 1.231 (0.45), 2.337 (0.50), 2.462 (0.75), 2.518 (5.39), 2.523 (3.75), 2.540 (1.79), 2.552 (0.82), 2.575 (0.82), 2.620 (0.56), 2.679 (0.56), 2.692 (1.06), 2.904 (0.52), 3.357 (2.67), 3.641 (4.38), 3.706 (4.51), 4.192 (1.08), 6.067 (0.80), 6.071 (0.78), 7.291 (1.23), 7.296 (1.23), 7.485 (0.50), 7.507 (0.95), 7.511 (0.93), 7.519 (1.19), 7.528 (0.80), 7.535 (0.63), 7.977 (1.29), 7.997 (1.25), 8.025 (0.63), 8.040 (1.21), 8.060 (1.04).

Example 50

5-(1-methyl-1H-pyrazol-5-yl)-9-{2-[2-(trifluoromethyl)phenyl]propanoyl}-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Intermediate 1 the title compound was prepared starting from Intermediate 33 (100 mg, 351 µmol) and (2S)-2-[2-

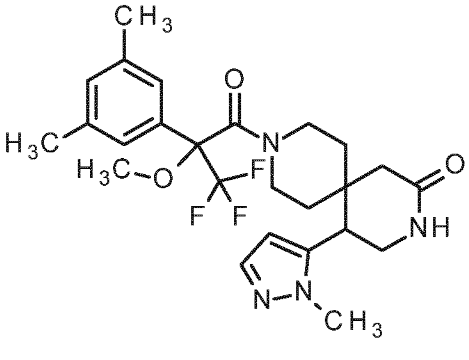
(trifluoromethyl)phenyl]propanoic acid (84.3 mg, 386 µmol; CAS: 1080023-02-4) to give the title compound 600 mg (37 % yield) after purification by preparative HPLC (Method 5).

Optical rotation (method OR1): 10.1°+/- 0.23°(met hanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.031 (0.43), -0.010 (0.74), 0.000 (0.74), 0.022 (0.43), 0.704 (0.62), 0.799 (0.43), 0.820 (0.74), 0.832 (0.74), 0.852 (0.47), 1.015 (1.76), 1.029 (13.66), 1.046 (14.99), 1.050 (4.45), 1.082 (1.64), 1.319 (2.46), 1.339 (7.02), 1.356 (9.68), 1.377 (6.48), 1.415 (1.87), 1.450 (0.59), 1.484 (1.29), 1.516 (1.21), 1.549 (0.51), 1.594 (0.43), 2.206 (1.17), 2.249 (1.37), 2.265 (0.55), 2.309 (1.13), 2.324 (1.17), 2.355 (0.70), 2.367 (1.40), 2.419 (1.64), 2.424 (2.22), 2.429 (1.64), 2.485 (0.43), 2.503 (1.25), 2.521 (1.33), 2.543 (1.60), 2.615 (9.09), 2.619 (5.66), 2.636 (1.80), 2.641 (2.11), 2.685 (1.37), 2.721 (1.76), 2.744 (0.82), 2.766 (4.33), 2.771 (3.51), 2.790 (1.25), 2.801 (1.25), 2.825 (1.01), 2.856 (0.66), 3.039 (0.70), 3.055 (0.94), 3.071 (0.70), 3.121 (1.37), 3.133 (1.64), 3.151 (2.73), 3.203 (4.49), 3.216 (2.15), 3.249 (0.59), 3.313 (0.59), 3.344 (2.46), 3.358 (2.11), 3.376 (2.34), 3.577 (16.00), 3.622 (0.82), 3.660 (0.74), 3.780 (14.36), 3.898 (9.13), 4.132 (1.17), 4.148 (1.17), 4.231 (1.91), 4.248 (1.80), 4.265 (0.94), 4.296 (1.01), 4.330 (0.94), 4.424 (0.70), 4.459 (0.66), 5.690 (2.97), 5.695 (2.97), 6.181 (3.12), 6.186 (3.12), 6.227 (1.25), 6.231 (1.29), 6.242 (1.21), 6.247 (1.21), 7.091 (1.52), 7.111 (1.80), 7.274 (1.91), 7.294 (2.58), 7.313 (0.90), 7.430 (0.90), 7.455 (3.98), 7.459 (3.67), 7.470 (3.86), 7.500 (3.79), 7.505 (3.28), 7.531 (0.59), 7.549 (1.21), 7.567 (0.78), 7.610 (2.15), 7.619 (3.00), 7.628 (2.11), 7.693 (2.03), 7.733 (3.71), 7.762 (2.03), 7.784 (2.03), 7.809 (1.29), 7.831 (1.37), 7.838 (1.17), 7.854 (1.09).

Example 51

9-[2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoyl]-5-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)



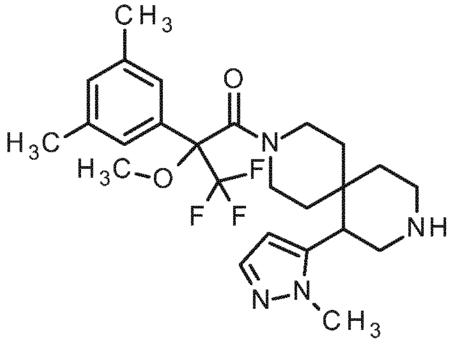
Using an analogous method as described for Intermediate 1 the title compound was prepared starting from Intermediate 33 (70.0 mg, 246 µmol) and Intermediate 38 (70.9 mg, 270 µmol) to give the title compound 67 mg (53 % yield) after purification by preparative HPLC (Method 5).

Optical rotation (method OR1): -1.2°+/- 0.72°(met hanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.479 (0.41), 0.490 (0.41), 0.705 (0.54), 0.735 (0.42), 0.920 (1.38), 0.935 (8.29), 0.951 (8.25), 1.510 (0.62), 1.543 (0.51), 2.118 (0.48), 2.265 (16.00), 2.272 (10.14), 2.317 (1.08), 2.413 (0.71), 2.430 (0.55), 2.465 (0.73), 2.518 (1.03), 2.522 (0.73), 2.530 (0.96), 2.825 (0.46), 2.854 (0.80), 2.888 (0.44), 3.072 (1.07), 3.104 (1.42), 3.112 (1.20), 3.133 (0.81), 3.148 (0.43), 3.153 (0.48), 3.177 (0.41), 3.243 (1.85), 3.266 (2.26), 3.553 (5.03), 3.582 (0.48), 3.617 (0.40), 3.700 (10.54), 3.790 (5.54), 4.258 (0.55), 4.291 (0.41), 5.751 (2.20), 5.756 (2.25), 6.145 (1.13), 6.150 (1.11), 6.924 (3.54), 7.051 (0.90), 7.094 (1.73), 7.336 (3.63), 7.341 (3.47), 7.585 (1.30), 7.646 (0.69).

Example 52

2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxy-1-[7-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-3-yl]propan-1-one (Stereoisomer 1)

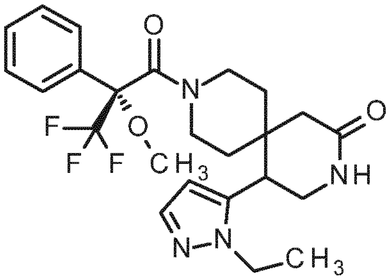


Using an analogous method as described for Example 49, the title compound was prepared starting from Example 51 (40 mg, 81.2 µmol) to give the title compound 26 mg (62 % yield) after purification by preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 2.211 (5.21), 2.267 (2.73), 2.322 (0.43), 2.327 (0.58), 2.331 (0.43), 2.518 (2.72), 2.522 (1.77), 2.659 (0.43), 2.664 (0.56), 2.669 (0.76), 2.673 (0.68), 2.678 (0.52), 2.687 (0.43), 2.742 (0.46), 3.261 (0.67), 3.536 (1.70), 3.695 (3.84), 3.738 (2.08), 4.190 (1.23), 5.663 (0.48), 5.667 (0.47), 6.872 (1.01), 6.930 (0.55), 7.062 (0.60), 7.272 (0.75), 7.276 (0.76), 7.289 (0.44), 7.293 (0.42).

