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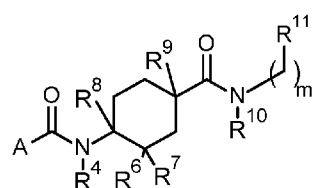
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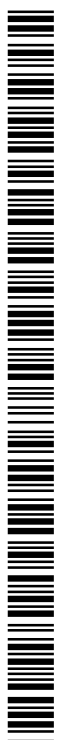
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(54) Title: AMIDO-SUBSTITUTED CYCLOHEXANE DERIVATIVES



(I)

(57) Abstract: The present invention relates to amido-substituted cyclohexane compounds of general formula (I) : in which m, A, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are as defined herein, to methods of preparing said compounds, to intermediate compounds useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of neoplasms, as a sole agent or in combination with other active ingredients.



AMIDO-SUBSTITUTED CYCLOHEXANE DERIVATIVES

The present invention relates to amido-substituted cyclohexane compounds of general formula (I) as described and defined herein, to methods of preparing said compounds, to intermediate compounds useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of neoplasms, as a sole agent or in combination with other active ingredients.

BACKGROUND OF THE INVENTION

Cancer is the leading cause of death in developed countries and the second leading cause of death in developing countries. Deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030. While substantial progress has been made in developing effective therapies, there is a need for additional therapeutic modalities that target cancer and related diseases.

The complexity of cancer disease arises after a selection process for cells with acquired functional capabilities to enhance survival and/or resistance towards apoptosis and a limitless proliferative potential. In addition, bi-direction interaction of cancer cells and stromal cells provides further advantage of cancer cell survival and distant metastasis to the secondary organs and tissues [Liotta LA, Kohn EC. *The microenvironment of the tumour-host interface. Nature 2001, 411:375*]. Furthermore, cancer stem cells (CSCs) represent the apex in the hierarchical model of tumor genesis, heterogeneity and metastasis. CSCs possess the capacity for unlimited self-renewal, the ability to give rise to progeny cells, and also an innate resistance to cytotoxic therapeutics [Meacham CE and Morrison SJ. *Tumour heterogeneity and cancer cell plasticity. Nature 2013, 501:328*]. Thus, there is need to develop drugs for cancer therapy addressing distinct features of established tumors.

The discovery that Drosophila segment polarity gene Wingless had a common origin with the murine oncogene Int-1 led to intensive studies on Wnt signaling pathway and identification of 19 mammalian Wnts and 10 Wnt receptors [Rijsewijk F, Schuermann M, Wagenaar E, Parren P, Weigel D, Nusse R. *The Drosophila homolog of the mouse mammary oncogene int-1 is identical to the segment polarity gene wingless. Cell. 1987, 50: 649*]. Wnts are secreted glycoproteins which bind to cell surface receptors to initiate signaling cascades. Wnt signaling cascades have classified into two categories: canonical and non-canonical, differentiated by their dependence on β -catenin. Non-canonical Wnt pathways, such as the planar cell polarity (PCP) and Ca^{2+} pathway, function through β -catenin independent mechanisms. Canonical Wnt signalling is initiated when a Wnt ligand engages co-receptors of the Frizzled (Fzd) and low-density lipoprotein receptor related protein (LRP) families, ultimately leading to β -catenin

- stabilization, nuclear translocation and activation of target genes [Angers S, Moon RT. Proximal events in Wnt signal transduction. *Nat Rev Mol Cell Biol.* 2009, 10: 468. Cadigan KM, Liu YI. Wnt signaling: complexity at the surface. *J Cell Sci.* 2006, 119: 395. Gordon MD, Nusse R. Wnt signaling: multiple pathways, multiple receptors, and multiple transcription factors. *J Biol Chem.* 2006, 281: 22429. Huang H, He X. Wnt/beta-catenin signaling: new (and old) players and new insights. *Curr Opin Cell Biol.* 2008, 20: 119. Polakis P. The many ways of Wnt in cancer. *Curr Opin Genet Dev.* 2007, 17: 45. Rao TP, Kuhl M. An updated overview on Wnt signaling pathways: a prelude for more. *Circ Res.* 2010, 106: 1798].
- 10 In the absence of Wnt stimulus, β -catenin is held in an inactive state by a multimeric “destruction” complex comprised of adenomatous polyposis coli (APC), Axin, glycogen synthase kinase 3 β (GSK3 β) and casein kinase 1 α (CK1 α). APC and Axin function as a scaffold, permitting GSK3 β - and CK1 α -mediated phosphorylation of critical residues within β -catenin. These phosphorylation events mark β -catenin for ubiquitination recognition by the E3
- 15 ubiquitin ligase β -transducin-repeat-containing protein and lead to subsequent proteasomal degradation [He X, Semenov M, Tamai K, Zeng X. LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: arrows point the way. *Development.* 2004, 131:1663. Kimelman D, Xu W. beta-catenin destruction complex: insights and questions from a structural perspective. *Oncogene* 2006, 25: 7482].
- 20
- In the presence of Wnt stimulus, Axin, GSK3 β and Dvl are recruited to the co-receptor complex Fzd and LRP5/6 and lead to disruption of the β -catenin destruction complex. Therefore, β -catenin is stabilized and translocated to the nucleus. Once in the nucleus, β -catenin forms a complex with members of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of
- 25 transcription factors, recruiting co-factors such as CBP, p300, TNIK, Bcl9 and Pygopus, and ultimately driving transcription of target genes including c-myc, Oct4, cyclin D, survivin. [Curtin JC and Lorenzi MV. *Drug Discovery Approaches to Target Wnt Signaling in Cancer Stem Cells.* *Oncotarget* 2010, 1: 552].
- 30 Tankyrases play a key role in the destruction complex by regulating the stability of the rate-limiting AXIN proteins, RNF146 and tankyrase itself. The E3 ubiquitin ligase RNF146 recognizes tankyrase-mediated PARsylation and eartags AXIN, tankyrase and itself for proteasome-mediated degradation. Thus, tankyrases control the protein stability and turnover of key components of the destruction complex, and consequently the cellular levels of β -catenin [Huang SMA, Mishina YM, Liu S, Cheung A, Stegmeier F, et al. Tankyrase inhibition
- 35 stabilizes axin and antagonizes Wnt signalling. *Nature* 2009, 461:614, Zhang Y, Liu S,

Mickanin C, Feng Y, Charlat O, et al. *RNF146 is a poly(ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signalling. Nature Cell Biology 2011, 13:623, 2011].*

Aberrant regulation of the Wnt/ β -catenin signaling pathway is a common feature across a broad spectrum of human cancers and evolves as a central mechanism in cancer biology. First of all, Wnt overexpression could lead to malignant transformation of mouse mammary tissue [Klaus A, Birchmeier W. *Wnt signalling and its impact on development and cancer. Nat Rev Cancer 2008, 8: 387*]. Second, tumor genome sequencing discovered the mutations in Wnt/ β -catenin pathway components as well as epigenetic mechanisms that altered the expression of genes relevant to Wnt/ β -catenin pathway [Ying Y. et al. *Epigenetic disruption of the WNT/beta-catenin signaling pathway in human cancers. Epigenetics 2009, 4:307*]. Third, Wnt/ β -catenin pathway also cooperates with other oncogenic signaling pathways in cancer and regulates tumorigenesis, growth, and metastasis [Klaus A, Birchmeier W. *Wnt signalling and its impact on development and cancer. Nat Rev Cancer 8: 387–398, 2008*]. In addition, there is an additional role of WNT signaling between tumor and stromal cell interaction leading to tumorigenesis and metastasis [Shahi P, Park D, Pond AC, Seethammagari M, Chiou S-H, Cho K, et al. *Activation of Wnt signaling by chemically induced dimerization of LRP5 disrupts cellular homeostasis. PLoS ONE 2012, 7: e30814*]. Furthermore, growing body of evidence indicates a critical role of β -catenin in CSCs [Eaves CJ, Humphries RK. *Acute myeloid leukemia and the Wnt pathway. N Engl J Med. 2010, 362: 2326*; Nusse R, Fuerer C, Ching W, Harnish K, Logan C, Zeng A, ten Berge D, Kalani Y. *Wnt signaling and stem cell control. Cold Spring Harb Symp Quant Biol. 2008, 73: 59*; Reya T, Clevers H. *Wnt signalling in stem cells and cancer. Nature 2005, 434: 843*]. For example, stem-like colon cells with a high level of β -catenin signaling have a much greater tumorigenic potential than counterpart cells with low β -catenin signaling [Vermeulen L, De Sousa EMF, van der Heijden M, Cameron K, de Jong JH, Borovski T, Tuynman JB, Todaro M, Merz C, Rodermond H, Sprick MR, Kemper K, Richel DJ, Stassi G, Medema JP. *Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. Nat Cell Biol. 2010, 12: 468*]. Finally, activation of Wnt/ β -catenin signalling pathway is also one of the major mechanism causing tumor recurrence and drug resistance. All these provide clear rationale to develop therapeutics targeting Wnt/ β -catenin signaling pathway for the treatment of cancer.

One of the approaches to inhibit Wnt/ β -catenin signaling pathway is to target druggable tankyrases. Tankyrase 1 (TNKS1) and tankyrase 2 (TNKS2) are poly(ADP-ribosyl)ases that are distinguishable from other members of the enzyme family by the structural features of the catalytic domain, and the presence of a sterile α -motif multimerization domain and an ankyrin

repeat protein-interaction domain. Inhibition of TNKS blocks PARsylation of AXIN1 and AXIN2 and prevents their proteasomal degradation. As the consequence, TNKS inhibition enhances the activity of the β -catenin destruction complex and suppresses β -catenin nuclear translocation and the expression of β -catenin target genes.

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In addition to its function in Wnt signaling through modulation of β -catenin destruction, tankyrases are also implicated in other cellular functions, including telomere homeostasis, mitotic spindle formation, vesicle transport linked to glucose metabolism, and viral replication. In these processes, tankyrases interact with target proteins, catalyze poly (ADP-ribose)ylation, and regulate protein interactions and stability. For example, TNKS1 controls telomere homeostasis, which promotes telomeric extension by PARsylation of TRF1. TRF1 is then targeted for proteasomal degradation by the E3 ubiquitin ligases F-box only protein 4 and/or RING finger LIM domain-binding protein (RLIM/RNF12), which facilitates telomere maintenance [Donigian JR and de Lange T. *The role of the poly(ADP-ribose) polymerase tankyrase1 in telomere length control by the TRF1 component of the shelterin complex. J Biol Chem* 2007, 282:22662]. In addition, telomeric end-capping also requires canonical DNA repair proteins such as DNA-dependent protein kinase (DNAPK). TNKS1 stabilizes the catalytic subunit of DNAPK (DNAPKcs) by PARsylation [Dregalla RC, Zhou J, Idate RR, Battaglia CL, Liber HL, Bailey SM. *Regulatory roles of tankyrase 1 at telomeres and in DNA repair: suppression of T-SCE and stabilization of DNA-PKcs. Aging* 2010, 2(10):691]. Altered expression of TNKS1 and/or TNKS2, as well as genetic alterations in the tankyrase locus, have been detected in multiple tumors, e.g. fibrosarcoma, ovarian cancer, glioblastoma, pancreatic adenocarcinoma, breast cancer, astrocytoma, lung cancer, gastric cancer, and colon cancer [Lehti L, Chi N-W and Krauss S. *Tankyrases as drug targets. FEBS Journal* 2013, 280: 3576]. In addition, tankyrases appear to have impact on viral infections. For example, in HSV infection, it was shown that the virus cannot replicate efficiently in cells with depletion of both TNKS1 and TNKS2 [Li Z, Yamauchi Y, Kamakura M, Murayama T, Goshima F, Kimura H, Nishiyama Y, *Herpes Simplex Virus Requires Poly(ADP-Ribose) Polymerase Activity for Efficient Replication and Induces Extracellular Signal-Related Kinase-Dependent Phosphorylation and ICP0-Dependent Nuclear Localization of Tankyrase 1. Journal of Virology* 2012, 86(1): 492].

Furthermore, a connection between tankyrases and glucose metabolism has been indicated. Thus, DNA polymorphism in a chromosomal region encoding tankyrase/methionine sulfoxide reductase A is robustly associated with early-onset obesity. TNKS1 knockout mice appeared to

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have reduced fat pads, suggesting a potential connection of TNKS and obesity. TNKS may also play a role in tissue fibrosis.

In summary, tankyrases are promising drug targets in regulating WNT signaling, telomere length (e.g. telomere shortening and DNA damage induced cell death), lung fibrogenesis, myelination and viral infection. The invention presented here describes a novel class of tankyrase inhibitors and their potential clinical utility for the treatment of various diseases, such as cancer, aging, metabolic diseases (e.g. diabetes and obesity), fibrosis (e.g. lung fibrogenesis) and viral infection.

The following list of selected references relates to inhibitors of TNKS1 and/or TNKS2 described in the literature or in patents. However, the chemical structures and compound classes of the inhibitors described in these references are completely different from the chemical structures of the present invention:

Cancer Research 2013, 73 (10): 3132; J Med Chem 2013, 56 (16): 6495; J Med Chem 2013, 56(3): 1341; J Med Chem 2013, 56(17): 7049; J Med Chem 2013, 56(24): 10003; J Med Chem 2013, 56(7): 3012; J Med Chem 2013, 56(20): 7880; J Med Chem 2013, 56(11): 4320; ChemMedChem 2013, 8(12): 1978; ACS Med Chem Lett 2013, 4(12): 1173; ACS Med Chem Lett 2013, 4(12): 1218; Acta Crystallogr Sect F Struct Biol Cryst Commun 2012, 68(Part 2): 115; J Med Chem 2012, 55(3): 1360; WO 2009059994, WO2013164061, WO2014023390, WO 2012076898, WO 2013093508, WO 2013010092, WO 2013189905, WO 2013189865, WO 2013177349, WO 2013012723, WO 2013134079, WO 2013182546, ACS Med Chem Lett, 2014, 6(3): 254, WO 2015150449, WO2017/055313, WO2017/055316.

WO2016/177658 discloses amido-substituted cyclohexane derivatives which inhibit TNKS 1 and/or TNKS 2 and that may be useful for the treatment of disorders mediated by TNKS1 and/or TNKS2.

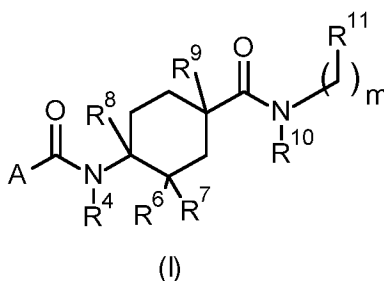
However, the state of the art described above does not describe the specific substituted cyclohexane compounds of general formula (I) of the present invention.

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

In particular, said compounds of the present invention have surprisingly been found to effectively inhibit TNKS1 and/or TNKS2 and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses mediated by TNKS1 and/or TNKS2 and/or mediated by the Wnt pathway, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof. Compounds of the present invention may additionally show improved selectivity for TNKS1 and/or TNKS2 (e.g. over other PARP (poly(ADP-ribose)-polymerase) enzymes), for the treatment of TNKS1 and/or TNKS2 driven diseases, by reaching sufficient efficacious dose without inducing toxicity driven by, for example, other PARPs inhibition.