Example 53

5-(1-ethyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)

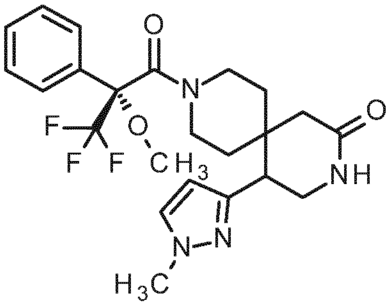


Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(1-ethyl-1H-pyrazol-5-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (451 mg, 866 µmol, Intermediate 39) and gave the title compound 291 mg (67 %) after preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.208 (0.55), -0.186 (0.94), -0.175 (0.98), -0.153 (0.55), 0.402 (0.65), 0.414 (0.65), 0.434 (0.42), 0.631 (0.91), 0.661 (1.79), 0.693 (1.07), 0.798 (1.04), 0.814 (1.11), 0.821 (1.14), 0.840 (0.78), 0.849 (0.55), 0.870 (0.81), 0.886 (0.94), 0.904 (1.59), 0.912 (0.52), 0.923 (0.72), 1.035 (7.80), 1.052 (16.00), 1.070 (7.71), 1.111 (5.17), 1.129 (11.38), 1.147 (5.40), 1.236 (4.33), 1.254 (9.04), 1.266 (2.80), 1.272 (4.46), 1.282 (4.59), 1.300 (2.11), 1.434 (1.98), 1.446 (2.05), 1.498 (1.11), 1.536 (0.55), 1.987 (0.62), 2.093 (1.63), 2.137 (1.82), 2.211 (0.46), 2.255 (0.52), 2.278 (1.11), 2.322 (2.67), 2.331 (1.33), 2.374 (0.52), 2.413 (0.42), 2.423 (0.72), 2.434 (0.85), 2.518 (5.66), 2.522 (3.51), 2.529 (1.76), 2.652 (2.28), 2.664 (1.17), 2.669 (1.50), 2.673 (1.11), 2.696 (1.92), 2.797 (1.27), 2.830 (1.76), 2.850 (1.11), 3.006 (2.41), 3.036 (2.93), 3.070 (2.18), 3.085 (1.27), 3.110 (1.76), 3.121 (1.92), 3.136 (1.95), 3.250 (1.50), 3.276 (3.54), 3.291 (1.69), 3.376 (0.52), 3.404 (1.89), 3.417 (1.53), 3.422 (3.09), 3.435 (3.67), 3.440 (3.54), 3.452 (3.06), 3.457 (1.20), 3.469 (1.24), 3.487 (2.44), 3.556 (10.67), 3.577 (8.62), 3.623 (0.68), 3.717 (0.94), 3.735 (1.30), 3.751 (1.76), 3.770 (1.53), 3.787 (0.46), 3.808 (0.46), 3.825 (1.50), 3.843 (1.72), 3.860 (1.27), 3.878 (0.85), 3.969 (0.68), 3.987 (1.01), 4.004 (1.46), 4.021 (1.27), 4.045 (0.46), 4.063 (1.27), 4.080 (1.66), 4.098 (1.43), 4.115 (1.43), 4.133 (0.98), 4.156 (0.81), 4.163 (0.68), 4.182 (0.59), 4.199 (0.52), 4.236 (0.78), 4.268 (0.85), 4.346 (1.82), 4.359 (3.93), 4.372 (2.24), 4.398 (0.85), 5.605 (3.45), 5.609 (3.51), 5.758 (6.08), 6.133 (1.37), 6.137 (1.43), 6.150 (4.33), 6.155 (4.62), 6.164 (1.27), 7.091 (0.68), 7.112 (4.98), 7.126 (12.03), 7.268 (2.96), 7.289 (4.52), 7.304 (1.01), 7.310 (0.55), 7.343 (1.43), 7.351 (1.56), 7.365 (1.69), 7.370 (1.40), 7.376 (1.63), 7.381 (1.53), 7.411 (1.89), 7.430 (5.37), 7.440 (3.28), 7.449 (4.36), 7.490 (4.00), 7.494 (4.75), 7.514 (2.21), 7.524 (4.75), 7.528 (4.88), 7.566 (2.02), 7.610 (0.68), 7.641 (2.83).

Example 54

5-(1-methyl-1H-pyrazol-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)

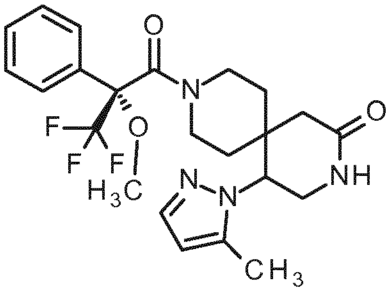


Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(1-methyl-1H-pyrazol-3-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (192 mg, 379 µmol, Intermediate 40) and gave the title compound 98 mg (53 %) after preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.174 (0.66), 0.184 (0.66), 0.207 (0.42), 0.447 (0.53), 0.458 (0.53), 0.592 (0.76), 0.625 (0.66), 0.705 (0.69), 0.740 (0.69), 1.233 (0.84), 1.244 (0.79), 1.265 (0.79), 1.330 (1.34), 1.356 (1.27), 1.378 (1.11), 1.445 (0.74), 1.466 (0.90), 1.475 (0.98), 1.500 (0.47), 1.757 (1.16), 1.800 (0.84), 1.843 (0.61), 1.887 (0.71), 1.908 (1.19), 1.953 (1.32), 2.023 (1.03), 2.067 (1.24), 2.074 (1.63), 2.239 (0.82), 2.282 (0.71), 2.307 (1.05), 2.332 (1.13), 2.350 (0.92), 2.518 (7.59), 2.522 (5.03), 2.534 (2.14), 2.539 (1.56), 2.551 (1.98), 2.594 (1.77), 2.673 (1.24), 2.699 (1.00), 2.714 (1.05), 2.725 (1.11), 2.739 (0.84), 2.800 (0.61), 2.815 (0.76), 2.824 (0.90), 2.838 (0.76), 2.865 (0.45), 2.897 (0.82), 2.912 (0.53), 2.922 (0.55), 2.938 (0.79), 3.034 (0.87), 3.048 (2.00), 3.064 (2.00), 3.079 (1.85), 3.121 (1.66), 3.153 (1.45), 3.177 (1.08), 3.199 (0.69), 3.207 (0.61), 3.223 (0.47), 3.271 (2.45), 3.287 (2.29), 3.351 (0.87), 3.391 (0.98), 3.418 (4.48), 3.480 (0.63), 3.521 (3.48), 3.577 (10.46), 3.599 (0.61), 3.739 (7.59), 3.765 (9.33), 3.801 (14.18), 3.834 (16.00), 4.119 (0.61), 4.153 (0.55), 4.267 (0.66), 4.301 (0.61), 5.770 (2.93), 5.775 (2.93), 5.947 (3.32), 5.952 (3.32), 6.043 (1.58), 6.048 (1.69), 6.055 (2.00), 6.061 (1.95), 7.176 (0.69), 7.197 (3.32), 7.213 (8.28), 7.230 (0.84), 7.258 (1.85), 7.276 (2.77), 7.341 (1.92), 7.359 (3.80), 7.366 (2.79), 7.372 (2.95), 7.380 (4.09), 7.388 (3.03), 7.431 (2.74), 7.435 (2.82), 7.444 (4.16), 7.449 (3.93), 7.458 (4.11), 7.477 (2.00), 7.495 (1.87), 7.519 (1.69), 7.550 (1.48), 7.555 (1.45), 7.575 (1.77), 7.580 (1.74), 7.639 (2.71), 7.644 (2.66), 7.661 (3.03), 7.666 (3.00).

Example 55

5-(5-methyl-1H-pyrazol-1-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)

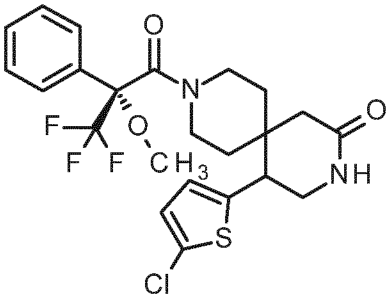


Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-cyano(5-methyl-1H-pyrazol-1-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (210 mg, 415 µmol, Intermediate 41) and gave the title compound 165 mg (81 %) after silica chromatography (dichloromethane:ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.720 (0.42), 0.798 (0.44), 0.815 (0.45), 0.822 (0.46), 0.905 (0.51), 1.035 (3.55), 1.053 (6.69), 1.070 (3.86), 1.082 (0.41), 1.089 (0.43), 1.945 (0.42), 2.038 (5.74), 2.145 (5.03), 2.172 (0.53), 2.216 (0.62), 2.283 (2.84), 2.287 (2.93), 2.347 (0.47), 2.390 (0.82), 2.518 (2.00), 2.522 (1.51), 2.538 (0.88), 2.582 (0.55), 2.684 (0.80), 2.727 (0.69), 2.850 (0.47), 2.885 (0.56), 3.048 (0.45), 3.082 (0.49), 3.350 (0.82), 3.365 (0.49), 3.391 (1.47), 3.405 (0.66), 3.418 (0.63), 3.422 (1.49), 3.435 (1.71), 3.440 (1.71), 3.452 (1.47), 3.457 (0.60), 3.469 (0.67), 3.499 (0.44), 3.525 (1.63), 3.571 (5.61), 3.646 (0.40), 4.150 (0.40), 4.165 (0.53), 4.174 (0.50), 4.183 (0.47), 4.197 (0.66), 4.291 (0.43), 4.343 (0.92), 4.356 (1.59), 4.369 (0.79), 5.758 (16.00), 5.990 (1.15), 5.992 (1.16), 6.025 (0.62), 6.027 (0.60), 6.038 (0.59), 6.041 (0.57), 6.090 (1.30), 6.093 (1.28), 7.219 (3.16), 7.237 (1.51), 7.257 (0.47), 7.321 (1.53), 7.331 (0.99), 7.348 (2.80), 7.352 (2.63), 7.363 (0.84), 7.428 (0.84), 7.433 (1.75), 7.437 (2.38), 7.442 (3.63), 7.456 (1.38), 7.461 (2.29), 7.475 (1.09), 7.537 (0.70), 7.566 (0.69).

Example 56

5-(5-chlorothiophen-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)

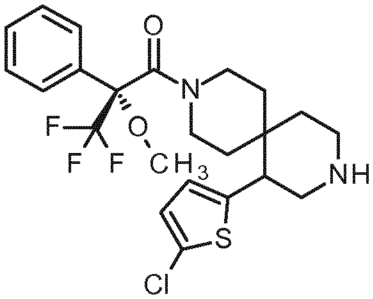


Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[(5-chlorothiophen-2-yl)(cyano)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (360 mg, 663 µmol, Intermediate 43) and gave the title compound 120 mg (39 %) after preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.188 (0.44), 0.210 (0.69), 0.221 (0.73), 0.242 (0.47), 0.391 (0.55), 0.403 (0.55), 0.664 (0.95), 0.698 (0.88), 0.905 (0.44), 1.189 (0.84), 1.200 (0.91), 1.222 (0.99), 1.232 (1.10), 1.322 (0.44), 1.361 (0.55), 1.396 (1.61), 1.429 (1.28), 1.444 (1.97), 1.854 (0.66), 1.898 (0.80), 1.944 (0.58), 1.988 (0.88), 2.004 (1.35), 2.048 (1.53), 2.149 (1.02), 2.176 (0.99), 2.192 (1.39), 2.220 (0.73), 2.246 (0.99), 2.290 (0.84), 2.331 (1.42), 2.336 (0.69), 2.407 (1.75), 2.451 (1.57), 2.518 (11.76), 2.522 (7.78), 2.530 (3.76), 2.574 (1.97), 2.586 (0.47), 2.673 (1.64), 2.900 (0.88), 2.929 (1.42), 2.960 (0.73), 3.084 (1.94), 3.095 (1.35), 3.119 (3.29), 3.132 (1.42), 3.144 (1.28), 3.152 (1.61), 3.172 (0.66), 3.191 (1.42), 3.203 (1.42), 3.228 (1.02), 3.244 (1.53), 3.273 (1.83), 3.299 (1.42), 3.415 (1.06), 3.434 (1.42), 3.452 (5.26), 3.466 (2.01), 3.533 (0.66), 3.557 (3.40), 3.581 (12.38), 3.915 (0.44), 4.182 (0.55), 4.217 (0.55), 4.286 (0.69), 4.320 (0.66), 5.758 (16.00), 6.645 (1.57), 6.649 (1.68), 6.654 (1.75), 6.657 (1.68), 6.818 (1.94), 6.821 (2.08), 6.827 (2.19), 6.829 (2.08), 6.965 (2.85), 6.968 (1.57), 6.977 (1.86), 6.980 (1.50), 6.984 (1.42), 6.994 (1.46), 7.003 (0.77), 7.007 (1.35), 7.015 (0.88), 7.033 (1.79), 7.042 (1.83), 7.046 (1.94), 7.055 (1.90), 7.060 (2.41), 7.069 (2.23), 7.073 (2.45), 7.082 (2.30), 7.135 (1.28), 7.155 (3.40), 7.173 (2.89), 7.213 (3.43), 7.231 (2.01), 7.277 (3.00), 7.296 (4.13), 7.310 (0.73), 7.313 (0.95), 7.372 (2.12), 7.377 (3.36), 7.383 (2.96), 7.388 (3.25), 7.397 (5.30), 7.410 (1.57), 7.418 (2.52), 7.426 (2.74), 7.430 (2.45), 7.447 (5.30), 7.452 (3.03), 7.457 (2.89), 7.460 (3.32), 7.464 (1.75), 7.480 (1.35), 7.498 (3.84), 7.511 (2.26), 7.514 (2.41), 7.589 (1.57), 7.626 (2.78).

Example 57

(2R)-1-[7-(5-chlorothiophen-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropan-1-one (mixture of stereoisomers)

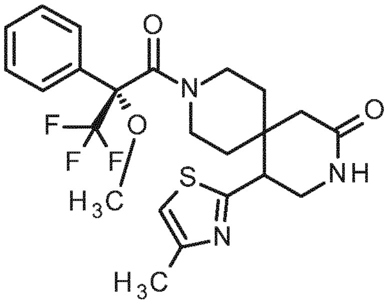


Using an analogous method as described for Example 49, the title compound was prepared starting from Example 55 (80 mg, 155 µmol) to give the title compound 30 mg (38 % yield) after purification by preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.107 (16.00), 1.144 (0.50), 1.353 (0.46), 2.323 (1.08), 2.326 (1.40), 2.331 (1.12), 2.580 (0.76), 2.617 (1.22), 2.636 (1.62), 2.652 (1.36), 2.664 (1.74), 2.669 (2.01), 2.673 (1.74), 2.907 (0.46), 2.940 (0.54), 2.962 (0.48), 3.418 (0.54), 3.577 (2.87), 3.590 (4.13), 3.616 (1.80), 4.189 (1.76), 6.394 (0.76), 6.404 (0.76), 6.625 (0.62), 6.634 (0.64), 6.773 (0.50), 6.783 (0.64), 6.812 (0.52), 6.822 (0.64), 6.856 (0.72), 6.866 (0.60), 6.891 (0.82), 6.900 (0.68), 6.917 (0.76), 6.926 (0.76), 6.970 (0.92), 6.979 (0.90), 7.306 (0.60), 7.324 (2.79), 7.335 (3.45), 7.353 (1.18), 7.372 (0.72), 7.407 (1.96), 7.419 (1.42), 7.439 (0.74), 7.450 (1.48), 7.455 (1.54), 7.469 (0.62).