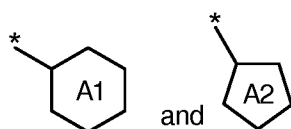
DESCRIPTION of the INVENTION

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

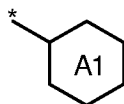


in which,

A represents a ring group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

5 said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

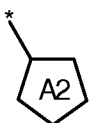
- 10 a) a phenyl ring,
 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and
 c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

15 wherein said rings are fused with ring A1,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or,

20 whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from $(C=O)$, NR^{20} , O, S, $S(=O)$ and $S(=O)_2$;



25 ring A2 represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or

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- a 5-membered heterocyclic ring, optionally partially unsaturated, which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two carbon atoms of the heterocyclic ring are optionally replaced by a heteroatom-containing group selected from (C=O), N, NR²⁰, O, S, S(=O) and S(=O)₂;

5

said 5-membered heteroaryl and 5-membered heterocyclic rings being optionally substituted one, two or three times, independently from each other, with R⁵,

whereby two substituents R⁵ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

10

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one ring carbon atom is optionally further replaced by a nitrogen atom,

15

wherein said rings are fused with ring A2,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R⁵;

or

20

whereby two substituents R⁵ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethylenedioxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR²⁰, O, S, S(=O) and S(=O)₂;

25

R⁴ represents a hydrogen atom,

R⁵ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

30

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, OR¹³;

R⁵ represents, independently of each other, a group selected from :

9

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

5 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, OR¹³;

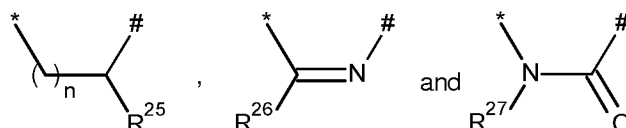
R⁶ represents hydrogen, halogen, hydroxy, C₁-C₃-alkyl or C₁-C₃-alkoxy;

R⁷ represents hydrogen; or

R⁶, R⁷ represent, independently of each other, halogen;

10 R⁸ represents hydrogen, or C₁-C₃-alkyl, and

R⁹ and R¹⁰ together represent a group selected from:



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

15 and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰;

R¹¹ represents a group selected from :

aryl, and heteroaryl,

wherein aryl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

20 C₁-C₆-alkyl, C₁-C₃-alkoxy, C₁-C₃-hydroxyalkyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, nitro, hydroxy, (C₁-C₆-alkyl)-S-, (C₁-C₆-alkyl)-S(=O)-, (C₁-C₆-alkyl)-S(=O)₂-, -S(=O)(=NR²¹)R²², -N(R¹⁴)R¹⁵, R¹⁴(R¹⁵)N-(C₁-C₆-alkyl)-, R¹⁴(R¹⁵)N-(C₂-C₆-alkoxy)-, phenyl, phenoxy, -N(R¹⁶)C(=O)R¹⁷, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

25 whereby two substituents of said aryl group, when they are in ortho-position to one another, can be linked to one another in such a way that they jointly form methanediylbisoxo, ethane-1,2-diylbisoxo, propane-1,3-diyl, or butane-1,4-diyl,

R¹³ represents a group selected from :

C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-hydroxyalkyl-, and (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)-,

30 R¹⁴ and R¹⁵ are, independently of each other, selected from :

10

hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₆-alkyl)-, C₂-C₆-hydroxyalkyl, (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)-, (C₁-C₃-haloalkoxy)-(C₂-C₆-alkyl)-, C₁-C₆-haloalkyl, H₂N-(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)N(H)(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)₂N(C₂-C₆-alkyl)-, HOC(=O)-(C₁-C₆-alkyl)-, R¹³OC(=O)-(C₁-C₆-alkyl)-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl, heteroaryl, aryl-(C₁-C₆-alkyl)-, and heteroaryl-(C₁-C₆-alkyl)-,

wherein 4- to 6-membered heterocycloalkyl groups are optionally substituted with one, two, three or four substituents, which are independently of each other selected from :

C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -NH₂, -NH(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)₂, hydroxy, a halogen atom, and cyano,

and,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

or,

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, O, S, S(=O) and S(=O)₂, and in which one additional ring atom is optionally replaced by C(=O),

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from:

C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

whereby when two substituents are attached to the same ring carbon atom, together with the carbon atom to which they are attached, can be linked to one another in such a way that they jointly form a cyclobutane, cyclopentane, azetidine, pyrrolidine, oxetane, tetrahydrofuran, thietane, tetrahydrothiophene, thietane 1-oxide, tetrahydrothiophene 1-oxide, thietane 1,1-dioxide or tetrahydrothiophene 1,1-dioxide group;

R¹⁶ represents, independently of each other, hydrogen, or C₁-C₃-alkyl,

11

R¹⁷ represents hydrogen, C₁-C₆-alkyl, C₁-C₆-hydroxyalkyl, C₃-C₆-cycloalkyl, C₁-C₆-haloalkyl, (C₁-C₃-alkoxy)-(C₁-C₆-alkyl)-, aryl, or heteroaryl,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from:

5 C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, and hydroxy,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₃-C₄-cycloalkyl, -C(=O)C₁-C₄-alkyl, -C(=O)OC₁-C₄-alkyl and phenyl,

10 R²¹ represents hydrogen, cyano, (C₁-C₃-alkyl)-C(=O)-, or (C₁-C₃-haloalkyl)-C(=O)-,

R²² represents C₁-C₄-alkyl, or C₃-C₄-cycloalkyl,

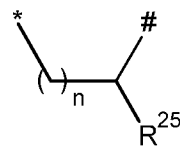
R²⁵ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-,

15 R²⁶ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-,

R²⁷ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-,

n is 1 or 2,

m is 0, 1 or 2,



20 with the proviso that when R⁹ and R¹⁰ together represent a group or 2,

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

25 Definitions

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent.

When any variable occurs more than one time in any compound of general formula (I) as described herein, each definition is independent. For example, when R⁵, R^{5'}, R^{5a}, R^{5b}, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R²⁰, R²¹, and/or R²² occur more than one time in any compound of formula (I) each definition of R⁵, R^{5'}, R^{5a}, R^{5b}, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R²⁰, R²¹, and R²² is independent.

A hyphen at the beginning or at the end of the constituent marks the point of attachment to the rest of the molecule. Should a ring be substituted the substituent could be at any suitable position of the ring, also on a ring nitrogen atom if suitable.

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

The term “comprising” when used in the specification includes “consisting of”.

If it is referred to “as mentioned above” or “mentioned above” “as mentioned supra” , “as described supra” within the description it is referred to any of the disclosures made within the specification in any of the preceding pages.

If it is referred to “as mentioned herein”, “as described herein”, “as defined herein”, “as provided herein” or “as stated herein” within the description it is referred to any of the disclosures made within the specification in any of the preceding or subsequent pages.

The term “halogen”, “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

25

The term “C₁-C₆-alkyl” is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5, or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-

13

methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C₁-C₄-alkyl"), *e.g.* a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms ("C₁-C₃-alkyl"), *e.g.* a methyl, ethyl, n-propyl- or iso-propyl group, more particularly 1 or 2 carbon atoms ("C₁-C₂-alkyl"), *e.g.* a methyl, ethyl group, even more particularly 1 carbon atom ("C₁-alkyl"), a methyl group.

The term "C₁-C₆-hydroxyalkyl" is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C₁-C₆-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a hydroxy group, *e.g.* a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 1,3-dihydroxypropan-2-yl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl group.

15

The term "C₁-C₆-haloalkyl" is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C₁-C₆-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in identically or differently, *i.e.* one halogen atom being independent from another. Particularly, said halogen atom is F. Said C₁-C₆-haloalkyl group is, for example, -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, or -CH₂CH₂CF₃.

20

The term "C₁-C₄-alkoxy" is to be understood as meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula -O-alkyl having 1, 2, 3, or 4 carbon atoms, in which the term "alkyl" is defined *supra*, *e.g.* a methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, or tert-butoxy, or an isomer thereof.

25

The term "C₁-C₄-haloalkoxy" is to be understood as meaning a linear or branched, saturated, monovalent C₁-C₄-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said C₁-C₄-haloalkoxy group is, for example, -OCF₃, -OCHF₂, -OCH₂F, -OCF₂CF₃, or -OCH₂CF₃.

30

The term "C₃-C₆-cycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms ("C₃-C₆-cycloalkyl"). Said C₃-C₆-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring.

The term "C₃-C₆-cycloalkoxy" is to be understood as meaning a saturated, monovalent, hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms of formula -O-cycloalkyl, in which the term "cycloalkyl" is defined *supra*, *e.g.* a cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy.

Unless stated otherwise, the terms "4- to 7-membered heterocycloalkyl" and "4- to 6-membered heterocycloalkyl", are to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring with 4 to 7 or, respectively, 4 to 6 ring atoms in total, and which contains a heteroatom-containing group selected from N, NR²⁰, O, S, S(=O) and S(=O)₂, wherein:

- one ring carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, O, S, S(=O) and S(=O)₂, in which R²⁰ represents a hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₃-C₄-cycloalkyl, -C(=O)C₁-C₄-alkyl, -C(=O)OC₁-C₄-alkyl and phenyl, and

- one additional ring carbon atom is optionally replaced by C(=O);

it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom.

The term "heteroatom-containing group" as defined herein is to be understood as meaning a group containing a heteroatom, such as NR²⁰, S(=O) and S(=O)₂, and/or a heteroatom such as N, O and S, wherein R²⁰ is as defined herein.

Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidiny, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxoliny, pyrrolidiny, imidazolidiny, pyrazolidiny, or a 6-membered ring, such as tetrahydropyranyl, piperidiny, morpholiny, dithianyl, thiomorpholiny, piperaziny, or N-methylpiperaziny. Optionally, said heterocycloalkyl can be benzo fused. Particularly, without being limited thereto, 4- to 6-membered heterocycloalkyl can be selected from piperaziny, tetrahydro-2H-pyranyl, tetrahydrofuranyl, pyrrolidiny, piperidiny, morpholiny, azetidiny, 2-oxoimidazolidiny,

15

2-oxopyrrolidinyl and 1,1-dioxidothiomorpholinyl. More particularly, without being limited thereto, 4- to 6-membered heterocycloalkyl can be selected from piperazin-1-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-4-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, morpholin-4-yl, azetidin-1-yl, tetrahydrofuran-2-yl, 2-oxoimidazolidin-1-yl, 2-oxopyrrolidin-1-yl and 1,1-dioxidothiomorpholin-4-yl.

In certain embodiments, R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4-to 7- membered heterocycloalkyl group, in which one ring carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, O, S, S(=O) and S(=O)₂, and one additional ring carbon atom is optionally replaced by C(=O),

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

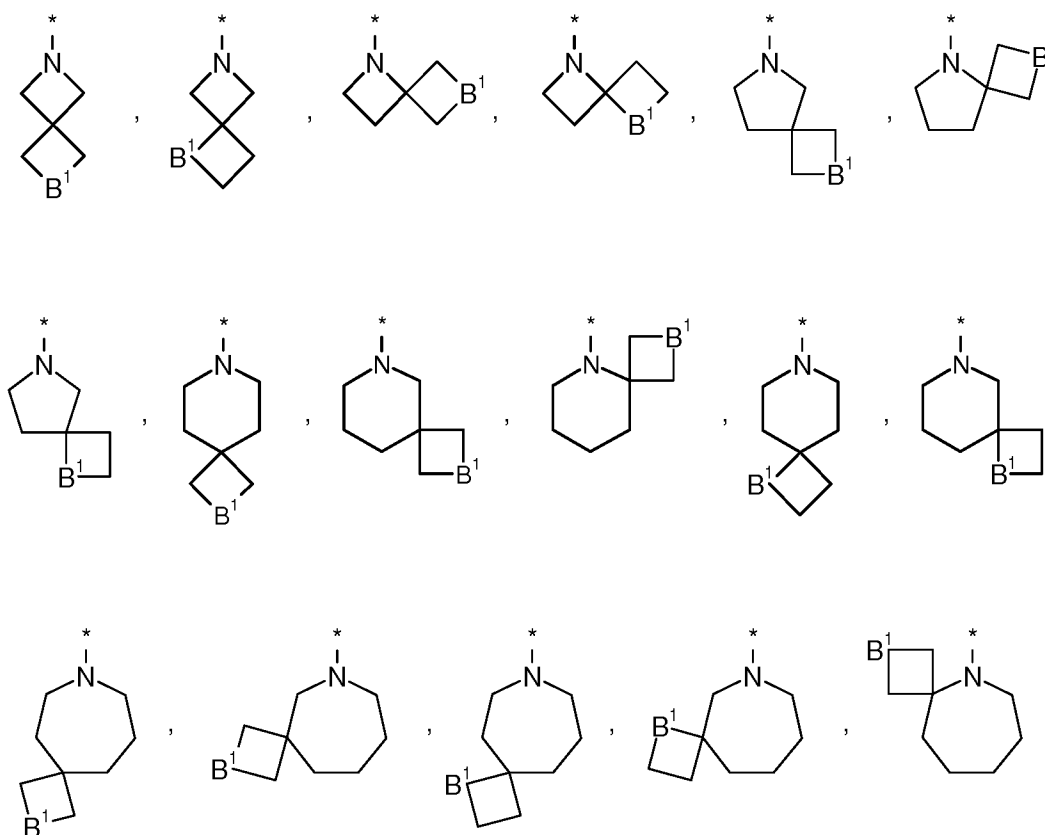
C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, N(H)₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

whereby when two substituents are attached to the same ring carbon atom, together with the carbon atom to which they are attached, can be linked to one another in such a way that they jointly form a cyclobutanyl, cyclopentanyl, azetidine, pyrrolidine, oxetane, tetrahydrofuran, thietane, tetrahydrothiophene, thietane 1-oxide, tetrahydrothiophene 1-oxide, thietane 1,1-dioxide or tetrahydrothiophene 1,1-dioxide group;

20

Particularly, without being limited thereto, when two substituents are attached to the same ring carbon atom of said 4- to 7-membered heterocycloalkyl group, together with the carbon atom to which they are attached, can be linked to one another in such a way that they jointly form groups according to the present invention such as the ones represented below:

16



wherein:

* indicates the point of attachment of said group with the rest of the molecule, and

B¹ represents CH₂, -CH₂CH₂-, NH, -CH₂-NH-, N(C₁-C₃-alkyl), -CH₂-N(C₁-C₃-alkyl), N(C₁-C₃-
 5 haloalkyl), -CH₂-N(C₁-C₃-haloalkyl)-, O, -CH₂-O-, S, -CH₂-S-, S(O), -CH₂-S(O)-, S(O)₂, or -CH₂-
 S(O)₂-.

The present invention includes all R¹⁴, R¹⁵ groups described *supra*.

Unless defined otherwise, the term “aryl” is to be understood as meaning a monovalent,
 10 aromatic or partially aromatic, mono- or bicyclic hydrocarbon ring having 6, 7, 8, 9 or 10 carbon
 atoms (a “C₆-C₁₀-aryl” group), particularly a ring having 6 carbon atoms (a “C₆-aryl” group), *e.g.*
 a phenyl group; or a ring having 9 carbon atoms (a “C₉-aryl” group), *e.g.* an indanyl or indenyl
 group, or a ring having 10 carbon atoms (a “C₁₀-aryl” group), *e.g.* a tetralinyl, dihydronaphthyl,
 or naphthyl group.

Unless, defined otherwise, the term "heteroaryl" is understood as meaning a monovalent, monocyclic aromatic ring system having 5 or 6 ring atoms (a "5- to 6-membered heteroaryl" group), which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen, NH or sulfur. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl *etc.*, or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.* More particularly, without being limited thereto, heteroaryl can be selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thienyl, and furanyl. Even more particularly, without being limited thereto, heteroaryl can be selected from oxazolylimidazolyl, pyrazolyl, pyridinyl, pyridazinyl, pyrimidinyl and thiazolyl.

In general, and unless otherwise mentioned, the heteroaryl or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridinyl or pyridinylene includes pyridin-2-yl, pyridin-2-ylen, pyridin-3-yl, pyridin-3-ylen, pyridin-4-yl and pyridin-4-ylen; or the term thienyl or thienylene includes thien-2-yl, thien-2-ylen, thien-3-yl and thien-3-ylen.

In general, and unless otherwise mentioned, the heteroaryl radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridinyl includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

In general, and unless otherwise mentioned, aromatic and non-aromatic (hetero)cyclic groups, may optionally be substituted as defined herein. The substituents may be present both when said aromatic and non-aromatic (hetero)cyclic groups exist as a (unitary) constituent, such as, for example, C₃-C₆-cycloalkyl, 4- to 6-membered heterocycloalkyl, aryl and heteroaryl groups, or as part of a constituent composed of more than one part, such as, for example, (C₃-C₆-cycloalkyl)-C₁-C₆-alkyl-, (4- to 6-membered heterocycloalkyl)-(C₂-C₆-alkyl)-, aryl-(C₁-C₆-alkyl)-, and heteroaryl-(C₁-C₆-alkyl)-, for example. The present invention includes all suitably substituted aromatic and non-aromatic (hetero)cyclic groups both as a (unitary) constituent, or as part of a constituent composed of more than one part.

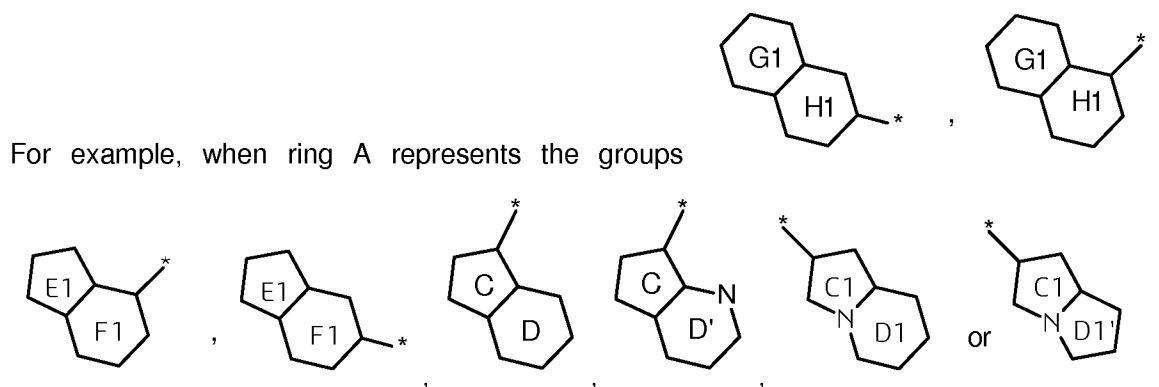
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In the context of the present invention “suitably” is to be understood as meaning chemically possible to be made by methods within the knowledge of a skilled person.

According to the present invention ring A is a mono or bicyclic ring as defined herein, in which
 5 ring A is connected to the rest of the compound of formula (I) via a carbon atom the ring.

According to certain embodiments ring A represents a bicyclic aromatic ring. Unless defined otherwise, the total count of nitrogen atoms on each member of the bicyclic system includes any nitrogen atoms which are shared by both rings.

10



wherein * indicates the point of attachment of said group with the rest of the molecule, said point of attachment being a carbon atom of the ring, and rings G1, H1, E1, F1, C, D, D', C1, D1, D1' being as defined herein, the total count of nitrogen atoms on each member of the bicyclic system includes any nitrogen atoms which are shared by both rings.
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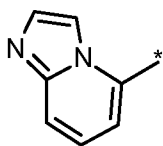
According to certain embodiments ring A represents a 6-membered heteroaryl ring which contains one or two nitrogen atoms, said 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,
 20

whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

- a) a phenyl ring,
- 25 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

19

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms. It is understood that in such embodiments, if suitable, a nitrogen atom of ring A may be shared between the fused rings, such as, for example, in:



5

According to certain embodiments ring A contains at least one NH heteroatom. It is understood that in such embodiments, if suitable, a substituent R⁵ or R^{5'} may replace the hydrogen atom in said NH group, including to form a ring with an adjacent R⁵ or R^{5'} substituent, as defined herein.