Example 58

5-(4-methyl-1,3-thiazol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers)



Using an analogous method as described for Intermediate 11, the title compound was prepared starting from ethyl {4-[cyano(4-methyl-1,3-thiazol-2-yl)methyl]-1-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]piperidin-4-yl}acetate (590 mg, 1.13 mmol, Intermediate 44) and gave the title compound 245 mg (43 %) after preparative HPLC (Method 5).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.131 (0.46), 0.152 (0.73), 0.162 (0.73), 0.185 (0.46), 0.196 (0.41), 0.545 (0.69), 0.576 (0.50), 0.743 (1.38), 0.773 (1.28), 0.889 (0.41), 1.235 (0.50), 1.269 (0.73), 1.279 (0.78), 1.301 (0.96), 1.312 (1.05), 1.333 (0.92), 1.388 (0.73), 1.424 (1.01), 1.448 (1.15), 1.462 (0.83), 1.480 (1.15), 1.514 (1.10), 1.546 (0.60), 1.641 (0.46), 1.663 (0.73), 1.674 (0.69), 1.841 (1.10), 1.885 (1.24), 1.944 (0.69), 1.986 (0.87), 2.027 (1.38), 2.070 (1.65), 2.074 (2.93), 2.163 (1.56), 2.206 (1.83), 2.291 (6.37), 2.293 (6.28), 2.309 (1.33), 2.322 (11.28), 2.324 (11.37), 2.331 (2.52), 2.348 (14.17), 2.350 (14.81), 2.374 (1.65), 2.413 (14.21), 2.415 (14.67), 2.518 (11.78), 2.523 (7.84), 2.540 (0.64), 2.552 (2.06), 2.595 (2.20), 2.638 (2.02), 2.665 (2.20), 2.669 (2.93), 2.673 (2.29), 2.804 (0.50), 2.828 (0.41), 2.918 (0.55), 2.950 (0.92), 2.977 (0.60), 2.999 (0.60), 3.026 (0.96), 3.056 (0.60), 3.103 (0.64), 3.118 (0.69), 3.140 (1.19), 3.163 (0.78), 3.184 (0.92), 3.204 (1.42), 3.211 (1.93), 3.226 (3.26), 3.240 (1.88), 3.269 (2.38), 3.280 (2.66), 3.296 (2.93), 3.308 (2.38), 3.364 (1.65), 3.438 (1.70), 3.458 (1.88), 3.492 (6.14), 3.586 (16.00), 3.858 (0.78), 3.892 (0.73), 4.122 (0.78), 4.155 (0.73), 4.262 (0.73), 4.295 (0.73), 7.140 (1.88), 7.165 (4.08), 7.184 (3.62), 7.198 (5.59), 7.201 (6.83), 7.232 (3.90), 7.251 (2.25), 7.259 (4.54), 7.261 (4.36), 7.292 (3.39), 7.310 (5.50), 7.328 (0.92), 7.347 (2.70), 7.365 (4.45), 7.385 (4.17), 7.396 (2.98), 7.404 (2.25), 7.433 (3.30), 7.438 (3.76), 7.451 (6.14), 7.457 (5.64), 7.464 (2.57), 7.469 (2.11), 7.476 (1.15), 7.565 (3.71), 7.610 (2.25).

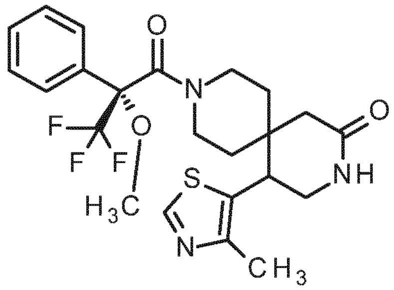
Example 59 and Example 60

(5S)-5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

(5R)-5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

Example 59

5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 1)

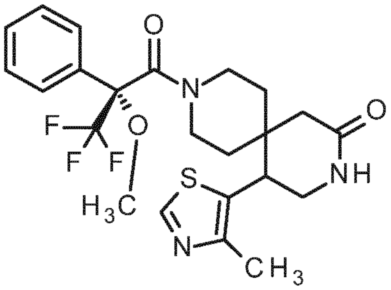


To a solution of intermediate 47 (162 mg, 309 µmol) in methanol (5.8 ml) was added cobalt (II) chloride (80.3 mg, 619 µmol). To the reaction was added portionwise NaBH4 (58.5 mg, 1.55 mmol) over 15 mins. The reaction was stirred for 16h, then another portion of NaBH4 (2eq) added and stirred for 1h at RT. The reaction was added water then the pH was adjusted to pH 7 with 2M HCl (aq) and concentrated to remove the organic solvents. The residue was diluted with sat. ammonium chloride (aq) and extracted with EtOAc. The organics filtered through an hydrophobic filter and concentrated under reduced pressure. The title compound (21 mg, 13%) was obtained after silica chromatography (dichloromethane:ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.044 (0.46), -0.033 (0.46), 0.705 (0.52), 0.738 (0.48), 0.921 (0.48), 0.939 (1.00), 0.957 (0.91), 0.976 (1.49), 0.996 (0.73), 1.179 (16.00), 1.303 (0.87), 1.327 (0.46), 1.351 (0.53), 1.360 (0.62), 1.368 (0.77), 1.420 (0.73), 1.445 (0.66), 1.472 (1.28), 1.482 (1.23), 1.503 (0.50), 2.155 (10.55), 2.190 (0.80), 2.234 (0.89), 2.280 (1.16), 2.364 (0.43), 2.390 (0.44), 2.395 (0.98), 2.399 (1.37), 2.403 (1.09), 2.408 (0.78), 2.450 (2.63), 2.535 (0.52), 2.590 (5.45), 2.595 (3.83), 2.690 (1.12), 2.736 (1.44), 2.741 (1.49), 2.745 (1.03), 2.750 (0.48), 2.928 (0.43), 3.139 (0.59), 3.177 (0.62), 3.191 (0.50), 3.200 (0.66), 3.218 (0.52), 3.243 (1.01), 3.265 (1.78), 3.546 (0.66), 3.576 (0.64), 3.582 (0.64), 3.631 (1.32), 3.643 (5.05), 4.261 (1.76), 4.306 (0.43), 4.313 (0.44), 4.320 (0.41), 4.410 (0.46), 4.447 (0.41), 7.137 (0.80), 7.158 (1.90), 7.176 (1.41), 7.247 (1.78), 7.266 (1.25), 7.318 (0.77), 7.336 (1.21), 7.354 (0.52), 7.425 (0.52), 7.443 (0.43), 7.503 (1.17), 7.508 (0.98), 7.515 (0.68), 7.520 (0.77), 7.525 (0.53), 7.543 (0.41), 7.736 (1.07), 8.160 (2.55), 8.966 (0.75), 9.121 (3.43).

Example 60

5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (Stereoisomer 2)



Using an analogous method as described for Example 59, the title compound was prepared starting from Intermediate 48 (141 mg, 269 µmol) to give the title compound 14 mg (10 % yield) after after silica chromatography (dichloromethane:ethanol).

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.350 (0.63), 0.361 (0.63), 0.382 (0.43), 0.526 (0.80), 0.556 (0.57), 0.799 (0.40), 0.852 (0.43), 0.860 (0.54), 0.905 (0.46), 0.967 (1.40), 1.107 (16.00), 1.128 (0.48), 1.144 (1.22), 1.161 (1.02), 1.172 (0.91), 1.194 (0.71), 1.209 (0.94), 1.232 (1.40), 1.256 (0.54), 1.270 (0.54), 1.296 (0.68), 1.349 (1.17), 1.389 (0.57), 1.413 (0.68), 1.422 (0.57), 1.431 (0.48), 1.524 (0.80), 1.553 (0.65), 2.084 (4.70), 2.133 (0.60), 2.162 (0.40), 2.209 (15.74), 2.291 (1.40), 2.318 (0.68), 2.323 (1.48), 2.327 (2.22), 2.336 (3.39), 2.361 (2.19), 2.381 (5.72), 2.405 (0.65), 2.518 (8.11), 2.523 (5.69), 2.618 (0.51), 2.665 (1.57), 2.669 (1.96), 2.673 (1.37), 2.679 (0.63), 2.857 (0.63), 2.891 (1.31), 2.910 (0.83), 2.918 (1.11), 2.936 (0.80), 2.942 (0.83), 3.022 (0.46), 3.055 (0.94), 3.084 (0.71), 3.171 (0.46), 3.200 (1.05), 3.214 (1.17), 3.230 (0.85), 3.354 (1.17), 3.366 (0.91), 3.383 (0.51), 3.396 (0.54), 3.408 (0.40), 3.424 (1.22), 3.447 (2.45), 3.475 (0.57), 3.504 (0.88), 3.510 (1.02), 3.559 (1.20), 3.579 (7.86), 3.603 (0.71), 4.189 (1.48), 4.295 (0.63), 4.325 (0.68), 4.369 (0.46), 6.544 (0.91), 7.086 (0.80), 7.104 (0.60), 7.176 (0.77), 7.197 (0.68), 7.264 (0.51), 7.336 (1.94), 7.354 (3.47), 7.377 (0.85), 7.412 (1.22), 7.416 (1.68), 7.433 (4.07), 7.443 (2.76), 7.449 (3.07), 7.453 (3.02), 7.467 (1.71), 7.471 (2.36), 7.475 (1.45), 7.482 (0.88), 7.489 (2.02), 7.496 (0.43), 7.507 (0.51), 7.625 (1.85), 7.654 (0.83), 8.088 (0.68), 8.900 (1.79), 8.936 (4.78), 9.048 (1.59).