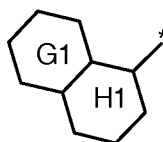
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More specifically, according to certain embodiments ring A represents:

- a 5-membered heteroaryl ring which contains one NH, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or
- 15 - a 5-membered heterocyclic ring, optionally partially unsaturated, which contains one NH group, in which one or two carbon atoms of the heterocycl ring are optionally replaced by a heteroatom-containing group selected from (C=O), N, NR²⁰, O and S,

said 5-membered heteroaryl and 5-membered heterocyclic rings being optionally substituted one, two or three times, independently from each other, with R^{5'}.

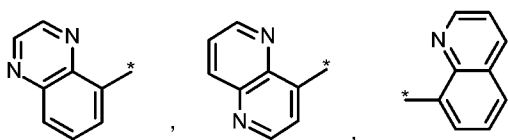
- 20 It is understood that in such embodiments, if suitable, a substituent R^{5'} may replace the hydrogen atom in the NH group, including to form a ring with an adjacent R^{5'} substituent, as defined herein.



Particularly, without being limited thereto, groups
25 invention can be as represented below:

according to the present

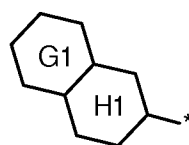
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wherein:

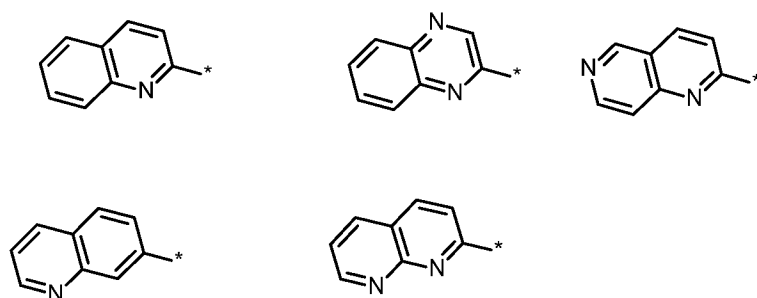
- * indicates the point of attachment of said group with the rest of the molecule, said groups being optionally substituted independently with one or two R^5 groups, and

5 - R^5 is as defined herein.



Particularly, without being limited thereto, groups according to the present invention can be as represented below:

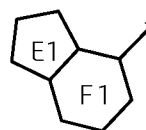
according to the present



- * indicates the point of attachment of said group with the rest of the molecule, said groups being optionally substituted independently with one or two R^5 groups, and

10

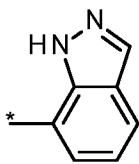
- R^5 is as defined herein.



Particularly, without being limited thereto, groups according to the present invention can be as represented below:

according to the present

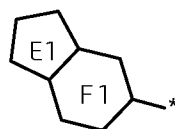
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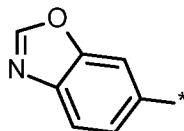
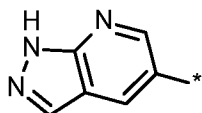
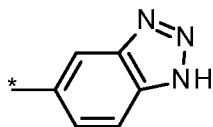
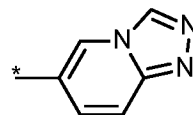
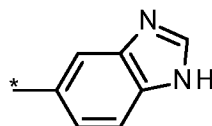
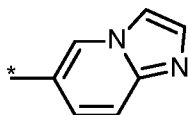
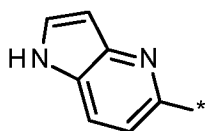
- * indicates the point of attachment of said group with the rest of the molecule, said group being optionally substituted independently with one or two R^5 groups, and

- R^5 is as defined herein.

5 Particularly, without being limited thereto, groups

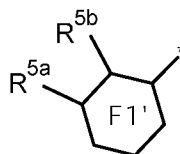


according to the present invention can be as represented below:



- * indicates the point of attachment of said group with the rest of the molecule, said group being optionally substituted independently with one or two R^5 groups, and

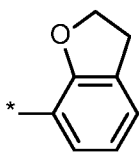
10 - R^5 is as defined herein.



Particularly, without being limited thereto, groups

according to the present invention can be as represented below:

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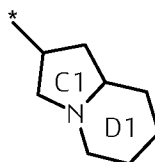


- * indicates the point of attachment of said group with the rest of the molecule,

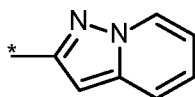
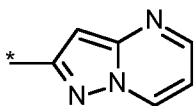
said ring F1' being optionally substituted one time with a group selected from :

5 fluorine, chlorine, bromine, hydroxy, C₁-C₄-alkyl, C₃-cycloalkyl, C₁-alkoxy, -NH₂, and - C(O)OR¹³,

wherein C₁-C₄-alkyl is optionally substituted one or two times with a group independently selected from fluorine, oxo (C=O), and -NH(C₁-alkyl).



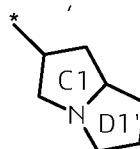
10 Particularly, without being limited thereto, groups according to the present invention can be as represented below:



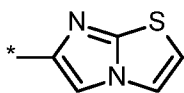
- * indicates the point of attachment of said group with the rest of the molecule, ring D1 being optionally substituted independently with one or two R^{5'} groups, and

- R^{5'} is as defined herein.

15



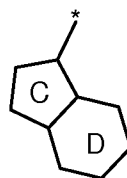
Particularly, without being limited thereto, groups according to the present invention can be as represented below:



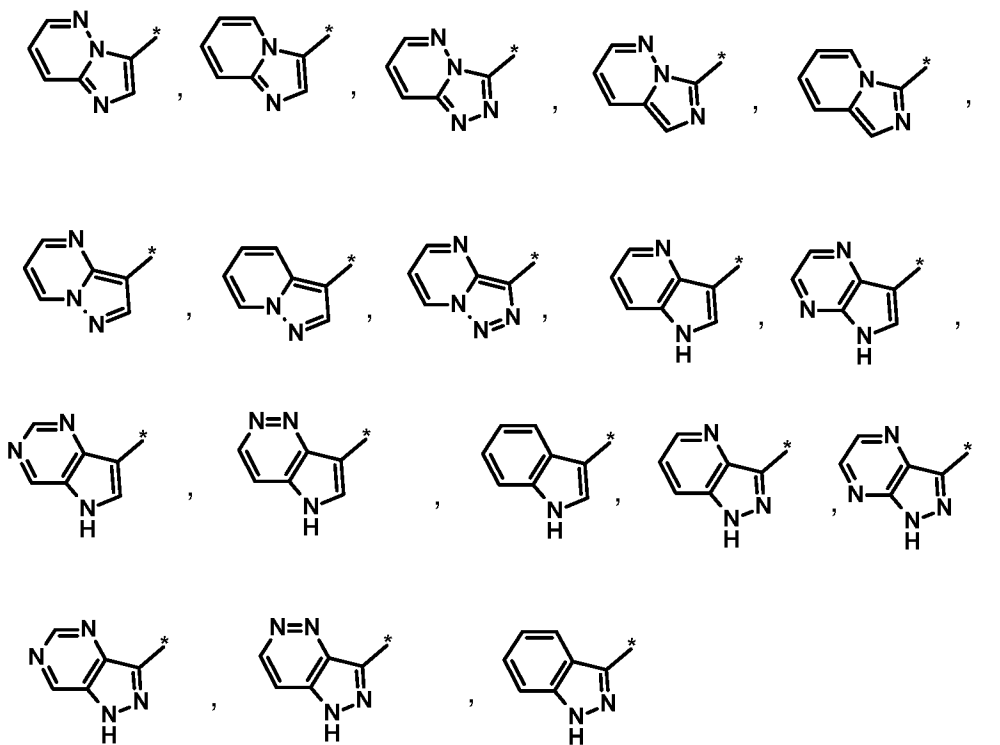
- * indicates the point of attachment of said group with the rest of the molecule, ring D1' being optionally substituted independently with one R^5 groups, and

- R^5 is as defined herein.

5



Particularly, without being limited thereto, groups according to the present invention can be as represented below:



wherein:

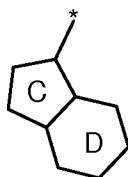
- * indicates the point of attachment of said group with the rest of the molecule, said point of attachment being a carbon atom of ring C;

- ring C is optionally substituted with one or two R^5 groups,

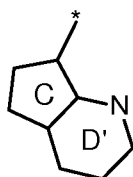
- when NH is present in ring C, the nitrogen atom is optionally substituted with C_1 - C_3 -alkyl,

24

- ring D is optionally substituted with one, two or three R^{12} groups, and
- $R^{5'}$ and R^{12} are as defined herein.



When said group represents, for example:



5

- * indicates the point of attachment of said group with the rest of the molecule, said point of attachment being a carbon atom of ring C;
- ring C represents a 5-membered heteroaryl group which contains one heteroatom-containing group selected from N, NH, and $N(C_1-C_3\text{-alkyl})$, in which one or two carbon atoms are optionally further replaced by one or two nitrogen atoms, said ring C being optionally substituted with one or two $R^{5'}$ groups,
- ring D' represents a 6-membered heteroaryl group which contains one N atom in the position shown, in which one carbon atom is optionally further replaced by a N atom, said ring D being optionally substituted with one, two or three R^{12} groups, and
- $R^{5'}$ and R^{12} are as defined herein.

15

The present invention includes all ring A groups described *supra*, including, but not limited to the ones depicted *supra*.

20

The term " C_1-C_6 ", as used throughout this text, *e.g.* in the context of the definition of " C_1-C_6 -alkyl", " C_1-C_6 -haloalkyl", or " C_1-C_6 -hydroxyalkyl" is to be understood as meaning 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. It is to be understood further that said term " C_1-C_6 " is to be interpreted as any sub-range comprised

therein, *e.g.* C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅; particularly C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more particularly C₁-C₄; in the case of "C₁-C₆-haloalkyl" or "C₁-C₆-haloalkoxy" even more particularly C₁-C₂.

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

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

- The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency
- 20 under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

- The term "optionally substituted" means optional substitution with the specified groups,
- 25 radicals or moieties.

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

As used herein, the term "one or more", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five, particularly one, two, three or four, more particularly one, two or three, even more particularly one or two".

5

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be
10 incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{125}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^3H or ^{14}C are incorporated,
15 are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence is preferred in some circumstances. Isotopic variations of a
20 compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the
25 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
30 efficacious therapeutic agent.

The compounds of this invention optionally contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms is present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric centre, and diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

The compounds of the present invention optionally contain sulphur atoms which are asymmetric, such as an asymmetric sulfoxide, of structure:



in which * indicates atoms to which the rest of the molecule can be bound.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention.

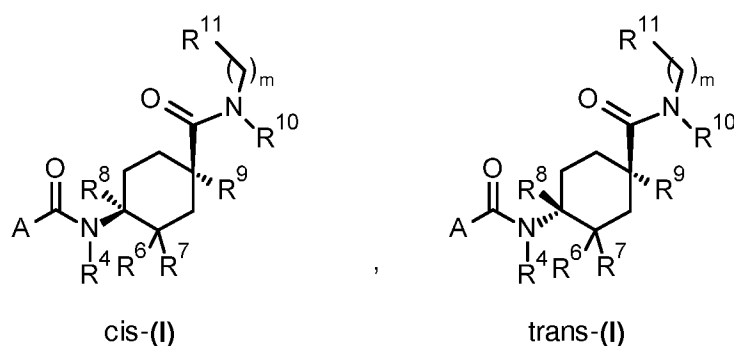
- 15 Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.
- 20 The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their
- 25 physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers.
- 30 Suitable chiral HPLC columns are manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without

derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

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

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* R- or S-isomers, E- or Z-isomers, or cis or trans, in any ratio. Isolation of a single stereoisomer, *e.g.* a
 10 single enantiomer or a single diastereomer, of a compound of the present invention is achieved by the methods provided herein or by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

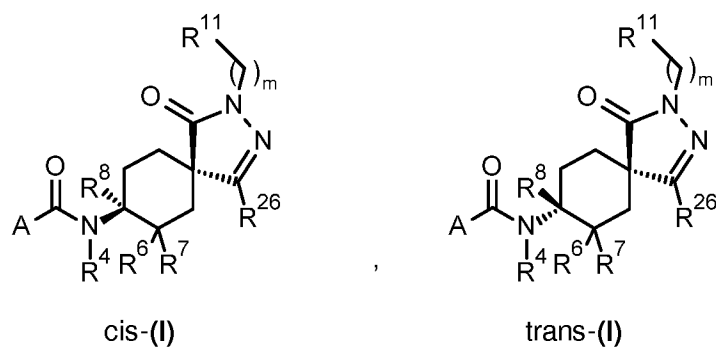
Particularly, the relative configuration of the amino substituent (NR⁴) relative to the carbonyl
 15 group on the central cyclohexane ring can be depicted as follows:



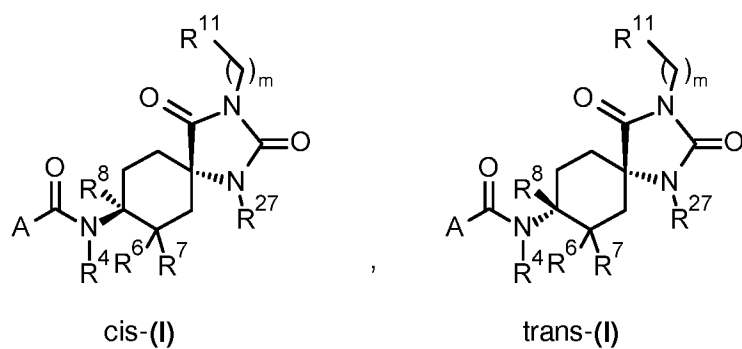
wherein m, ring A, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ are as defined herein for the compound of formula (I)

20 More specifically, for the following embodiments the relative configuration of the amino substituent (NR⁴) relative to the carbonyl group on the central cyclohexane ring can be depicted as follows:

29

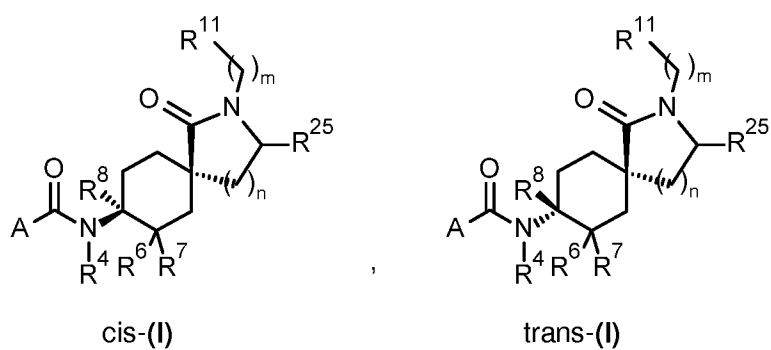


wherein m, ring A, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R²⁶ are as defined herein for the compound of formula (I);



5 wherein m, ring A, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R²⁷ are as defined herein for the compound of formula (I);

and



wherein n, ring A, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R²⁵ are as defined herein for the compound of
10 formula (I) and m is 1 or 2, preferably 1.

30

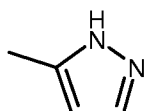
With respect to the cyclohexane ring, the relative configuration of the amino (NR^4) and carbonyl group substituents on said cyclohexane ring is to be understood as follows:

- the term “cis” is to be understood as the relative configuration in which said amino (NR^4) and carbonyl groups are on the same side of the cyclohexane ring (irrespective of substituents R^8 and R^9).

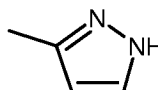
- the term “trans” is to be understood as the relative configuration in which said amino (NR^4) and carbonyl groups are on the opposite side of the cyclohexane ring (irrespective of substituents R^8 and R^9).

The present invention includes all cis and trans isomers of the compounds of the present invention as single isomers, or as any mixture of said isomers, in any ratio.

Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, namely :

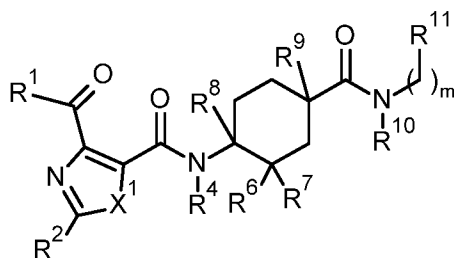


1H-tautomer

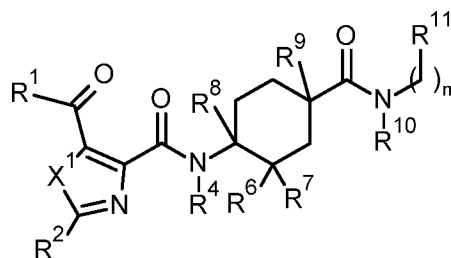


2H-tautomer

Particularly, when X^1 represents NR^3 , wherein R^3 represents a hydrogen atom, the present invention can exist as one of the below tautomers, or even in a mixture in any amount of the two tautomers, namely:



(I)



(II)

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

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

- 5 The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

10 The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may 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
15 includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable
20 organic or inorganic addition salt, customarily used in pharmacy.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, 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.

25 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, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic,
30 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, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methanesulfonic, 2-
35 naphthalenesulfonic, naphthalenedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic,

oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, 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 or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may 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 invention are prepared by reacting the compounds of the 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 such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF₃COOH", "x Na⁺", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.