EXPERIMENTAL SECTION – BIOLOGICAL ASSAYS

The parmacological activity of the compounds according to the invention can be assessed using *in vitro-* and/or *in vivo*-assays, as known to the person skilled in the art. The following examples describe the biological activity of the compounds according to the invention, without the invention being limited to said examples.

Example compounds according to the invention 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: Assay for the detection of inhibitory effects on enzymatic activity of purified human Geranylgeranyltransferase type 1 (GGTase-1)

The biochemical GGTase-1 assay measures the inhibitory effect of compounds on enzymatic activity of human GGTase-1. The assay principle uses the activity of GGTase-1 to transfer a Geranyl geranyl moiety from Geranylgeranyl pyrophosphate (GGPP) to a peptide or protein with the recognition sequence GCVLL. In the assay, GGTase-1 transfers the Geranylgeranyl moiety to a Dansyl-coupled GCVLL peptide resulting in a fluorescence intensity increase as Dansyl is protected from solvation by the prenyl residue in near proximity. The assay was established according to Mansha et al., European Journal of Medicinal Chemistry, 2016, further optimized and miniaturized to result in a high-throughput amenable add-only assay.

The human beta subunit of GGTase-1 (PGGT1b, amino acids M1-T377, protein sequence NP_005014.2) and the human alpha subunit of Farnesyltransferase (FNTA, amino acids M1-Q379, protein sequence NP_002018.1), which are essential to constitute the functional GGTase-1 complex, were expressed in insect Hi-5 cells and purified by size exclusion chromatography. The assay was performed in white 384-well microplates (Greiner Bio-One, Frickenhausen, Germany) with a total volume of five microliter (µl). Fifty nanoliter (nl) of a 100-fold concentrated solution of the test compound in DMSO were transferred into a 384-well microtiter test plate. For this, a Hummingbird liquid handler (Digilab, MA, USA) was used. Five nM (or 2nM, Assay 1*) of GGTase-1 in 2.5 µl assay buffer (50 mM Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 10 mM KCl, 50 µM $ZnCl_2$, 5 mM DTT, 0.04% n-Dodecyl beta-D-maltoside, 5 mM ATP) were added to the compounds. After a 15 minutes pre-incubation at room temperature the reaction was started by addition of 2.5 µl with 2 micromolar (µM) (or 0.3µM, Assay 1*) Dansyl-GCVLL peptide and 2 µM GGPP in assay buffer. Fluorescence intensity of the reaction mixture was measured after 60 minutes at room temperature with a Pherastar by BMG (Germany) by using a module for excitation at 380 nm and emission at 510 nm.

Data were normalized (neutral control containing complete reaction mixture but DMSO instead of a compound = 0% inhibition, inhibitor control containing complete reaction mixture but no enzyme and no compound = 100% inhibition). For dose-response evaluation, compounds were tested in duplicates at up to 11 concentrations (20 µM, 5.7 µM, 1.6 µM, 0.47 µM, 0.13 µM, 38 nM, 11 nM, 3.1 nM, 0.89 nM, 0.25 nM and 0.073 nM). Dilution series were made prior to the assay in a 100-fold concentrated form by serial dilution with two separate dilutions for each compound (n=2). IC_{50} values were calculated by 4-parameter fitting using a commercial software package (Genedata Screener, Switzerland).

Table 2: IC_{50} values of Example Compounds in Assay 1 (GGTase-1)

Example No.	**Assay 1**	**Assay 1***
	IC_{50} [M]	IC_{50} [M]
1		2.01E-07
2		
3	1.79 E-7	1.07E-07
4		1.04E-5 > 2.00E-5
5		
6		5.61E-06
7		1.79E-5 > 2.00E-5
8		
9		1.04E-05
10		4.40E-06
11		7.23E-06
12		1.69E-5 > 2.00E-5

Example No.	Assay 1	Assay 1*
	IC$_{50}$ [M]	IC$_{50}$ [M]
13		
14		> 2.00E-5 1.85E-5
15		
16		7.90E-06
17		
18		
19		4.08E-06
20		4.56E-07
21		
22	1.71E-07	1.18E-07
23		1.97E-07
24		4.78E-07
25	1.65E-07	6.45E-08
26		
27		8.82E-07
28		>2.00E-5
29		2.22E-07
30		
31		
32	3.66E-06	1.11E-05
33		
34		5.01E-06
35	2.21E-06	>2.00E-5
36		
37		5.30E-06
38		2.87E-06
39		
40		2.17E-06
41		
42		
43	3.12E-06	9.89E-06
44		
45		7.68E-09

Example No.	Assay 1	Assay 1*
	IC50 [M]	IC50 [M]
46	1.03E-08	1.19E-08
47		3.02E-06
48		1.76E-08
49		6.83E-08
50		9.86E-09
51	8.66E-09	9.66E-09
52		8.39E-08
53		1.06E-05
54		
55		
56		4.76E-06
57		2.48E-06
58		
59		1.13E-05
60		3.82E-06

Assay 2: Assay for the detection of YAP1/TAZ activity in MDA-MB-231-TEAD-Luc reporter cells

The YAP/TAZ Dual Reporter Assay quantifies the activity of endogenous YAP1 and/or TAZ in MDA-MB-231 cells. The cells contain a stable Firefly luciferase reporter under control of a TEAD-promoter, as described under SEQ ID No. 1, as well as a thymidine kinase (TK)-Renilla reporter construct (pGL4.74, Promega) for toxicity control. Signals are detected by measuring the firefly luminescence followed by the renilla luminescence using the DualGlo-luciferase assay system detection kit (Promega, part # E2920, E2940).

The cells were kept in routine culture in DMEM low glucose, 10% fetal bovine serum (FBS), 1% Glutamax, 250 µg/ml Hygromycin, 0,5 µg/ml Puromycin, harvested, cryopreserved in 90% culture medium + 10% dimethylsulphoxide (DMSO) and stored as frozen aliquots of typically 10-50 million cells/vial at -150℃ or below until f urther use.

For the assay, sufficient cells were rapidly thawed in a 37℃ water bath and pipetted into pre-warmed assay medium (DMEM/Ham's 12, 5 ml Glutamine, 5 ml Penicillin/Streptomycin, 4% FBS). The cells were centrifuged for 5 min at 44 x g (gravitational force). The supernatant was removed and the cell pellet was resuspended in fresh medium to give a suspension of 2.0E+05 cells / ml. The cell concentration may vary depending on the cryopreserved cell batch used. The inhibitor control solution contained assay medium without cells.

The assay was performed in white 384-well or 1536-well microplates (Greiner Bio-One, Frickenhausen, Germany) with a total volume of five microliter (µl) or four µl, respectively. Fifty nl (40 nl in 1536-well microplates) of a 100-fold concentrated solution of the test compound in DMSO were transferred into a 384-well microtiter test plate. For this, either a Hummingbird liquid handler (Digilab, MA, USA) or an Echo acoustic system (Labcyte, CA, USA) was used. Five µl of a freshly prepared cell suspension were added to the wells of a test plate. The inhibitor control cell suspension was added to empty wells at the side of the test plate, followed by incubation at 37℃ in a 5% carbon dioxide atmosp here for 20-24 hours.