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

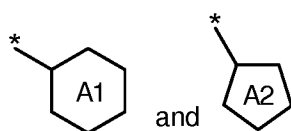
As used herein, the term “*in vivo* hydrolysable ester” is understood as meaning an *in vivo* hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C₁-C₆ alkoxyethyl esters, *e.g.* methoxyethyl, C₁-C₆ alkanoyloxyethyl esters, *e.g.* pivaloyloxyethyl, phthalidyl esters, C₃-C₈ cycloalkoxy-carbonyloxy-C₁-C₆ alkyl esters, *e.g.* 1-cyclohexylcarbonyloxyethyl ; 1,3-dioxolen-2-onylmethyl esters, *e.g.* 5-methyl-1,3-dioxolen-2-onylmethyl ; and C₁-C₆-alkoxycarbonyloxyethyl esters, *e.g.* 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this 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 [alpha]-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 [alpha]-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 benzoyl and phenylacetyl, alkoxy-carbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

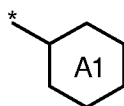
Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

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

A represents a group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

5 whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

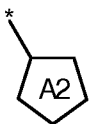
10 c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

15 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or,

20 whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;



ring A2 represents:

25 - a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

5 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,

wherein said rings are fused with ring A2,

10 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with $R^{5'}$;

or

15 whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;

R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :

20 halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, and -N(R^{14}) R^{15} ,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , and OR¹³;

25 $R^{5'}$ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R^{14}) R^{15} , phenyl and a 6-membered heteroaryl which contains one or two nitrogen atoms,

30 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , and OR¹³;

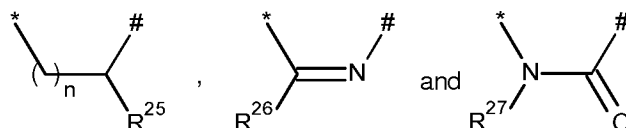
R^6 represents hydrogen;

36

R⁷ represents hydrogen;

R⁸ represents hydrogen,

R⁹ and R¹⁰ together represent a group selected from:



5 wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

R¹¹ represents a group selected from :

10 phenyl, and heteroaryl ,

wherein phenyl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-C₄-alkyl, C₁-C₂-alkoxy, C₁-C₃-hydroxyalkyl, C₃-C₄-cycloalkyl, C₁-C₂-haloalkoxy, halogen, cyano, and hydroxy,

15 R¹³ represents a group selected from :

C₁-C₃-alkyl, and C₃-C₄-cycloalkyl,

R¹⁴ and R¹⁵ are independently of each other selected from :

hydrogen, C₁-C₄-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₃-alkyl)-, C₂-C₃-hydroxyalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)-, (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-, and C₁-C₃-haloalkyl,

20

or,

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, and O, and in which one additional ring atom is optionally replaced by C(=O),

25

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-alkyl, C₁-haloalkyl, C₁-alkoxy, C₁-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

37

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl, and C₃-C₄-cycloalkyl,

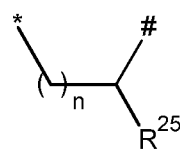
R²⁵ represents hydrogen, or C₁-C₃-alkyl,

R²⁶ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-

R²⁷ represents hydrogen,

n is 1 or 2,

m is 0, or 1,

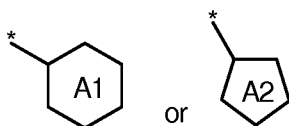


with the proviso that when R⁹ and R¹⁰ together represent a group 1,

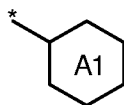
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

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

A represents a group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,

38

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

5 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

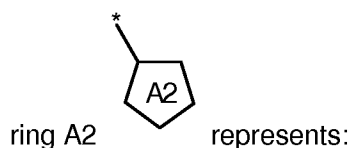
c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, and NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

10 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

or,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a ethyleneoxy, or
15 trimethyleneoxy;



- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

20 said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

25 a) a phenyl ring, or

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

wherein said rings are fused with ring A2,

said phenyl, and 6-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

30 R^4 represents a hydrogen atom,

39

R⁵ represents, independently of each other, a group selected from :

halogen, C₁-alkyl, and C₁-alkoxy,

R^{5'} represents C₁-alkyl,

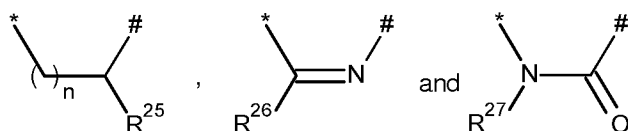
wherein C₁-alkyl is optionally substituted one, or two times with a group independently selected from oxo (C=O), and -N(R¹⁴)R¹⁵,

R⁶ represents hydrogen;

R⁷ represents hydrogen;

R⁸ represents hydrogen,

R⁹ and R¹⁰ together represent a group selected from:



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

R¹¹ represents a group selected from :

phenyl, and pyridinyl ,

wherein phenyl and pyridinyl groups are optionally substituted with one, two, or three groups, which are independently of each other selected from :

fluorine, and chlorine,

R¹³ represents a group C₁-C₃-alkyl,

R¹⁴ and R¹⁵ are independently of each other selected from :

hydrogen, C₁-C₃-alkyl, C₃-cycloalkyl, (C₁-alkoxy)-(C₂-alkyl)-, (C₁-haloalkoxy)-(C₂-alkyl)-, and C₂-haloalkyl,

or,

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰,

said 4- to 6-membered heterocycloalkyl group being optionally substituted with one, or two groups, which are independently of each other selected from :

C₁-alkyl, and a halogen atom, preferably fluorine ,

40

R²⁰ represents, independently of each other, a group selected from :

hydrogen, and C₁-alkyl,

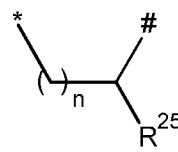
R²⁵ represents hydrogen, or C₁-alkyl,

R²⁶ represents hydrogen, C₁-C₂-alkyl, or (C₁-alkoxy)-(C₁-alkyl)-,

5 R²⁷ represents hydrogen,

n is 1,

m is 0, or 1,

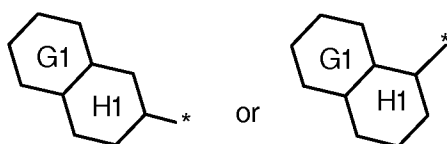


with the proviso that when R⁹ and R¹⁰ together represent a group , then m is 1,

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

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

15 ring A represents:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

ring G1 represents a phenyl or a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

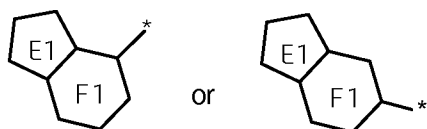
20 ring H1 represents phenyl or a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

with the proviso that when G1 or H1 is phenyl, then the other is a 6-membered heteroaryl group which contains one or two nitrogen atoms,

said ring G1 and ring H1 being optionally substituted independently with one or two R⁵ groups.

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



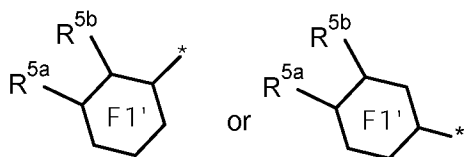
ring A represents: wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

- 5 ring F1 represents phenyl or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

ring E1 represents a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or

- 10 said ring E1 and ring F1 being optionally substituted independently with one or two R⁵ groups.

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



ring A represents: wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

- 15 ring F1' represents phenyl or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

R^{5a} and R^{5b} are linked to one another in such a way that they jointly form a ethyleneoxy, or a trimethyleneoxy group,

- 20 said ring F1' being optionally substituted one time with a group selected from :

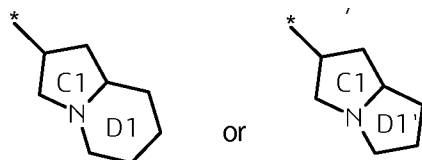
fluorine, chlorine, bromine, hydroxy, C₁-C₄-alkyl, C₃-cycloalkyl, C₁-alkoxy, -NH₂, and -C(O)OR¹³,

wherein C₁-C₄-alkyl is optionally substituted one or two times with a group independently selected from fluorine, oxo (C=O), and -NH(C₁-alkyl).

25

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

42



ring A represents:

wherein * indicates the point of

attachment of said groups with the rest of the molecule, and in which :

ring C1 represents a 5-membered heteroaryl ring in which one or two ring carbon atoms are optionally further replaced by a heteroatom selected from N, NR²⁰, O and S,

5 ring D1 is a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

ring D1' is a 5-membered heteroaryl ring in which one ring carbon atom is optionally further replaced by a heteroatom selected from N, NR²⁰, O and S,

said rings D1 and D1' being optionally substituted independently with one or two R^{5'} groups.

10

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

ring A represents a group selected from:

phenyl, pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl,

15 said groups being optionally substituted independently with one or two R⁵ groups.

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

ring A represents a group selected from:

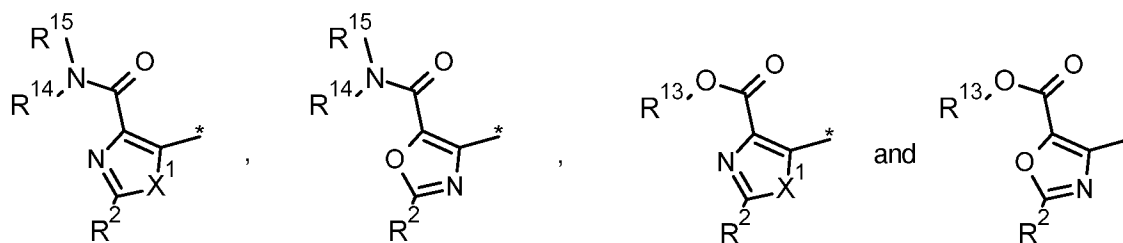
20 imidazolyl, pyrazolyl, 1,3-thiazolyl, and 1,2-oxazolyl,

said groups being optionally substituted independently with one or two R^{5'} groups.

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

25 ring A represents a group selected from:

43



X^1 represents NR^3 or O,

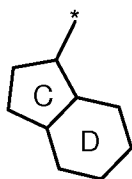
R^2 represents a group selected from :

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

5 R^3 represents a hydrogen atom.

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

ring A represents a group:



10 represents a bicyclic aromatic ring system, wherein ring C represents a 5-membered heteroaryl group which contains one heteroatom-containing group selected from N, NH, and $N(C_1-C_3\text{-alkyl})$, in which one or two carbon atoms are optionally further replaced by one or two N atoms,

said ring C being optionally substituted with one or two R^5 groups, and

15 ring D represents a phenyl group or a 6-membered heteroaryl group which contains one, or two nitrogen heteroatoms, said ring D being optionally substituted with one, two or three R^{12} groups;

R^{12} represents, independently of each other, halogen, hydroxy, C_1 - C_4 -alkyl, C_3 - C_4 -cycloalkyl, C_1 - C_3 -alkoxy, C_1 - C_3 -haloalkoxy, $-N(R^{14})R^{15}$,

20 wherein C_1 - C_4 -alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo ($C=O$), C_1 - C_3 -alkoxy, C_3 - C_6 -cycloalkyl, $-N(R^{14})R^{15}$, or OR^{13} .

In accordance with a twelveth aspect, the present invention covers a compound of general formula (I), *supra*, which is selected from the group consisting of :

25

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-6-methoxy-1,5-naphthyridine-4-carboxamide

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-2-carboxamide

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1,5-naphthyridine-4-carboxamide

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-methylpyridine-2-carboxamide

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-methylpyridine-2-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-6-methoxy-1,5-naphthyridine-4-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-a]pyridine-5-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-imidazole-2-carboxamide

5-bromo-N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-2,3-dihydro-1-benzofuran-7-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-

yl]quinoxaline-2-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoline-8-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-(methoxymethyl)-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrimidine-4-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-pyrrolo[2,3-b]pyridine-6-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5-methylpyridine-2-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-pyrrolo[3,2-b]pyridine-3-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-indazole-6-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-b]pyridazine-3-carboxamide

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-methyl-1H-imidazole-4,5-dicarboxamide

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-

ethyl-1H-imidazole-4,5-dicarboxamide

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(propan-2-yl)-1H-imidazole-4,5-dicarboxamide

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(2-methoxyethyl)-1H-imidazole-4,5-dicarboxamide

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-cyclopropyl-1H-imidazole-4,5-dicarboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-imidazole-5-carboxamide

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-[(3-fluoroazetidin-1-yl)carbonyl]-1H-imidazole-5-carboxamide

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(2,2,2-trifluoroethyl)-1H-imidazole-4,5-dicarboxamide

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-[2-(trifluoromethoxy)ethyl]-1H-imidazole-4,5-dicarboxamide

N-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-b]pyridazine-3-carboxamide

N-[(trans)-3-(3-chloropyridin-4-yl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(cis)-3-(2-chlorophenyl)-2,4-dioxo-1,3-diazaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-3-(2-chlorophenyl)-2,4-dioxo-1,3-diazaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(trans)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

N-[(cis)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-

carboxamide

N-[(3RS,trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

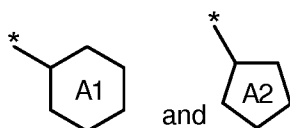
N-[(trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (enantiomer 1), and

N-[(trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (enantiomer 2),

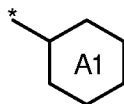
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In accordance with another aspect, the present invention covers compounds of general
5 formula (I), supra, in which :

A represents a group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



10 ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,

15 whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

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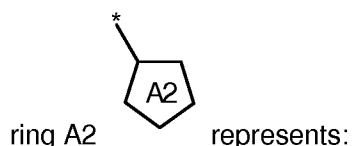
c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

5 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R⁵;

or,

whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in
10 which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR²⁰, O, S, S(=O) and S(=O)₂;



- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from
15 NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or

- a 5-membered heterocyclic ring, optionally partially unsaturated, which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two carbon atoms of the heterocyclic ring are optionally replaced by a heteroatom-containing group
20 selected from (C=O), N, NR²⁰, O, S, S(=O) and S(=O)₂;

said 5-membered heteroaryl and 5-membered heterocyclic rings being optionally substituted one, two or three times, independently from each other, with R⁵,

whereby two substituents R⁵ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are
25 attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group
30 selected from N, NR²⁰, O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,

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wherein said rings are fused with ring A2,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R⁵;

or

5 whereby two substituents R⁵ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR²⁰, O, S, S(=O) and S(=O)₂;

10 R⁴ represents a hydrogen atom,

R⁵ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

15 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, OR¹³;

R⁵ represents, independently of each other, a group selected from :

20 halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, OR¹³;

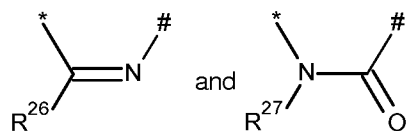
25 R⁶ represents hydrogen, halogen, hydroxy, C₁-C₃-alkyl or C₁-C₃-alkoxy;

R⁷ represents hydrogen; or

R⁶, R⁷ represent, independently of each other, halogen;

R⁸ represents hydrogen, or C₁-C₃-alkyl, and

R⁹ and R¹⁰ together represent a group selected from:



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wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

R¹¹ represents a group selected from :

5 aryl, and heteroaryl ,

wherein aryl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

10 C₁-C₆-alkyl , C₁-C₃-alkoxy , C₁-C₃-hydroxyalkyl , C₃-C₆-cycloalkyl, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl , C₁-C₃-haloalkoxy, halogen , cyano, nitro, hydroxy, (C₁-C₆-alkyl)-S-, (C₁-C₆-alkyl)-S(=O)-, (C₁-C₆-alkyl)-S(=O)₂-,
-S(=O)(=NR²¹)R²², -N(R¹⁴)R¹⁵, R¹⁴(R¹⁵)N-(C₁-C₆-alkyl)-, R¹⁴(R¹⁵)N-(C₂-C₆-alkoxy)-, phenyl, phenoxy, -N(R¹⁶)C(=O)R¹⁷, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

15 whereby two substituents of said aryl group, when they are in ortho-position to one another, can be linked to one another in such a way that they jointly form methanediylbisoxo, ethane-1,2-diylbisoxo, propane-1,3-diyl, or butane-1,4-diyl,

R¹³ represents a group selected from :

C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-hydroxyalkyl-, and (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)-,

20 R¹⁴ and R¹⁵ are, independently of each other, selected from :

hydrogen, C₁-C₆-alkyl , C₃-C₆-cycloalkyl , (C₃-C₆-cycloalkyl)-(C₁-C₆-alkyl)- , C₂-C₆-hydroxyalkyl , (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)- , (C₁-C₃-haloalkoxy)-(C₂-C₆-alkyl)-, C₁-C₆-haloalkyl ,
H₂N-(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)N(H)(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)₂N(C₂-C₆-alkyl)- , HOC(=O)-(C₁-C₆-alkyl)-, R¹³OC(=O)-(C₁-C₆-alkyl)-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-(C₁-C₆-alkyl)- , aryl, heteroaryl, aryl-(C₁-C₆-alkyl)-, and heteroaryl-(C₁-C₆-alkyl)-,

30 wherein 4- to 6-membered heterocycloalkyl groups are optionally substituted with one, two, three or four substituents, which are independently of each other selected from :

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C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -NH₂, -NH(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)₂, hydroxy, a halogen atom, and cyano,

and,

5 wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

10 or,

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, O, S, S(=O) and S(=O)₂, and in which one additional ring atom is optionally replaced by C(=O),