For luminescence detection, one µl of the Dual-Glo-Luciferase detection solution, prepared as recommended by the supplier, were added to all wells. The test plate was centrifuged for two minutes at 1200 rpm in a microplate centrifuge (Eppendorf model 5810), incubated at 20℃ for 10 min before measurement of the luminescence in a microplate reader (typically Pherastar by BMG, Germany, or ViewLux by Perkin-Elmer, USA). Then, one µl of the Dual-Glo-Stop&Glo Luciferase detection solution, prepared as recommended by the supplier, were added to all wells. The test plate was centrifuged for two minutes at 1200 rpm, incubated at 20℃ for 10 min before measurement of the renilla luminescence in a microplate reader

Data were normalized (control wells containing cell solution without inhibitor = 0% inhibition, assay medium control = 100% inhibition). For dose-response evaluation, compounds were tested in duplicates at up to 11 concentrations (for example 20 µM, 5.7 µM, 1.6 µM, 0.47 µM, 0.13 µM, 38 nM, 11 nM, 3.1 nM, 0.89 nM, 0.25 nM and 0.073 nM). Dilution series were made prior to the assay in a 100-fold concentrated form by serial dilution. IC_{50} values were calculated by 4-parameter fitting using a commercial software package (Genedata Screener, Switzerland).

Table 3: IC_{50} values of Example Compounds in Assay 2 (MDA-MB231-TEAD-Luc reporter cells)

Example No.	**Assay 2**	
	TEAD-Firefly IC_{50} [µM]	**TK-Renilla** IC_{50} [µM]
1	2.85 E-8	> 2.00 E-5
2	1.87 E-5	> 2.00 E-5
3	3.56 E-8	> 2.00 E-5
4	4.11 E-7	> 2.00 E-5
5	2.45 E-6	> 2.00 E-5
6	1.54 E-7	> 2.00 E-5

Example No.	Assay 2	
	TEAD-Firefly IC$_{50}$ [µM]	TK-Renilla IC$_{50}$ [µM]
7	8.51 E-7	> 2.00 E-5
8	4.25 E-6	> 2.00 E-5
9	3.07 E-7	> 2.00 E-5
10	1.97 E-7	> 2.00 E-5
11	3.02 E-7	> 2.00 E-5
12	8.89 E-7	> 2.00 E-5
13	1.45 E-6	> 2.00 E-5
14	6.60E-07	> 2.00E-5
15	>2.00E-5	> 2.00E-5
16	2.80E-07	> 2.00E-5
17	3.93E-06	> 2.00E-5
18	1.30E-05	> 2.00E-5
19	2.44E-07	> 2.00E-5
20	7.37E-08	> 2.00E-5
21	1.89E-05	> 2.00E-5
22	4.22E-08	> 2.00E-5
23	1.62E-07	> 2.00E-5
24	5.73E-08	> 2.00E-5
25	3.54E-08	> 2.00E-5
26	1.02E-05	> 2.00E-5
27	1.09E-07	> 2.00E-5
28	1.00E-05	> 2.00E-5
29	1.84E-07	> 2.00E-5
30	1.15E-06	> 2.00E-5
31	>2.00E-5	> 2.00E-5
32	3.27E-07	> 2.00E-5
33	1.66E-06	> 2.00E-5
34	1.97E-07	> 2.00E-5
35	1.08E-07	> 2.00E-5
36	> 2.00E-5	> 2.00E-5
37	2.74E-07	> 2.00E-5
38	1.67E-07	> 2.00E-5
39	>2.00E-5	> 2.00E-5

Example No.	Assay 2	
	TEAD-Firefly IC50 [µM]	TK-Renilla IC50 [µM]
40	1.26E-07	> 2.00E-5
41	1.38E-06	> 2.00E-5
42	>2.00E-5	> 2.00E-5
43	5.18E-07	> 2.00E-5
44	1.16E-06	> 2.00E-5
45	1.59E-09	> 2.00E-5
46	6.90E-10	> 2.00E-5
47	2.96E-08	> 2.00E-5
48	3.57E-09	> 2.00E-5
49	2.49E-09	> 2.00E-5
50	3.43E-08	> 2.00E-5
51	2.93E-09	> 2.00E-5
52	2.51E-08	> 2.00E-5
53	3.23E-07	> 2.00E-5
54	6.91E-06	> 2.00E-5
55	4.97E-06	> 2.00E-5
56	6.23E-07	> 2.00E-5
57	9.72E-07	5.18E-06
58	8.80E-06	> 2.00E-5
59	1.38E-06	> 2.00E-5
60	1.92E-07	> 2.00E-5

Assay 3: Cancer Cell proliferation assay

The Cancer Cell proliferation assay quantifies the effect of test compound addition on viability of cancer cells. Human breast cancer cells MDA-MB-231, human ovarian cancer cells IGR-OV1 and B16-F10 mouse melanoma cells were seeded at 1000 cells in 30 µl of their appropriate growth medium (MDA-MB-231: DMEM / Ham's F12; Biochrom; # FG 4815, with stable Glutamine, 10% FBS Biochrom FBS Superior # S0415); IGR-OV1 RPMI 1640; Biochrom; # FG 1215, with stable Glutamine, 10% FCS Biochrom; # S 0415); B16F10 DMEM / Ham's F12; Biochrom; # FG 4815, with stable Glutamine, 10% FCS Sigma; # F2442)) in 384-well plates and incubated in a humidified 37℃ incubator. Cells were allowed to recover for 24 h, then test compounds were added to cells by means of an HP D300 digital dispenser in a 10-

step 2.67-fold dilution series starting at a maximum final assay concentration of 10 µM. After 72 h incubation in a humidified 37℃ incubator, 30 µl Cell Titer-Glo Luminescent Cell Viability Assay reagent (Promega, G7573) was added and the incubation was continued for 10 min at room temperature. Luminescence, which corresponds to cell viability, was determined on a VICTOR V plate reader. (Perkin Elmer). The half-maximal growth inhibition (IC_{50}) was calculated as compound concentration, which was required to achieve 50% inhibition of luminescence. IC_{50} were determined by means of a 4-parameter fit on measurement data which were normalized to vehicle (DMSO) treated cells (=100%) and measurement readings taken immediately before compound exposure (=0%).

Table 4: IC_{50} values of Example Compounds in Assay 3 (cancer cell proliferation assay)

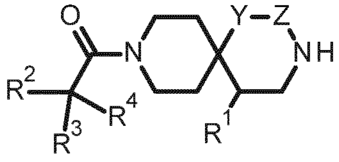
Example No.	**Assay 3**		
	MDA-MB-231 (Breast Cancer) IC_{50} [µM]	**B16F10 (Melanoma)** IC_{50} [µM]	**IGROV1 (Ovarian Cancer)** IC_{50} [µM]
1	2.62 E-7	2.82 E-8	2.02 E-7
2			
3	1.42 E-7	2.60 E-8	5.56 E-7
4	1.36 E-6	5.09 E-7	2.69 E-6
5			
6	8.70 E-7	2.08 E-7	> 3.00 E-6
7	1.80 E-6	4.63 E-7	> 3.00 E-6
8			
9	2.49 E-6	4.70 E-7	2.69 E-6
10			
11	8.43 E-7	3.49 E-7	1.82 E-6
12			
13			
14			
15			
16	6.02E-07	3.53E-07	
17			
18			
19			
20	4.08E-07	1.20E-07	
21			

Example No.	Assay 3		
	MDA-MB-231 (Breast Cancer) IC50 [µM]	**B16F10 (Melanoma)** IC50 [µM]	**IGROV1 (Ovarian Cancer)** IC50 [µM]
22	9.88E-08	3.64E-08	
23	1.42E-07	2.46E-07	
24	3.66E-07	2.65E-08	
25	1.88E-07	4.37E-08	
26			
27	1.05E-06	3.46E-07	
28			
29	3.07E-07	1.03E-07	
30			
31			
32	1.44E-06	1.37E-07	
33	2.49E-06	2.09E-06	
34	1.17E-06	1.29E-07	
35	4.21E-07	1.45E-07	
36			
37	7.01E-07	2.61E-07	
38	8.38E-07	1.48E-07	6.55E-07
39			
40	2.30E-07	4.44E-08	4.02E-07
41			
42			
43	1.36E-06	7.61E-07	
44			
45	4.69E-08	1.01E-09	
46	1.92E-07	1.63E-09	
47	1.71E-06	7.55E-08	
48	3.04E-09	1.54E-09	
49	3.50E-09	4.96E-09	
50	3.24E-07	9.15E-08	
51	9.99E-08	1.26E-08	
52	5.69E-07	9.07E-08	
53			

Example No.	**Assay 3**		
	MDA-MB-231 (Breast Cancer) IC_{50} [µM]	**B16F10 (Melanoma)** IC_{50} [µM]	**IGROV1 (Ovarian Cancer)** IC_{50} [µM]
54			
55			
56			
57			
58			
59			
60			

CLAIMS

1. A compound of general formula (I):



(I)

in which :

Y-Z represents a group selected from -CH_2-CH_2-, -CH_2-C(=O)-, and -N(H)-C(=O)-,

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_6-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_6-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_6-alkyl)-, C_1-C_6-haloalkyl , C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_6-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_6-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a group selected from phenyl and naphthyl,

which phenyl and naphthyl group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-hydroxyalkoxy and hydroxy,

R^4 represents a hydrogen atom or a group selected from

C_1-C_6-alkyl and C_1-C_6-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

2. The compound according to claim 1, wherein:

Y-Z represents a group selected from -CH_2-CH_2-, -CH_2-C(=O)-, and -N(H)-C(=O)-,

R^1 represents a 5- to 10-membered heteroaryl group,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a hydrogen atom or a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

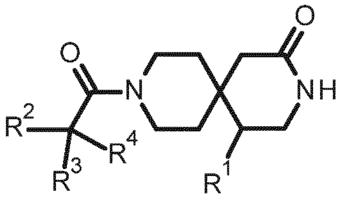
or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

3. The compound according to claim 1 or 2, which is of general formula (I-1),



(I-1) ,

in which :

R^1 represents a 5- to 10-membered heteroaryl group
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -$N(R^5)(R^6)$ and -(C_1-C_6-alkyl)-$N(R^5)(R^6)$,

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a hydrogen atom or a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from
C_1-C_4-alkyl and C_3-C_4-cycloalkyl,
or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

4. The compound according claim 1, 2 or 3, wherein:

R^1 represents a 5- to 10-membered heteroaryl group, which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, C_3-C_6-cycloalkyloxy and hydroxy,

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from
C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

and

R^4 represents a hydrogen atom or a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

5. The compound according claim 1, 2, 3 or 4, wherein:

R^1 represents a group selected from
pyrrolyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, pyridinyl and pyrazolo[1,5-a]pyridinyl,
which group is optionally substituted with a group selected from
fluorine atom, chlorine atom, methyl, ethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl and methoxy,

R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one, two, three or four times, each substituent independently selected from a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl ,

R^3 represents a group selected from C_1-C_4-alkyl, C_1-C_4-alkoxy and hydroxy,

and

R^4 represents a hydrogen atom or a C_1-C_4-haloalkyl group,

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

6. The compound according claim 1, 2, 3, 4 or 5, wherein:

R^1 represents a group selected from 1-methyl-1H-pyrrol-2-yl, 1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-2-yl, 5-chlorothiophen-2-yl, 4-methyl-1,3-thiazol-2-yl, 4-methyl-1,3-thiazol-5-yl, 3-fluoropyridin-2-yl, 5-methyl-1H-pyrazol-1-yl, 1-methyl-1H-pyrazol-3-yl, 1-methyl-1H-pyrazol-5-yl, 1-ethyl-1H-pyrazol-5-yl, 1-(2,2-difluoroethyl)-1H-pyrazol-5-yl, 1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl, 3-methylpyridin-2-yl, 3-methoxypyridin-2-yl, pyridin-3-yl, 2-chloropyridin-3-yl, 2-methylpyridin-3-yl, 4-methylpyridin-3-yl, 2-methoxypyridin-3-yl, 4-methoxypyridin-3-yl, pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl and pyrazolo[1,5-a]pyridin-7-yl,

R^2 represents a group selected from phenyl, 2-(trifluoromethyl)phenyl, 3,3-dimethylphenyl and 1-naphthyl,

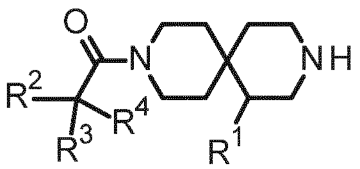
R^3 represents a group selected from methyl, methoxy and hydroxy,

and

R^4 represents a hydrogen atom or a trifluoromethyl group,

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

7. The compound according to claim 1 or 2, which is of general formula (I-2),



(I-2) ,

in which :

R^1 represents a 5- to 10-membered heteroaryl group

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogenatom or a group selected from

C_1-C_4-alkyl, C_3-C_6-cycloalkyl, (C_3-C_6-cycloalkyl)-(C_1-C_3-alkyl)-, (C_3-C_6-cycloalkyloxy)-(C_1-C_3-alkyl)-, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-hydroxyalkoxy, (C_1-C_2-alkoxy)-(C_2-C_4-alkoxy)-, (C_1-C_2-haloalkoxy)-(C_1-C_4-alkyl)-, C_3-C_6-cycloalkyloxy, -cyano, hydroxy, -N(R^5)(R^6) and -(C_1-C_6-alkyl)-N(R^5)(R^6),

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one, two, three or four times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyland C_1-C_4-haloalkoxy,

R^3 represents a group selected from

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,

R^4 represents a group selected from

C_1-C_4-alkyl and C_1-C_4-haloalkyl,

and

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group seleceted from

C_1-C_4-alkyl and C_3-C_4-cycloalkyl,

or

R^5 and R^6 together with the nitrogen to which they are attached represent a nitrogen containing 4- to 7-membered heterocycloalkyl group,

wherein said 4- to 7-membered nitrogen containing heterocycloalkyl group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_2-alkyl group and oxo,

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

8. The compound according claim 1, 2 or 7, wherein:

R^1 represents a 5- to 10-membered heteroaryl group

which group is optionally substituted, one, two or three times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and hydroxy,

R^2 represents a group selected from phenyl and naphthyl,

which group is optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from

C_1-C_4-alkyl, C_1-C_4-haloalkyl and C_1-C_4-haloalkoxy,

R^3 represents a group selected from
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_2-C_4-hydroxyalkoxy and hydroxy,
R^4 represents a group selected from
C_1-C_4-alkyl and C_1-C_4-haloalkyl,

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

9. The compound according claim 1, 2, 7 or 8, wherein:

R^1 represents a group selected from
thiophenyl, pyrazolyl and pyridinyl,
which group is optionally substituted with a group selected from chlorine atom methyl, methoxy and hydroxy,
R^2 represents a group selected from phenyl and naphthyl,
which group is optionally substituted, one or two times, each substituent independently selected from a C_1-C_4-alkyl group,
R^3 represents a C_1-C_4-alkoxy group,
and
R^4 represents a C_1-C_4-haloalkyl group,

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

10. The compound according claim 1, 2, 7, 8 or 9, wherein:

R^1 represents a group selected from
5-chlorothiophen-2-yl, 1-methyl-1H-pyrazol-5-yl, 2-hydroxypyridin-3-yl, 2-methylpyridin-3-yl and 2-methoxypyridin-3-yl,
R^2 represents a group selected from
phenyl, 3,3-dimethylphenyl and 1-naphthyl,
R^3 represents a methoxy group,
and
R^4 represents a trifluoromethyl group,

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

11. The compound according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 which is selected from the group consisting of:

5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),
(5R)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(1-methyl-1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(3-methoxypyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5S)-5-(3-methylpyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(thiophen-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(thiophen-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(pyrazolo[1,5-a]pyridin-4-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(furan-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5S)-5-(pyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(pyridin-4-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(3-fluoropyridin-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(2-chloropyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(2-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(2R)-3,3,3-trifluoro-2-methoxy-1-[7-(2-methylpyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-phenylpropan-1-one,