15 said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

20 whereby when two substituents are attached to the same ring carbon atom, together with the carbon atom to which they are attached, can be linked to one another in such a way that they jointly form a cyclobutane, cyclopentane, azetidine, pyrrolidine, oxetane, tetrahydrofuran, thietane, tetrahydrothiophene, thietane 1-oxide, tetrahydrothiophene 1-oxide, thietane 1,1-dioxide or tetrahydrothiophene 1,1-dioxide group;

R¹⁶ represents, independently of each other, hydrogen, or C₁-C₃-alkyl,

25 R¹⁷ represents hydrogen, C₁-C₆-alkyl, C₁-C₆-hydroxyalkyl, C₃-C₆-cycloalkyl, C₁-C₆-haloalkyl, (C₁-C₃-alkoxy)-(C₁-C₆-alkyl)-, aryl, or heteroaryl,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

30 C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, and hydroxy,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₃-C₄-cycloalkyl, -C(=O)C₁-C₄-alkyl, -C(=O)OC₁-C₄-alkyl and phenyl,

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R²¹ represents hydrogen, cyano, (C₁-C₃-alkyl)-C(=O)-, or (C₁-C₃-haloalkyl)-C(=O)-,

R²² represents C₁-C₄-alkyl, or C₃-C₄-cycloalkyl,

R²⁶ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-,

5 R²⁷ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-,

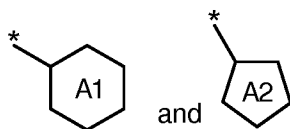
m is 0, 1 or 2,

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

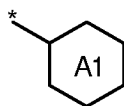
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In accordance with another aspect, the present invention covers compounds of general formula (I), supra, in which :

A represents a group selected from:



15 wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

20 said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,

whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

25 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

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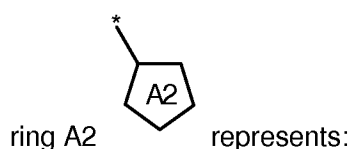
wherein said rings are fused with ring A1,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or,

- 5 whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;

10



- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or
- 15 - a 5-membered heterocyclic ring, optionally partially unsaturated, which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two carbon atoms of the heterocyclic ring are optionally replaced by a heteroatom-containing group selected from (C=O), N, NR^{20} , O, S, S(=O) and S(=O)₂;
- 20 said 5-membered heteroaryl and 5-membered heterocyclic rings being optionally substituted one, two or three times, independently from each other, with R^5 ,
- whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:
- 25 a) a phenyl ring,
- b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or
- c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,
- 30 wherein said rings are fused with ring A2,

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said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or

5 whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;

R^4 represents a hydrogen atom,

10 R^5 represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R^{14}) R^{15} , phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

15 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , OR¹³;

R^5 represents, independently of each other, a group selected from :

20 halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R^{14}) R^{15} , phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , OR¹³;

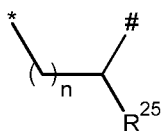
R^6 represents hydrogen, halogen, hydroxy, C₁-C₃-alkyl or C₁-C₃-alkoxy;

25 R^7 represents hydrogen; or

R^6 , R^7 represent, independently of each other, halogen;

R^8 represents hydrogen, or C₁-C₃-alkyl, and

R^9 and R^{10} together represent a group:



30 wherein * indicates the point of attachment of said group to the rest of the molecule at R^9 ,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

R¹¹ represents a group selected from :

aryl, and heteroaryl ,

wherein aryl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

5 C₁-C₆-alkyl , C₁-C₃-alkoxy , C₁-C₃-hydroxyalkyl , C₃-C₆-cycloalkyl, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl , C₁-C₃-haloalkoxy, halogen , cyano, nitro, hydroxy, (C₁-C₆-alkyl)-S-, (C₁-C₆-alkyl)-S(=O)-, (C₁-C₆-alkyl)-S(=O)₂-,
-S(=O)(=NR²¹)R²², -N(R¹⁴)R¹⁵, R¹⁴(R¹⁵)N-(C₁-C₆-alkyl)-,
10 R¹⁴(R¹⁵)N-(C₂-C₆-alkoxy)-, phenyl, phenoxy, -N(R¹⁶)C(=O)R¹⁷, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

whereby two substituents of said aryl group, when they are in ortho-position to one another, can be linked to one another in such a way that they jointly form methanediylbisoxo, ethane-1,2-diylbisoxo, propane-1,3-diyl, or butane-1,4-diyl,

15 R¹³ represents a group selected from :

C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-hydroxyalkyl-, and (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)-,

R¹⁴ and R¹⁵ are, independently of each other, selected from :

20 hydrogen, C₁-C₆-alkyl , C₃-C₆-cycloalkyl , (C₃-C₆-cycloalkyl)-(C₁-C₆-alkyl)- , C₂-C₆-hydroxyalkyl , (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)- , (C₁-C₃-haloalkoxy)-(C₂-C₆-alkyl)-, C₁-C₆-haloalkyl ,
H₂N-(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)N(H)(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)₂N(C₂-C₆-alkyl)- , HOC(=O)-(C₁-C₆-alkyl)-,
25 R¹³OC(=O)-(C₁-C₆-alkyl)-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-(C₁-C₆-alkyl)- , aryl, heteroaryl, aryl-(C₁-C₆-alkyl)-, and heteroaryl-(C₁-C₆-alkyl)-,

wherein 4- to 6-membered heterocycloalkyl groups are optionally substituted with one, two, three or four substituents, which are independently of each other selected from :

30 C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -NH₂, -NH(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)₂, hydroxy, a halogen atom, and cyano,
and,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

5 C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy,
C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, -C(=O)OH,
-C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

or,

10 R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, O, S, S(=O) and S(=O)₂, and in which one additional ring atom is optionally replaced by C(=O),

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

15 whereby when two substituents are attached to the same ring carbon atom, together with the carbon atom to which they are attached, can be linked to one another in such a way that they jointly form a cyclobutane, cyclopentane, azetidine, pyrrolidine, oxetane, tetrahydrofuran, thietane, tetrahydrothiophene, thietane 1-oxide, tetrahydrothiophene 1-oxide, thietane 1,1-dioxide or tetrahydrothiophene 1,1-dioxide group;

20 R¹⁶ represents, independently of each other, hydrogen, or C₁-C₃-alkyl,

R¹⁷ represents hydrogen, C₁-C₆-alkyl, C₁-C₆-hydroxyalkyl, C₃-C₆-cycloalkyl, C₁-C₆-haloalkyl, (C₁-C₃-alkoxy)-(C₁-C₆-alkyl)-, aryl, or heteroaryl,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

25 C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy,
C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, and hydroxy,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₃-C₄-cycloalkyl, -C(=O)C₁-C₄-alkyl, -C(=O)OC₁-C₄-alkyl and phenyl,

30 R²¹ represents hydrogen, cyano, (C₁-C₃-alkyl)-C(=O)-, or (C₁-C₃-haloalkyl)-C(=O)-,

R²² represents C₁-C₄-alkyl, or C₃-C₄-cycloalkyl,

R²⁵ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-, (preferably hydrogen, or C₁-alkyl),

n is 1 or 2, (preferably 1),

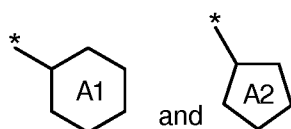
m is 1 or 2, (preferably 1),

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

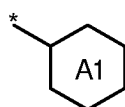
5

In accordance with another aspect, the present invention covers compounds of general formula (I), supra, in which :

A represents a group selected from:



10 wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

15 said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,

whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

20 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

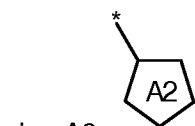
wherein said rings are fused with ring A1,

25 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R⁵;

or,

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whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;



ring A2 represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,

wherein said rings are fused with ring A2,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or

whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;

R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :

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halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, and -N(R¹⁴)R¹⁵,

5 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, and OR¹³;

R⁵ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and a 6-membered heteroaryl which contains one or two nitrogen atoms,

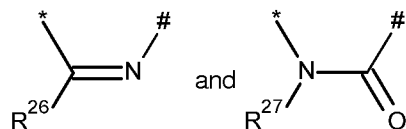
10 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, and OR¹³;

R⁶ represents hydrogen;

R⁷ represents hydrogen;

15 R⁸ represents hydrogen,

R⁹ and R¹⁰ together represent a group selected from:



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

20 and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

R¹¹ represents a group selected from :

phenyl, and heteroaryl ,

wherein phenyl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

25 C₁-C₄-alkyl, C₁-C₂-alkoxy, C₁-C₃-hydroxyalkyl, C₃-C₄-cycloalkyl, C₁-C₂-haloalkoxy, halogen, cyano, and hydroxy,

R¹³ represents a group selected from :

C₁-C₃-alkyl, and C₃-C₄-cycloalkyl,

R¹⁴ and R¹⁵ are independently of each other selected from :

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hydrogen, C₁-C₄-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₃-alkyl)-, C₂-C₃-hydroxyalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)-, (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-, and C₁-C₃-haloalkyl,

or,

- 5 R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, and O, and in which one additional ring atom is optionally replaced by C(=O),

10 said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-alkyl, C₁-haloalkyl, C₁-alkoxy, C₁-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl, and C₃-C₄-cycloalkyl,

- 15 R²⁶ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-,

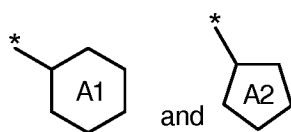
R²⁷ represents hydrogen,

m is 0, or 1,

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

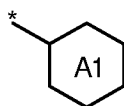
In accordance with another aspect, the present invention covers compounds of general formula (I), supra, in which :

A represents a group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;

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ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

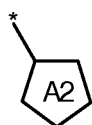
c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethylenedioxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;



ring A2 represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

5 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,

wherein said rings are fused with ring A2,

10 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with $R^{5'}$;

or

15 whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;

R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :

20 halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, and -N(R^{14}) R^{15} ,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , and OR¹³;

25 $R^{5'}$ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R^{14}) R^{15} , phenyl and a 6-membered heteroaryl which contains one or two nitrogen atoms,

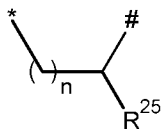
30 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , and OR¹³;

R^6 represents hydrogen;

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R⁷ represents hydrogen;

R⁸ represents hydrogen,



R⁹ and R¹⁰ together represent a group:

5 wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰;

R¹¹ represents a group selected from :

phenyl, and heteroaryl,

10 wherein phenyl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-C₄-alkyl, C₁-C₂-alkoxy, C₁-C₃-hydroxyalkyl, C₃-C₄-cycloalkyl, C₁-C₂-haloalkoxy, halogen, cyano, and hydroxy,

R¹³ represents a group selected from :

C₁-C₃-alkyl, and C₃-C₄-cycloalkyl,

15 R¹⁴ and R¹⁵ are independently of each other selected from :

hydrogen, C₁-C₄-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₃-alkyl)-, C₂-C₃-hydroxyalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)-, (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-, and C₁-C₃-haloalkyl,

or,

20 R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, and O, and in which one additional ring atom is optionally replaced by C(=O),

25 said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-alkyl, C₁-haloalkyl, C₁-alkoxy, C₁-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl, and C₃-C₄-cycloalkyl,

64

R^{25} represents hydrogen, or C_1 - C_3 -alkyl,

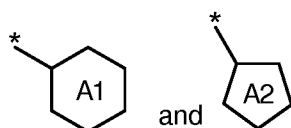
n is 1 or 2,

m is 1,

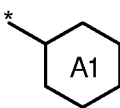
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In accordance with another aspect, the present invention covers compounds of general formula (I), supra, in which :

A represents a group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom;

ring A1  represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

15 said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

- 20 a) a phenyl ring,
 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and
 c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, and NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

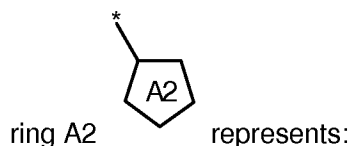
25 wherein said rings are fused with ring A1,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

or,

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whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a ethyleneoxy, or trimethyleneoxy;



- 5 - a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

- 10 whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring, or

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

- 15 wherein said rings are fused with ring A2,

said phenyl, and 6-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :

- 20 halogen, C_1 -alkyl, and C_1 -alkoxy,

$R^{5'}$ represents C_1 -alkyl,

wherein C_1 -alkyl is optionally substituted one, or two times with a group independently selected from oxo ($C=O$), and $-N(R^{14})R^{15}$,

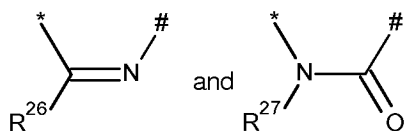
- 25 R^6 represents hydrogen;

R^7 represents hydrogen;

R^8 represents hydrogen,

R^9 and R^{10} together represent a group selected from:

66



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰;

5 R¹¹ represents a group selected from :

phenyl, and pyridinyl ,

wherein phenyl and pyridinyl groups are optionally substituted with one, two, or three groups, which are independently of each other selected from :

fluorine, and chlorine,

10 R¹³ represents a group C₁-C₃-alkyl,

R¹⁴ and R¹⁵ are independently of each other selected from :

hydrogen, C₁-C₃-alkyl, C₃-cycloalkyl, (C₁-alkoxy)-(C₂-alkyl)-, (C₁-haloalkoxy)-(C₂-alkyl)-, and C₂-haloalkyl,

or,

15 R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰,

said 4- to 6-membered heterocycloalkyl group being optionally substituted with one, or two groups, which are independently of each other selected from :

20 C₁-alkyl, and a halogen atom, preferably fluorine ,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, and C₁-alkyl,

R²⁶ represents hydrogen, C₁-C₂-alkyl, or (C₁-alkoxy)-(C₁-alkyl)-,

R²⁷ represents hydrogen,

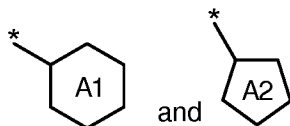
25 m is 0, or 1,

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

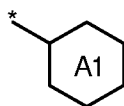
67

In accordance with another aspect, the present invention covers compounds of general formula (I), supra, in which :

A represents a group selected from:



- 5 wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

- 10 said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

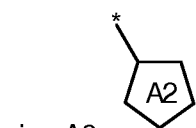
- a) a phenyl ring,
 15 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and
 c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, and NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

- 20 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

or,

- whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a ethyleneoxy, or
 25 trimethyleneoxy;



ring A2 represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

5 said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with $\text{R}^{5'}$,

whereby two substituents $\text{R}^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

10 a) a phenyl ring, or

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

wherein said rings are fused with ring A2,

said phenyl, and 6-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with $\text{R}^{5'}$;

15 R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :
halogen, C_1 -alkyl, and C_1 -alkoxy,

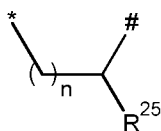
$\text{R}^{5'}$ represents C_1 -alkyl,

20 wherein C_1 -alkyl is optionally substituted one, or two times with a group independently selected from oxo ($\text{C}=\text{O}$), and $-\text{N}(\text{R}^{14})\text{R}^{15}$,

R^6 represents hydrogen;

R^7 represents hydrogen;

R^8 represents hydrogen,



25 R^9 and R^{10} together represent a group:

wherein * indicates the point of attachment of said group to the rest of the molecule at R^9 ,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

R¹¹ represents a group selected from :

phenyl, and pyridinyl ,

wherein phenyl and pyridinyl groups are optionally substituted with one, two, or three groups, which are independently of each other selected from :

fluorine, and chlorine,

R¹³ represents a group C₁-C₃-alkyl,

R¹⁴ and R¹⁵ are independently of each other selected from :

hydrogen, C₁-C₃-alkyl, C₃-cycloalkyl, (C₁-alkoxy)-(C₂-alkyl)-, (C₁-haloalkoxy)-(C₂-alkyl)-, and C₂-haloalkyl,

or,

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰,

said 4- to 6-membered heterocycloalkyl group being optionally substituted with one, or two groups, which are independently of each other selected from :

C₁-alkyl, and a halogen atom, preferably fluorine ,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, and C₁-alkyl,

R²⁵ represents hydrogen, or C₁-alkyl,

R²⁶ represents hydrogen, C₁-C₂-alkyl, or (C₁-alkoxy)-(C₁-alkyl)-,

R²⁷ represents hydrogen,

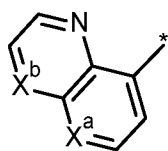
n is 1,

m is 1,

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

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), *supra*, wherein ring A represents:

70



wherein * indicates the point of attachment of said groups with the rest of the molecule, in which:

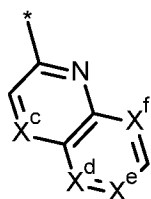
X^b represents CH or N,

5 X^a represents CH or N,

said ring A being optionally substituted independently with one or two R^5 groups.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), *supra*, wherein ring A represents:

10



wherein * indicates the point of attachment of said groups with the rest of the molecule, in which:

X^c represents CH or N,

15 X^d represents CH or N,

X^e represents CH or N,

X^f represents CH or N,

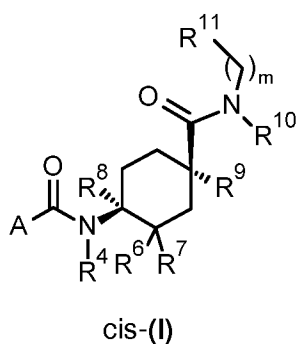
with the proviso that when one of X^c , X^d , X^e , or X^f is N the others are CH,

said ring A being optionally substituted independently with one or two R^5 groups.

20

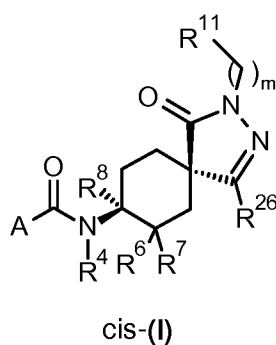
In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the cis configuration :

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wherein A, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and m are as defined herein for the compound of formula (I).

- 5 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the cis configuration :



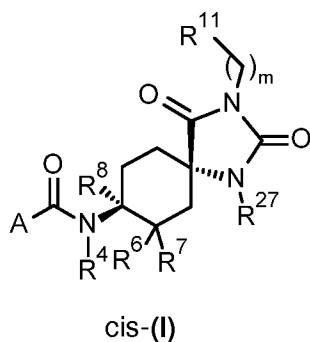
in which m is 0, 1 or 2, and

wherein A, R⁴, R⁶, R⁷, R⁸, R¹¹ and R²⁶ are as defined herein for the compound of formula (I).

10

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the cis configuration :

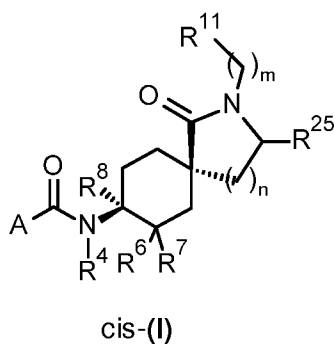
72



in which m is 0, 1 or 2, and

wherein A , R^4 , R^6 , R^7 , R^8 , R^{11} and R^{27} are as defined herein for the compound of formula (I).

- 5 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the cis configuration :



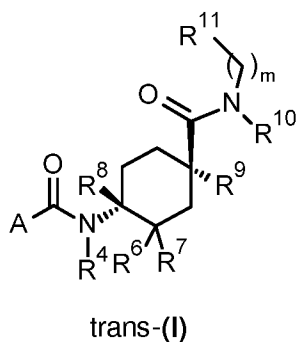
in which m is 1 or 2, and

wherein n , A , R^4 , R^6 , R^7 , R^8 , R^{11} and R^{25} are as defined herein for the compound of formula (I).

10

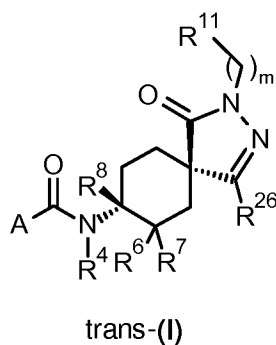
In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the trans configuration :

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wherein m, A, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ and are as defined herein for the compound of formula (I).

- 5 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the trans configuration :

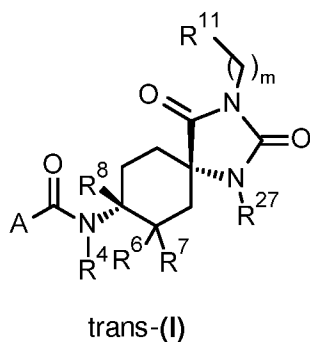


in which m is 0, 1 or 2, and

wherein A, R⁴, R⁶, R⁷, R⁸, R¹¹ and R²⁶ are as defined herein for the compound of formula (I).

10

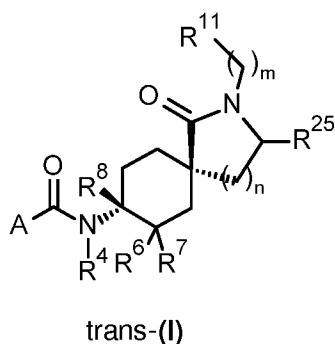
In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the trans configuration :



in which m is 0, 1 or 2, and

wherein A, R⁴, R⁶, R⁷, R⁸, R¹¹ and R²⁷ are as defined herein for the compound of formula (I).

- 5 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein the compound of formula (I) has the trans configuration :



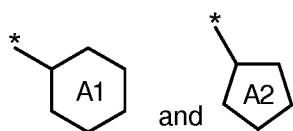
in which m is 1 or 2, and

wherein n, A, R⁴, R⁶, R⁷, R⁸, R¹¹ and R²⁵ are as defined herein for the compound of formula (I).

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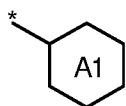
In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

A represents a group selected from:



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wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

5 whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

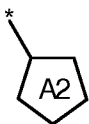
10 c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

15 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or,

20 whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethylenedioxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;



ring A2 represents:

25 - a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or

- a 5-membered heterocyclic ring, optionally partially unsaturated, which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two carbon atoms of the heterocyclic ring are optionally replaced by a heteroatom-containing group selected from (C=O), N, NR^{20} , O, S, S(=O) and S(=O)₂;

said 5-membered heteroaryl and 5-membered heterocyclic rings being optionally substituted one, two or three times, independently from each other, with $R^{5'}$,

whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

- a) a phenyl ring,
- b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or
- c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,

wherein said rings are fused with ring A2,

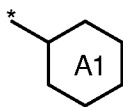
said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with $R^{5'}$;

or

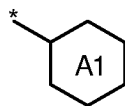
whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethylenedioxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

A represents a group:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

- a) a phenyl ring,
- b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and
- c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

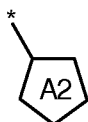
said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or,

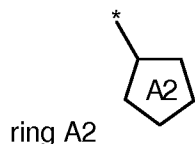
whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from $(C=O)$, NR^{20} , O, S, $S(=O)$ and $S(=O)_2$.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

A represents a group:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



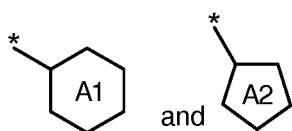
represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or
- 5 - a 5-membered heterocyclic ring, optionally partially unsaturated, which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two carbon atoms of the heterocyclic ring are optionally replaced by a heteroatom-containing group selected from $(\text{C}=\text{O})$, N, NR^{20} , O, S, $\text{S}(=\text{O})$ and $\text{S}(=\text{O})_2$;
- 10 said 5-membered heteroaryl and 5-membered heterocyclic rings being optionally substituted one, two or three times, independently from each other, with R^5 ,
- whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:
- a) a phenyl ring,
- 15 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or
- c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one ring carbon atom is optionally further replaced by a nitrogen atom,
- wherein said rings are fused with ring A2,
- 20 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;
- or
- whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy,
- 25 ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from $(\text{C}=\text{O})$, NR^{20} , O, S, $\text{S}(=\text{O})$ and $\text{S}(=\text{O})_2$.

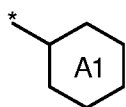
In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

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A represents a group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

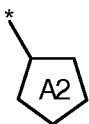
- a) a phenyl ring,
- b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and
- c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, and NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

or,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a ethyleneoxy, or trimethyleneoxy;



ring A2 represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

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said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring, or

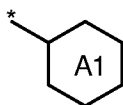
b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

wherein said rings are fused with ring A2,

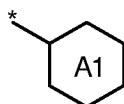
said phenyl, and 6-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 .

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

A represents a group:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

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c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, and NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

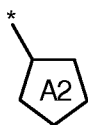
5 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

or,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a ethyleneoxy, or
10 trimethyleneoxy.

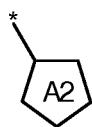
In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

A represents a group:



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wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom;



ring A2 represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from
20 NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are
25 attached they jointly form:

a) a phenyl ring, or

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

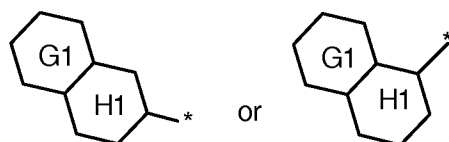
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wherein said rings are fused with ring A2,

said phenyl, and 6-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R⁵.

- 5 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

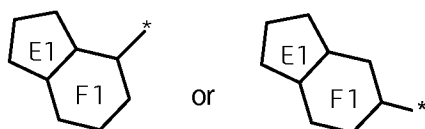
- 10 ring G1 represents a phenyl or a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

ring H1 represents phenyl or a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

with the proviso that when G1 or H1 is phenyl, then the other is a 6-membered heteroaryl group which contains one or two nitrogen atoms,

- 15 said ring G1 and ring H1 being optionally substituted independently with one or two R⁵ groups.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :



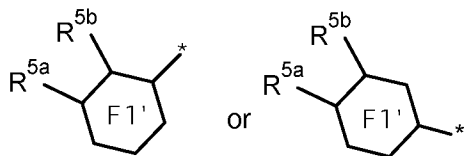
- 20 ring A represents: wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

ring F1 represents phenyl or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

- ring E1 represents a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or

said ring E1 and ring F1 being optionally substituted independently with one or two R⁵ groups.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :



ring A represents: wherein * indicates the point of

5 attachment of said groups with the rest of the molecule, and in which :

ring F1' represents phenyl or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

R^{5a} and R^{5b} are linked to one another in such a way that they jointly form a ethyleneoxy, or a trimethyleneoxy group,

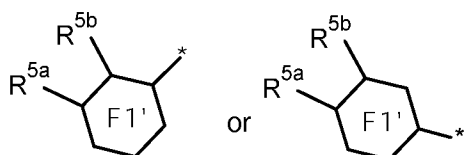
10 said ring F1' being optionally substituted one time with a group selected from :

fluorine, chlorine, bromine, hydroxy, C₁-C₄-alkyl, C₃-cycloalkyl, C₁-alkoxy, -NH₂, and -C(O)OR¹³,

wherein C₁-C₄-alkyl is optionally substituted one or two times with a group independently selected from fluorine, oxo (C=O), and -NR¹⁴R¹⁵.

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In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :



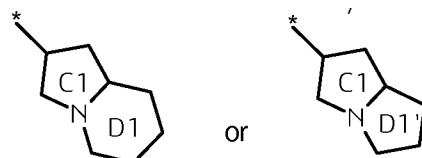
ring A represents: wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

20 ring F1' represents phenyl or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

R^{5a} and R^{5b} are linked to one another in such a way that they jointly form a ethyleneoxy, or a trimethyleneoxy group.

25 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

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ring A represents:

attachment of said groups with the rest of the molecule, and in which :

ring C1 represents a 5-membered heteroaryl ring in which one or two ring carbon atoms are optionally further replaced by a heteroatom selected from N, NR²⁰, O and S,

5 ring D1 is a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

ring D1' is a 5-membered heteroaryl ring in which one ring carbon atom is optionally further replaced by a heteroatom selected from N, NR²⁰, O and S,

said rings D1 and D1' being optionally substituted independently with one or two R^{5'} groups.

10 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents a group selected from:

phenyl, pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl,

said groups being optionally substituted independently with one or two R⁵ groups.

15

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents a group selected from:

pyridinyl, and pyrimidinyl,

20 said groups being optionally substituted independently with one or two R⁵ groups.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents a group selected from:

25 imidazolyl, pyrazolyl, 1,3-thiazolyl, and 1,2-oxazolyl,

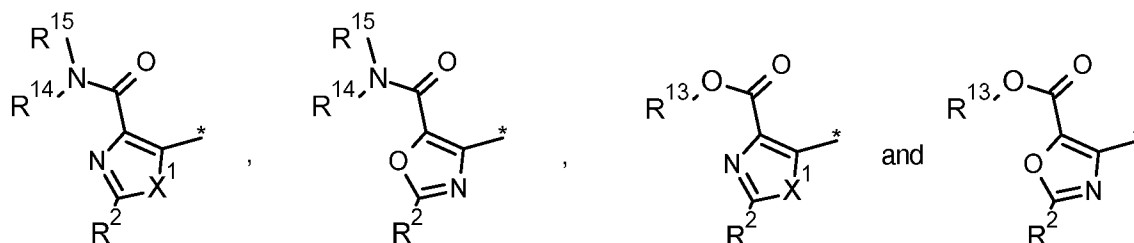
said groups being optionally substituted independently with one or two R⁵ groups.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents imidazolyl, optionally substituted independently with one or two R^5 groups.

- 5 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents a group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and in

- 10 which :

X^1 represents NR^3 or O,

R^2 represents a group selected from :

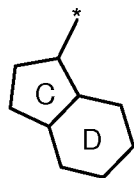
hydrogen, C_1 - C_3 -alkyl, and C_3 - C_4 -cycloalkyl, preferably hydrogen,

R^3 represents a hydrogen atom.

- 15

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents a group:



represents a bicyclic aromatic ring system, wherein * indicates the point of attachment of said group with the rest of the molecule, and in which :

- 20

ring C represents a 5-membered heteroaryl group which contains one heteroatom-containing group selected from N, NH, and $N(C_1$ - C_3 -alkyl), in which one or two carbon atoms are optionally further replaced by one or two N atoms,

said ring C being optionally substituted with one or two R^5 groups, and

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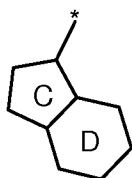
ring D represents a phenyl group or a 6-membered heteroaryl group which contains one, or two nitrogen heteroatoms, said ring D being optionally substituted with one, two or three R^{12} groups;

5 R^{12} represents, independently of each other, halogen, hydroxy, C_1 - C_4 -alkyl, C_3 - C_4 -cycloalkyl, C_1 - C_3 -alkoxy, C_1 - C_3 -haloalkoxy, $-N(R^{14})R^{15}$,

wherein C_1 - C_4 -alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo ($C=O$), C_1 - C_3 -alkoxy, C_3 - C_6 -cycloalkyl, $-N(R^{14})R^{15}$, OR^{13} .

10 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

ring A represents a group:



represents a bicyclic aromatic ring system, wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

15 ring C represents a 5-membered heteroaryl group which contains one heteroatom-containing group selected from N, NH, and $N(C_1-C_3\text{-alkyl})$, in which one or two carbon atoms are optionally further replaced by one or two N atoms,

ring D represents a phenyl group or a 6-membered heteroaryl group which contains one, or two nitrogen heteroatoms, said ring D being optionally substituted with two R^{12} groups;

20 R^{12} represents C_1 -alkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^4 represents a hydrogen atom.

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In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^5 represents, independently of each other, a group selected from :

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halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

5 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, OR¹³.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

10 R⁵ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, and -N(R¹⁴)R¹⁵,

15 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, and OR¹³.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁵ represents, independently of each other, a group selected from :

20 halogen, C₁-alkyl, and C₁-alkoxy.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁵ represents, independently of each other, a group selected from :

25 halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

30 wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, OR¹³.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{5'} represents, independently of each other, a group selected from :

5 halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵, phenyl and a 6-membered heteroaryl which contains one or two nitrogen atoms,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, and OR¹³.

10

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{5'} represents C₁-alkyl,

15 wherein C₁-alkyl is optionally substituted one, or two times with a group independently selected from oxo (C=O), and -N(R¹⁴)R¹⁵.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁶ represents hydrogen, halogen , hydroxy, C₁-C₃-alkyl or C₁-C₃-alkoxy.

20

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁷ represents hydrogen.

25 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁶, R⁷ represent, independently of each other, halogen.

30 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁶ represents hydrogen.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁶ represents hydrogen;

5 R^7 represents hydrogen.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁸ represents hydrogen, or C₁-C₃-alkyl.

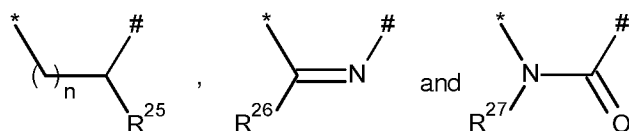
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In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R⁸ represents hydrogen.

15 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

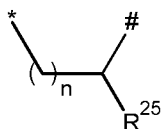
R⁹ and R¹⁰ together represent a group selected from:



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

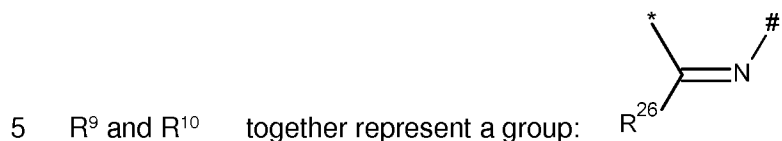


25 R^9 and R^{10} together represent a group:

wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

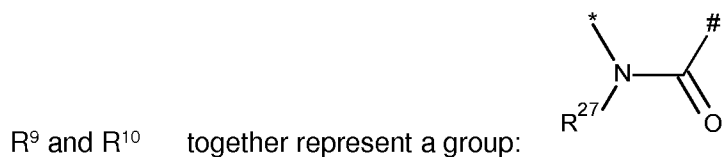
In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰.

10 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹¹ represents a group selected from :

20 aryl, and heteroaryl ,

wherein aryl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

25 C₁-C₆-alkyl , C₁-C₃-alkoxy , C₁-C₃-hydroxyalkyl , C₃-C₆-cycloalkyl, C₃-C₆-cycloalkoxy,
C₁-C₃-haloalkyl , C₁-C₃-haloalkoxy, halogen , cyano, nitro, hydroxy,
(C₁-C₆-alkyl)-S-, (C₁-C₆-alkyl)-S(=O)-, (C₁-C₆-alkyl)-S(=O)₂-,
-S(=O)(=NR²¹)R²², -N(R¹⁴)R¹⁵, R¹⁴(R¹⁵)N-(C₁-C₆-alkyl)-,

91

$R^{14}(R^{15})N-(C_2-C_6\text{-alkoxy})-$, phenyl, phenoxy, $-N(R^{16})C(=O)R^{17}$, $-C(=O)OH$, $-C(=O)OR^{13}$, and $-C(=O)N(R^{16})_2$,

whereby two substituents of said aryl group, when they are in ortho-position to one another, can be linked to one another in such a way that they jointly form
 5 methanediylbisoxo, ethane-1,2-diylbisoxo, propane-1,3-diyl, or butane-1,4-diyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{11} represents a group selected from :
 10 phenyl, and heteroaryl ,
 wherein phenyl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :
 C_1-C_4 -alkyl, C_1-C_2 -alkoxy, C_1-C_3 -hydroxyalkyl, C_3-C_4 -cycloalkyl, C_1-C_2 -haloalkoxy, halogen, cyano, and hydroxy.