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5R)-5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5S)-5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(2R)-3,3,3-trifluoro-2-methoxy-1-[7-(2-methoxypyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-phenylpropan-1-one,

(2R)-3,3,3-trifluoro-1-[7-(2-hydroxypyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-methoxy-2-phenylpropan-1-one,

5-(2-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-hydroxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one

5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(4-methoxypyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-

diazaspiro[5.5]undecan-2-one,

5-(4-methylpyridin-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

(5S)-5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(pyrazolo[1,5-a]pyridin-7-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(1H-pyrrol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

(5S)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-(1-methyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2- one (mixture of stereosiomers),

(5S)-5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,
(5R)-5-[1-(2,2-difluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereosiomers),

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

(5R)-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-methoxy-2-(naphthalen-1-yl)propanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

5-(1-methyl-1H-pyrazol-5-yl)-9-[3,3,3-trifluoro-2-hydroxy-2-(naphthalen-1-yl)propanoyl]-3,9-

diazaspiro[5.5]undecan-2-one,

3,3,3-trifluoro-2-methoxy-1-[7-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-2-(naphthalen-1-yl)propan-1-one,

5-(1-methyl-1H-pyrazol-5-yl)-9-{2-[2-(trifluoromethyl)phenyl]propanoyl}-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

9-[2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropanoyl]-5-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-2-one,

2-(3,5-dimethylphenyl)-3,3,3-trifluoro-2-methoxy-1-[7-(1-methyl-1H-pyrazol-5-yl)-3,9-diazaspiro[5.5]undecan-3-yl]propan-1-one,

5-(1-ethyl-1H-pyrazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(1-methyl-1H-pyrazol-3-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(5-methyl-1H-pyrazol-1-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

5-(5-chlorothiophen-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

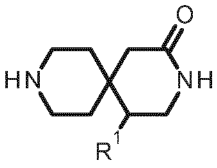
(2R)-1-[7-(5-chlorothiophen-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropan-1-one (mixture of stereoisomers),

5-(4-methyl-1,3-thiazol-2-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one (mixture of stereoisomers),

(5S)-5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one, and
(5R)-5-(4-methyl-1,3-thiazol-5-yl)-9-[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]-3,9-diazaspiro[5.5]undecan-2-one,

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

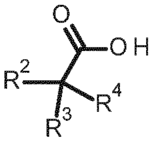
12. A method of preparing a compound of general formula (I) according to any one of claims 1, 2, 3, 4, 5, 6 or 11, said method comprising the step of allowing an intermediate compound of general formula (II) :



(II),

in which R^1 is as defined for the compound of general formula (I) according to any one of claims 1, 2, 3, 4, 5, 6 or 7,

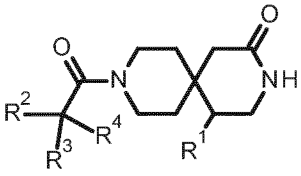
to react with a compound of general formula (XXI) :



(XXI),

in which R^2, R^3 and R^4 are as defined for the compound of general formula (I) according to any one of claims 1, 2, 3, 4, 5, 6 or 7,

thereby giving a compound of general formula (I-1) :



(I-1),

in which R^1, R^2, R^3 and R^4 are as defined for the compound of general formula (I-1) according to any one of claims 1, 2, 3, 4, 5, 6 or 7,

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.

13. A compound of general formula (I) according to any one of claims 1 to 11 or of general formula (I-1) according to any one of claims 1, 2, 3, 4, 5, 6, or 11, or of general formula (I-2) according to any one of claims 1, 2, 7, 8, 9 or 10 or 11, for use in the treatment and/or prophylaxis of a disease.

14. A pharmaceutical composition comprising a compound of general formula (I) according to any one of claims 1 to 11 or of general formula (I-1) according to any one of claims 1, 2, 3, 4, 5, 6, or 11, or of general formula (I-2) according to any one of claims 1, 2, 7, 8, 9 or 10 or 11, and one or more pharmaceutically acceptable excipients.

15. 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 11 or of general formula (I-1) according to any one of claims 1, 2, 3, 4, 5, 6, or 11, or of general formula (I-2) according to any one of claims 1, 2, 7, 8, 9 or 10 or 11, and
- one or more further active ingredients, in particular anti-cancer agents.

16. Use of a compound of general formula (I) according to any one of claims 1 to 11 or of general formula (I-1) according to any one of claims 1, 2, 3, 4, 5, 6, or 11, or of general formula (I-2) according to any one of claims 1, 2, 7, 8, 9 or 10 or 11, for the treatment and/or prophylaxis of a disease.

17. Use of a compound of general formula (I) according to any one of claims 1 to 11 or of general formula (I-1) according to any one of claims 1, 2, 3, 4, 5, 6, or 11, or of general formula (I-2) according to any one of claims 1, 2, 7, 8, 9 or 10 or 11, for the preparation of a medicament for the treatment or prophylaxis of a disease.

18. Use according to claim 13, 16 or 17, wherein the disease is a hyperproliferative disorder.

19. Use according to claim 18, wherein the disease is a cancer.

20. Use according to claim 19, wherein the cancer disease is selected from breast cancer, melanoma and ovarian cancer.

FIGURES

Figure 1

```
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Figure 1 (continued)

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```

Figure 2

```
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121 tggaatgact gcaagcttga gacaggaatg tgtggaatga ctgcaagctt
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221 atgactgcaa gcttgagaca ggaatgtgtg gaatgactgc aagcttgaga
271 caggaatgtg tggaatgact gcaagcttga gaca
```

Figure 3

```
Gly Cys Val Leu Leu
1               5
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/072877

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07D471/10 A61K31/438
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)
A61P C07D A61K

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 2007/030061 A1 (ASTRAZENECA AB [SE]; BOERJESSON LENA [SE] ET AL.) 15 March 2007 (2007-03-15) page 49 page 229; claim 1	1-10, 12-20 11
X A	EP 1 889 622 A1 (ONO PHARMACEUTICAL CO [JP]) 20 February 2008 (2008-02-20) page 31, line 42 - line 43 page 51; claim 8	1-10, 12-20 11
X A	WO 2010/138487 A1 (EXELIXIS INC [US]; AAY NAING [US] ET AL.) 2 December 2010 (2010-12-02) page 4, paragraph 8 page 98; compound 155	1-10, 12-20 11

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☒ See patent family annex.

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Date of the actual completion of the international search 17 September 2019	Date of mailing of the international search report 02/10/2019
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Jeanjean, Fabien

1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007030061 A1	15-03-2007	AR 055630 A1	29-08-2007
		AU 2006287976 A1	15-03-2007
		BR PI0615634 A2	24-05-2011
		CA 2621187 A1	15-03-2007
		CN 101305005 A	12-11-2008
		EC SP088329 A	28-04-2008
		EP 1926730 A1	04-06-2008
		JP 2009507070 A	19-02-2009
		KR 20080043396 A	16-05-2008
		TW 200800999 A	01-01-2008
		US 2009156575 A1	18-06-2009
		UY 29781 A1	30-04-2007
		WO 2007030061 A1	15-03-2007
		ZA 200801511 B	26-11-2008
EP 1889622 A1	20-02-2008	EP 1889622 A1	20-02-2008
		JP WO2006129679 A1	08-01-2009
		US 2011052612 A1	03-03-2011
		WO 2006129679 A1	07-12-2006
WO 2010138487 A1	02-12-2010	AR 076922 A1	20-07-2011
		AU 2010254200 A1	08-12-2011
		CA 2763008 A1	02-12-2010
		CN 102459248 A	16-05-2012
		EP 2435426 A1	04-04-2012
		ES 2425091 T3	11-10-2013
		HK 1168349 A1	21-02-2014
		JP 2012528165 A	12-11-2012
		KR 20120087808 A	07-08-2012
		NZ 596552 A	28-02-2014
		US 2012258953 A1	11-10-2012
		WO 2010138487 A1	02-12-2010