15 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{11} represents a group selected from :
 phenyl, and pyridinyl ,
 20 wherein phenyl and pyridinyl groups are optionally substituted with one, two, or three groups, preferably one or two groups, which are independently of each other selected from :
 fluorine, and chlorine.

25 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{13} represents a group selected from :
 C_1-C_6 -alkyl, C_3-C_6 -cycloalkyl, C_2-C_6 -hydroxyalkyl-, and $(C_1-C_3\text{-alkoxy})-(C_2-C_6\text{-alkyl})-$.

30 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹³ represents a group selected from :

C₁-C₃-alkyl, and C₃-C₄-cycloalkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds
5 of formula (I), wherein :

R¹³ represents a group C₁-C₃-alkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds
of formula (I), wherein :

10 R¹⁴ and R¹⁵ are, independently of each other, selected from :

hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₆-alkyl)-,
C₂-C₆-hydroxyalkyl, (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)-, (C₁-C₃-haloalkoxy)-(C₂-C₆-alkyl)-, C₁-
C₆-haloalkyl, H₂N-(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)N(H)(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)₂N(C₂-C₆-
15 alkyl)-, HOC(=O)-(C₁-C₆-alkyl)-, R¹³OC(=O)-(C₁-C₆-alkyl)-, 4- to 6-membered
heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl, heteroaryl,
aryl-(C₁-C₆-alkyl)-, and heteroaryl-(C₁-C₆-alkyl)-,

wherein 4- to 6-membered heterocycloalkyl groups are optionally substituted with one,
two, three or four substituents, which are independently of each other selected from :

20 C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-
cycloalkoxy, -NH₂, -NH(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)₂, hydroxy, a halogen atom, and
cyano,

and,

25 wherein aryl and heteroaryl groups are optionally substituted with one or two
substituents, which are independently of each other selected from :

C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-
haloalkoxy, halogen, cyano, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds
30 of formula (I), wherein :

R¹⁴ is selected, independently of each other, from hydrogen, C₁-C₆-alkyl and C₃-C₆-
cycloalkyl,

R¹⁵ is selected, independently of each other, from :

hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₆-alkyl)-, C₂-C₆-hydroxyalkyl, (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)-, (C₁-C₃-haloalkoxy)-(C₂-C₆-alkyl)-, C₁-C₆-haloalkyl, H₂N-(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)N(H)(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)₂N(C₂-C₆-alkyl)-, HOC(=O)-(C₁-C₆-alkyl)-, R¹³OC(=O)-(C₁-C₆-alkyl)-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl, heteroaryl, aryl-(C₁-C₆-alkyl)-, and heteroaryl-(C₁-C₆-alkyl)-,

10

wherein 4- to 6-membered heterocycloalkyl groups are optionally substituted with one, two, three or four substituents, which are independently of each other selected from :

C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -NH₂, -NH(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)₂, hydroxy, a halogen atom, and cyano,

15

and,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂.

20

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, O, S, S(=O) and S(=O)₂, and in which one additional ring atom is optionally replaced by C(=O),

25

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

30

C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

whereby when two substituents are attached to the same ring carbon atom, together with the carbon atom to which they are attached, can be linked to one another in such a way that they jointly form a cyclobutane, cyclopentane, azetidine, pyrrolidine, oxetane, tetrahydrofuran, thietane, tetrahydrothiophene, thietane 1-oxide, tetrahydrothiophene 1-oxide, thietane 1,1-dioxide or tetrahydrothiophene 1,1-dioxide group.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹⁴ and R¹⁵ are independently of each other selected from :

hydrogen, C₁-C₄-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₃-alkyl)-, C₂-C₃-hydroxyalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)-, (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-, and C₁-C₃-haloalkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹⁴ is, independently of each other, selected from hydrogen, C₁-C₄-alkyl and C₃-C₆-cycloalkyl.

R¹⁵ is, independently of each other, selected from :

hydrogen, C₁-C₄-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₃-alkyl)-, C₂-C₃-hydroxyalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)-, (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-, and C₁-C₃-haloalkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, and O, and in which one additional ring atom is optionally replaced by C(=O),

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-alkyl, C₁-haloalkyl, C₁-alkoxy, C₁-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹⁴ and R¹⁵ are independently of each other selected from :

5 hydrogen, C₁-C₃-alkyl, C₃-cycloalkyl, (C₁-alkoxy)-(C₂-alkyl)-, (C₁-haloalkoxy)-(C₂-alkyl)-, and C₂-haloalkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹⁴ is selected, independently of each other, hydrogen, C₁-C₃-alkyl, and C₃-cycloalkyl,

10 R¹⁵ is, independently of each other, selected from :

hydrogen, C₁-C₃-alkyl, C₃-cycloalkyl, (C₁-alkoxy)-(C₂-alkyl)-, (C₁-haloalkoxy)-(C₂-alkyl)-, and C₂-haloalkyl.

15 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R¹⁶ represents, independently of each other, hydrogen, or C₁-C₃-alkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

20 R¹⁷ represents hydrogen, C₁-C₆-alkyl, C₁-C₆-hydroxyalkyl, C₃-C₆-cycloalkyl, C₁-C₆-haloalkyl, (C₁-C₃-alkoxy)-(C₁-C₆-alkyl)-, aryl, or heteroaryl,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

25 C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, and hydroxy.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R²⁰ represents, independently of each other, a group selected from :

30 hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₃-C₄-cycloalkyl, -C(=O)C₁-C₄-alkyl, -C(=O)OC₁-C₄-alkyl and phenyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

- 5 R^{20} represents, independently of each other, a group selected from :
hydrogen, C_1 - C_2 -alkyl , C_1 - C_2 -haloalkyl, and C_3 - C_4 -cycloalkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

- 10 R^{20} represents, independently of each other, a group selected from :
hydrogen, and C_1 -alkyl.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

- 15 R^{21} represents hydrogen, cyano, $(C_1$ - C_3 -alkyl)- $C(=O)-$, or $(C_1$ - C_3 -haloalkyl)- $C(=O)-$.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{22} represents C_1 - C_4 -alkyl, or C_3 - C_4 -cycloalkyl.

20

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{25} represents hydrogen, C_1 - C_3 -alkyl, C_1 - C_3 -haloalkyl, $(C_1$ - C_2 -alkoxy)- $(C_1$ - C_3 -alkyl)- or $(C_1$ - C_2 -haloalkoxy)- $(C_1$ - C_3 -alkyl)-.

25

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R^{26} represents hydrogen, C_1 - C_3 -alkyl, C_1 - C_3 -haloalkyl, $(C_1$ - C_2 -alkoxy)- $(C_1$ - C_3 -alkyl)- or $(C_1$ - C_2 -haloalkoxy)- $(C_1$ - C_3 -alkyl)-.

30

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R²⁷ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-.

5

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R²⁵ represents hydrogen, or C₁-C₃-alkyl.

10 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R²⁶ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-.

15 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R²⁷ represents hydrogen.

20 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R²⁵ represents hydrogen, or C₁-alkyl, preferably hydrogen.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

25 R²⁶ represents hydrogen, C₁-C₂-alkyl, or (C₁-alkoxy)-(C₁-alkyl)-.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

R²⁷ represents hydrogen.

30

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

n is 1 or 2.

- 5 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

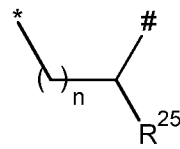
n is 1.

- 10 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

m is 0, 1 or 2.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

- 15 m is 0, 1 or 2,



with the proviso that when R⁹ and R¹⁰ together represent a group or 2.

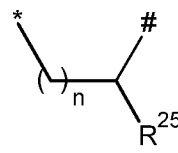
- 20 In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

m is 0, or 1.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein :

- 25 m is 0, or 1,

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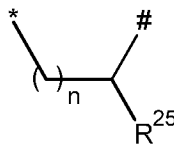
with the proviso that when R^9 and R^{10} together represent a group
1, then m is

In a further embodiment of the above-mentioned aspects, the invention relates to compounds
5 of formula (I), wherein :

m is 0.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds
10 of formula (I), wherein :

m is 0

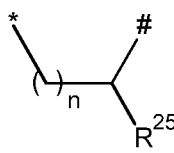


with the proviso that R^9 and R^{10} is not a group

In a further embodiment of the above-mentioned aspects, the invention relates to compounds
15 of formula (I), wherein :

m is 1.

In accordance with a preferred embodiment the present invention relates to compounds of
formula (I) as described herein, in which:



20 when R^9 and R^{10} together represent a group
defined herein, then m is 1 or 2, preferably 1.

In a further embodiment of the above-mentioned aspects, the invention relates to compounds
of formula (I), according to any of the above-mentioned embodiments, in the form of or a

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

It is to be understood that the present invention relates to any sub-combination within any
5 embodiment or aspect of the present invention of compounds of general formula (I), *supra*.

More particularly still, the present invention covers compounds of general formula (I) which are disclosed in the Example section of this text, *infra*.

10 In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the Experimental Section herein.

Another aspect of the invention relates to the the intermediates described herein and their use
15 for preparing a compound of formula (I) as defined *supra* or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

The intermediates used for the synthesis of the compounds of claims 1 to 12 as described below, as well as their use for the synthesis of the compounds of claims 1 to 12, are one
20 further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

Experimental section

1. Syntheses of Compounds:

25 The compounds of the present invention can be prepared as described in the following section. Schemes 1 to 12 and the procedures described below illustrate general synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in Schemes 1 to 12 can be modified in various ways. The order of transformations as exemplified in the
30 Schemes 1 to 12 are therefore not intended to be limiting. In addition, interconversion of any of the substituents, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and -N(R¹⁴)R¹⁵ can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting

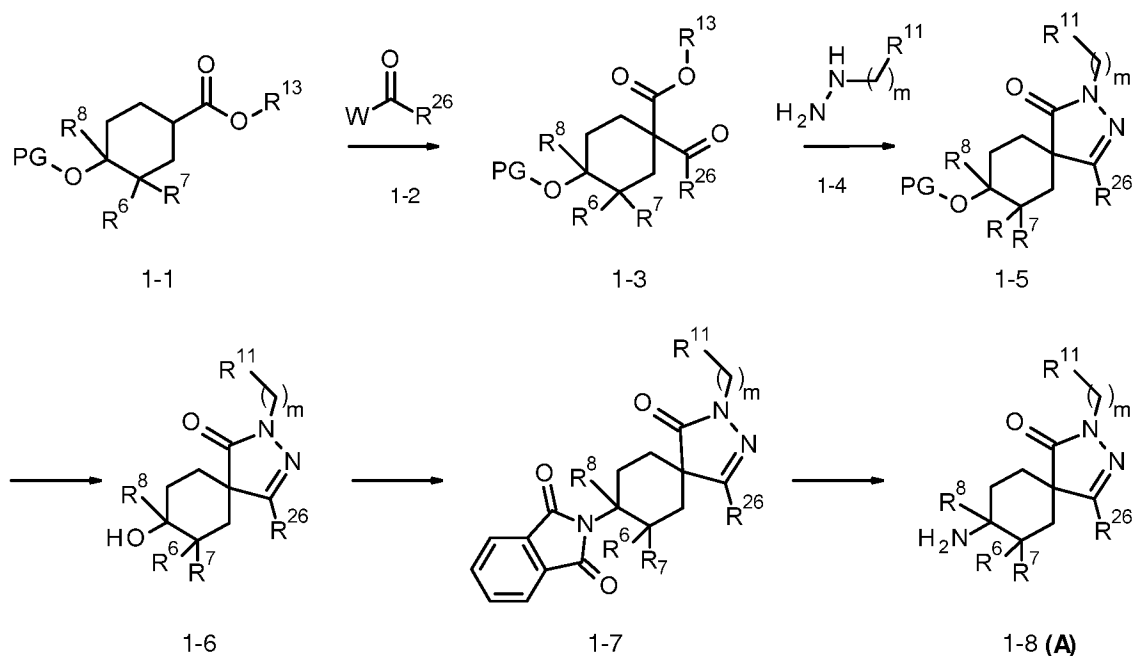
groups, cleavage of protecting groups, exchange, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs. Further, it is possible that two or more successive steps may be performed without work-up being performed between said steps, e.g. a “one-pot” reaction, as is well-known to the person skilled in the art.

- 10 In case mixtures of stereoisomers, such as, for example enantiomers, diastereomers, or cis/trans isomers are formed during a reaction, these isomers can be separated by methods described herein or by methods known to the person skilled in the art such as, but not limited to, chromatography, chiral chromatography and crystallization.

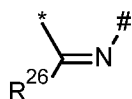
All reagents used for the preparation of the compounds of the invention are either commercially available or can be prepared as described.

1.1 Synthesis of amines intermediates

Amines intermediates of type **(A)** for the synthesis of compounds of the present invention can be synthesized as depicted in scheme 1 to 5.



- 20 **Scheme 1:** Synthesis of amine intermediates of type **(A)**, wherein R⁶, R⁷, R¹¹, R¹³, and R²⁶ are as defined herein for the compound of general formula (I), m is 0, 1 or 2, and R⁸ is hydrogen, and R⁹ and R¹⁰ (not shown) together represent a group:



, and in which PG represents a protecting group, such as a tert-butyl(dimethyl)silyl group, and W represents a halogen, such as, for instance a chloride.

Cyclohexanecarboxylate derivatives of type **1-1**, can be acylated at the appropriate position by treatment with a suitable base such as, for example, lithium diisopropylamide, in an appropriate solvent such as, for example, tetrahydrofuran, followed by addition of a suitable electrophile of type **1-2** to give compounds of type **1-3**.

Dicarbonyl derivatives of type **1-3** can be reacted with hydrazines of type **1.4** or their corresponding mineral acid salts, such as for example, hydrochloric acid salts, in an inert solvent such as for instance, toluene, xylene, or dioxane, at elevated temperatures (e.g. reflux) to give compounds of type **1.5**.

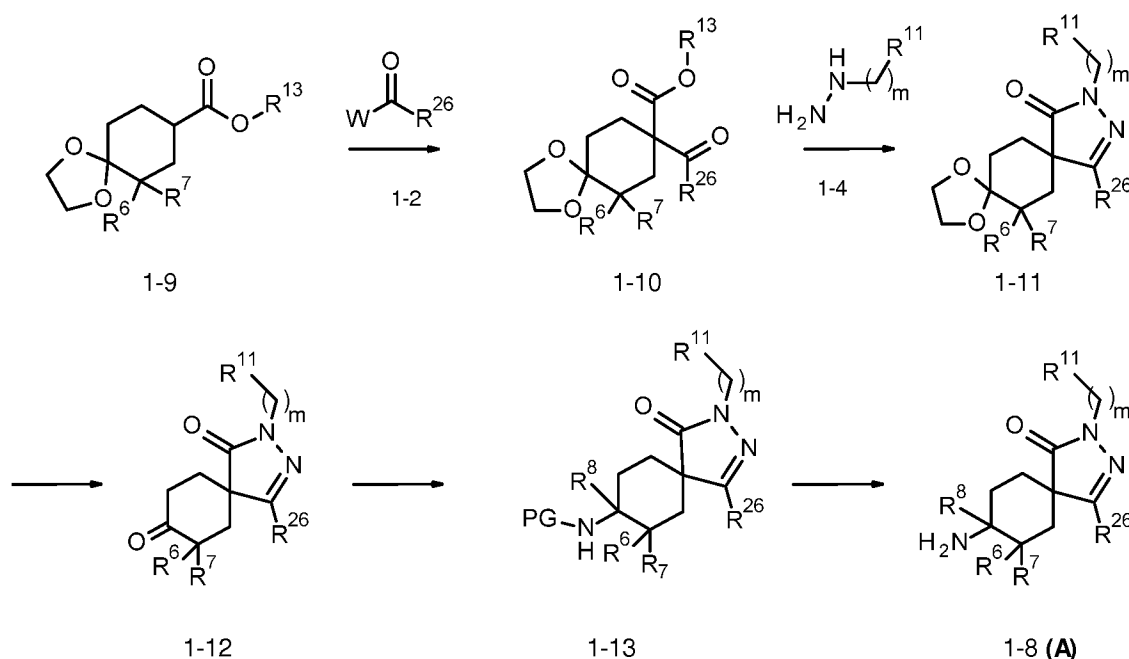
Deprotection of a protect alcohol of type **1-5**, in case of a tert-butyl(dimethyl)silyl group for example, employing tetra-N-butylammonium fluoride (TBAF) results in alcohol derivatives of type **1-6**.

Reaction of alcohol derivatives of type **1-6** with phthalimide under Mitsunobu reaction conditions, employing for example diisopropyl azodicarboxylate (DIAD) and triphenylphosphine as reagents, yields compounds of type **1-7**.

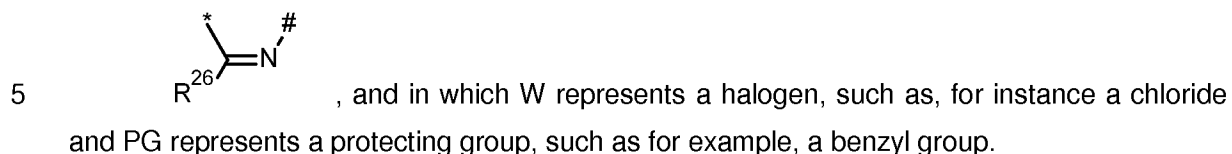
Deprotection of the protected amine of type **1-7** bearing a phthalimide group can be achieved, for example, by treatment with hydrazine hydrate or methylamine at elevated temperature (e.g. at reflux) to give amine derivatives of type **1-8 (A)**.

Alternatively compounds of type **1-8 (A)** can be obtained using the following route:

103



Scheme 2: Synthesis of amine intermediates of type (A), wherein R^6 , R^7 , R^8 , R^{11} , R^{13} , and R^{26} are as defined herein for the compound of general formula (I), m is 0, 1 or 2, and R^9 and R^{10} (not shown) together represent a group:



Cyclohexanecarboxylate derivatives of type **1-9**, can be acylated at the appropriate position by treatment with a suitable base such as, for example, lithium diisopropylamide, in an appropriate solvent such as, for example, tetrahydrofuran, followed by addition of a suitable electrophile of type **1-2** to give compounds of type **1-10**.

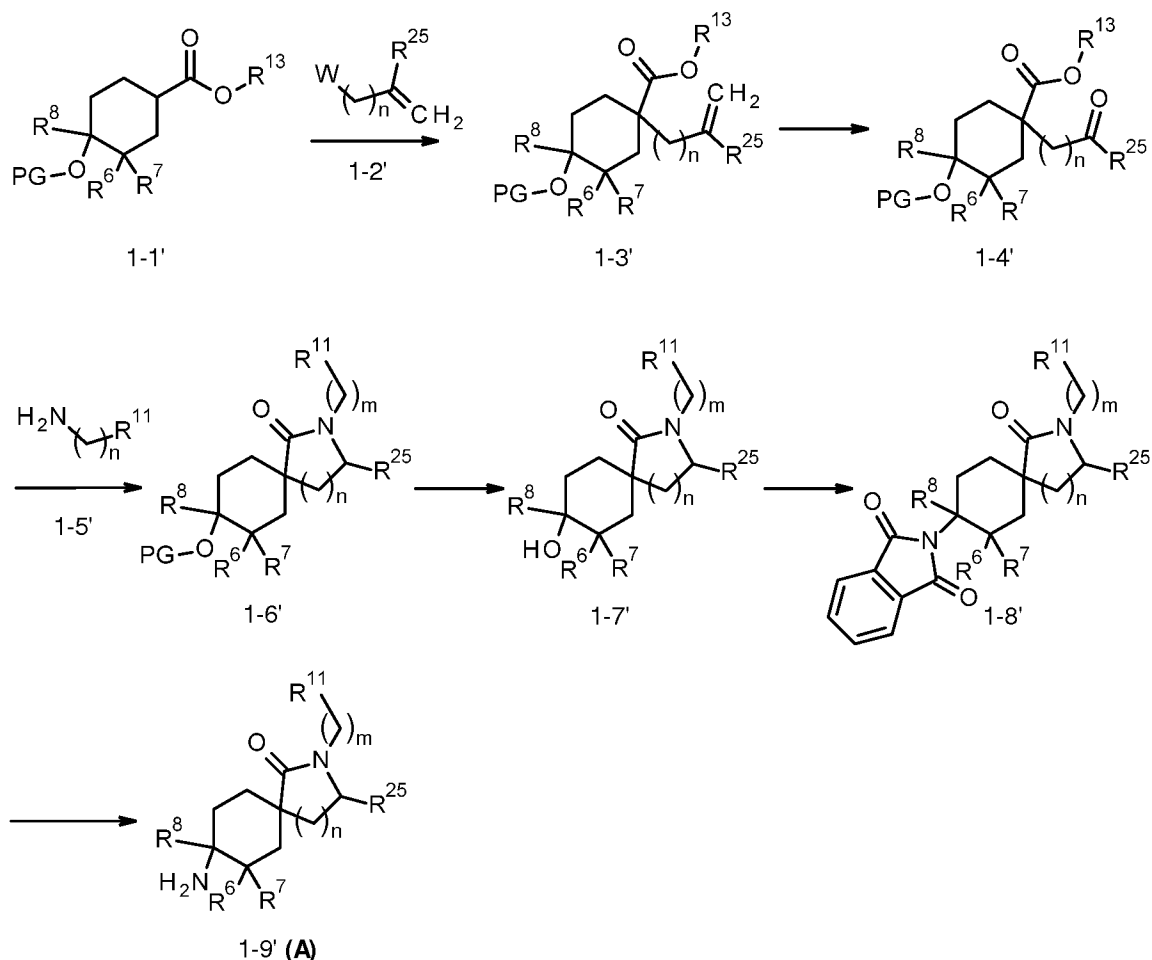
Dicarbonyl derivatives of type **1-10** can be reacted with hydrazines of type **1-4** or their corresponding hydrochloric acid salts in an inert solvent such as for instance, toluene, xylene, or dioxane, at elevated temperatures to give compounds of type **1-11**.

Treatment of compounds of type **1-11** with aqueous mineral acid give compounds of type **1-12**.

15 Reaction of ketones of type **1-12** with amines, such as for example benzyl amine, under standard reaction conditions for reductive animation reactions, employing for example sodium triacetoxyborohydride as reducing agent, yields protected amine derivatives of type **1-13**.

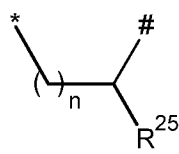
20 Deprotection of the protected amine of type **1-13**, in case of a benzyl protecting group for example, employing a palladium on charcoal catalyst and hydrogen gas, yields amine derivatives of type **1-8 (A)**.

Alternative compounds of type **(A)** can be obtained using the following routes (scheme 3 and scheme 4):



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Scheme 3: Synthesis of substituted 4-aminocyclohexanecarboxylate derivatives, wherein R^6 , R^7 , R^{11} , R^{13} and R^{25} are as defined for compounds of general formula (I) and R^8 is hydrogen, and R^9 and R^{10} (not shown) together represent a group:



10 tert-butyl(dimethyl)silyl group, W represents a leaving group such as for instance, a bromide, chloride, or iodide, and $m = 1$ or 2.

Cyclohexanecarboxylate derivatives of type **1-1'**, can be alkylated at the appropriate position by treatment with a suitable base such as, for example, lithium diisopropylamide, in an

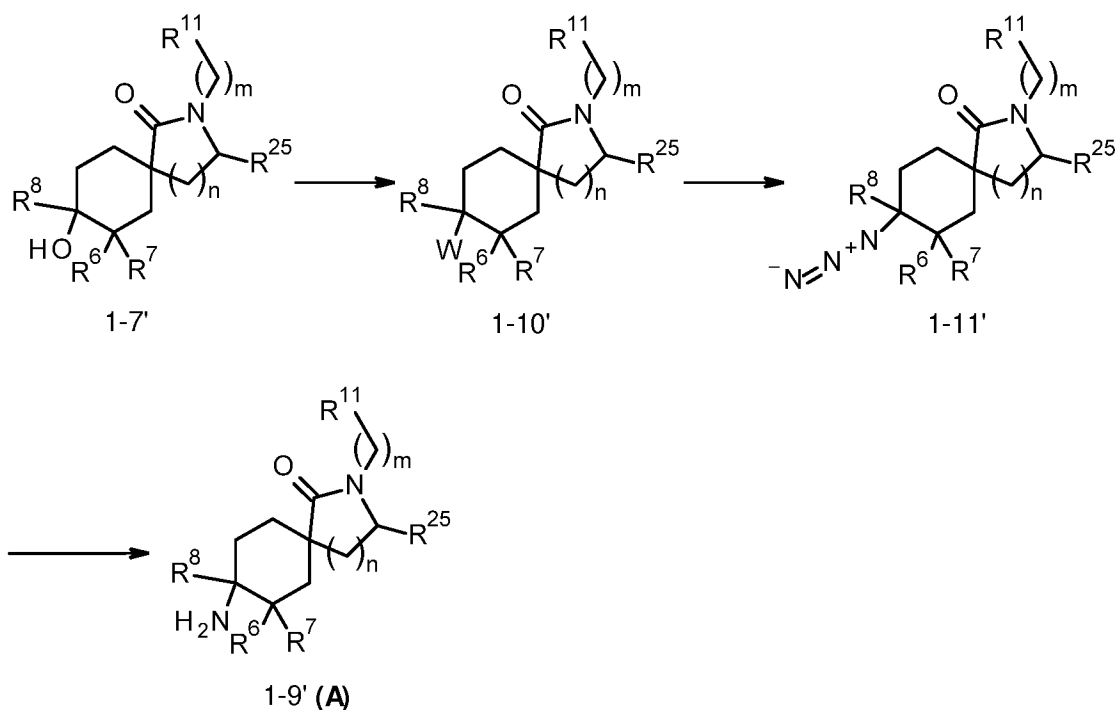
appropriate solvent such as, for example, tetrahydrofuran or diethylether, followed by addition of a suitable electrophile of type **1-2'** (e.g. allyl bromide) to give compounds of type **1-3'**.

- Oxidative cleavage of the double bond in compounds of type **1-3'**, for example using ozonolysis under standard reaction conditions for ozonolysis, yield carbonyl compounds of type **1-4'**. Carbonyl derivatives of type **1-4'** can react with primary amines of type **1-5'** under standard reaction conditions for reductive animation reactions, employing for example sodium triacetoxyborhydride as reducing agent, to give secondary amines which cyclizes directly to lactames of type **1-6'**.

- Deprotection of a protect alcohol of type **1-6'**, in case of a tert-butyl(dimethyl)silyl group for example, employing tetra-N-butylammonium fluoride (TBAF) results in alcohol derivatives of type **1-7'**.

Reaction of alcohol derivatives of type **1-7'** with phthalimide under Mitsunobu reaction conditions employing for example diisopropyl azodicarboxylate (DIAD) and triphenylphosphine as reagents yields compounds of type **1-8'**.

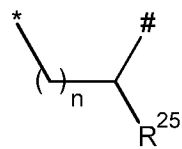
- Deprotection of the protected amine of type **1-8'** bearing a phthalimide group can be achieved, for example, by treatment with hydrazine hydrate or methylamine at elevated temperature (e.g. at reflux) to give amine derivatives of type **1-9' (A)**.



- Scheme 4:** Alternative synthesis of 4-aminocyclohexanecarboxylate derivatives, wherein R^6 , R^7 , R^{11} and R^{25} are as defined for the compound of general formula (I) and R^8 is hydrogen, and

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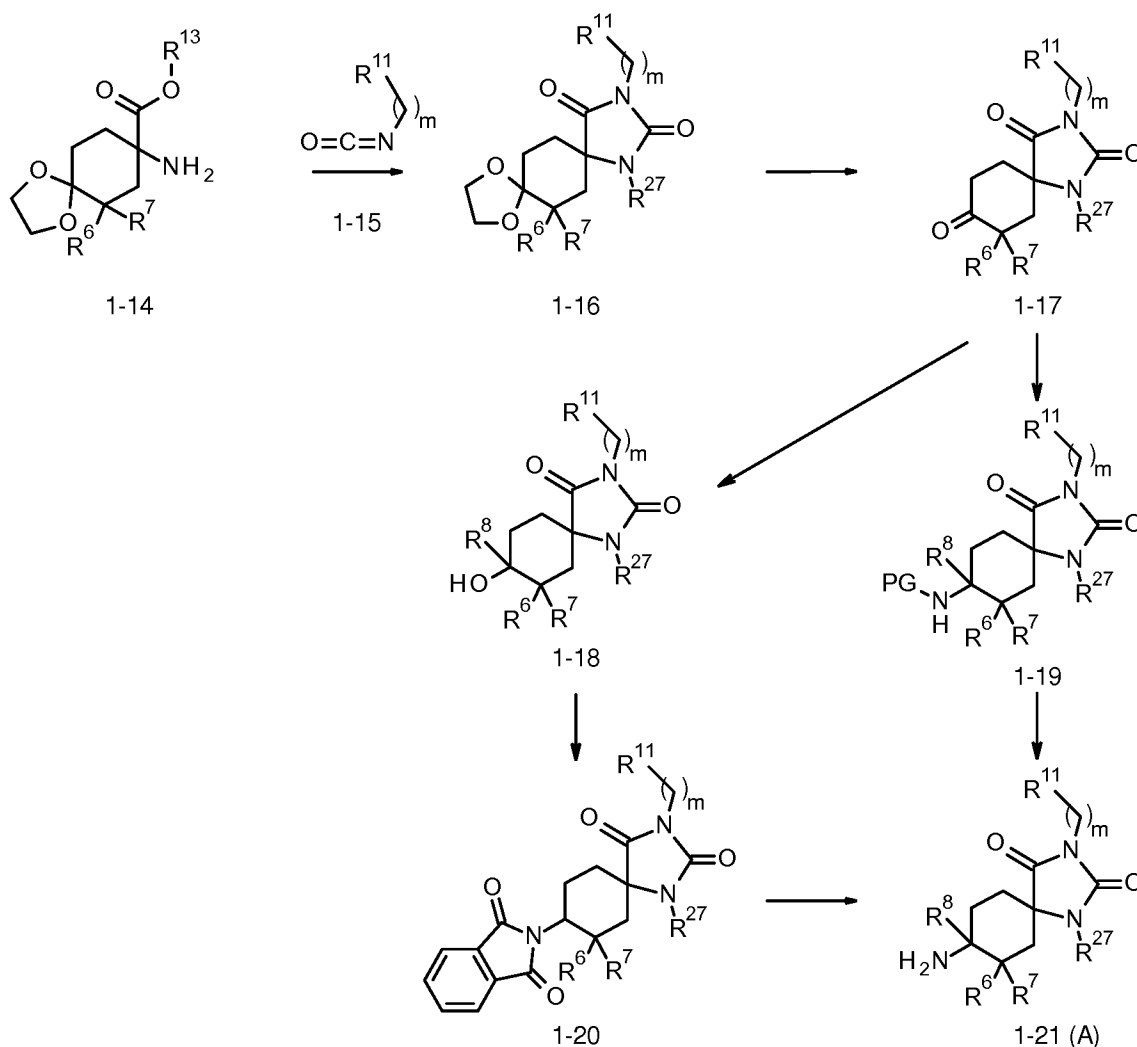
R^9 and R^{10} (not shown) together represent a group:



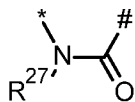
, n is 1 or 2, and in which W represents a leaving group such as, for instance a O -tosyl or O -mesyl group and m is 1 or 2.

- 5 In an alternative synthesis alcohol derivatives of type **1-7'** react with, for example, $W-Cl$ in the presence of a suitable base, for example pyridine, to yield compounds of type **1-10'**. Treatment of compounds of type **1-10'** with sodium azide in a suitable solvent, such as for instance DMF, yield compounds of type **1-11'**. Reduction of azide derivatives of type **1-11'** with, for instance, triphenylphosphine gives compounds of type **1-9' (A)**.

- 10 Alternative compounds of type **(A)** can be obtained using the following route:



Scheme 5: Synthesis of amine intermediates of type **(A)**, wherein R⁶, R⁷, R⁸, R¹¹, R¹³, and R²⁷ are as defined herein for the compound of general formula (I), m is 0, 1 or 2, and R⁹ and R¹⁰ (not shown) together represent a group:



, and in which PG represents a protecting group, such as for example, a

5 benzyl group.

Cyclohexanecarboxylate derivatives of type **1-14**, or their corresponding mineral acid salts, such as for example hydrochloric acid salts, can be reacted with isocyanates of type **1-15** in an appropriate solvent, such as for example dimethylsulfoxide, to form hydantoines of type **1-16**. The reaction can be carried out in the presence of an external base such as sodium carbonate and at elevated temperatures.

10

Treatment of compounds of type **1-16** with aqueous mineral acid gives compounds of type **1-17**.

Reaction of ketones of type **1-17** with amines, such as for example benzyl amine, under standard reaction conditions for reductive amination reactions, employing for example sodium triacetoxyborohydride as reducing agent, yields protected amine derivatives of type **1-19**. Deprotection of the protected amine of type **1-19**, in case of a benzyl protecting group for example, employing a palladium on charcoal catalyst and hydrogen gas, yields amine derivatives of type **1-21 (A)**.

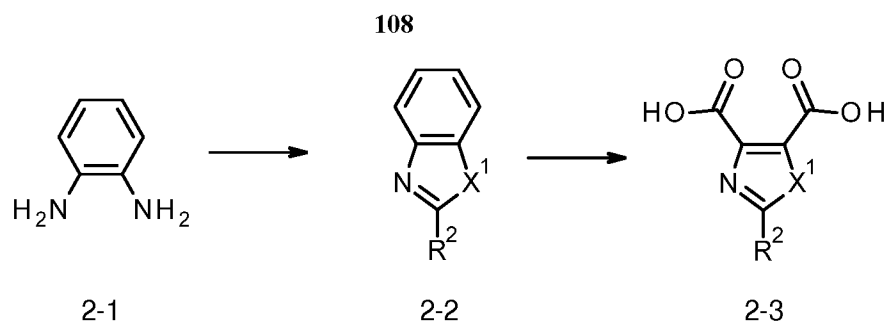
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Alternatively ketones of type **1-17** can be reduced to alcohols of type **1-18** applying standard reaction conditions for ketone reduction, employing for example sodium borohydride as reducing agent in an alcoholic solvent such as ethanol or methanol. Alcohols of type **1-18** can react with phthalimide under Mitsunobu reaction conditions, employing for example diisopropyl azodicarboxylate (DIAD) and triphenylphosphine as reagents, to yield compounds of type **1-20**. Deprotection of the protected amine of type **1-20** bearing a phthalimide group can be achieved, for example, by treatment with hydrazine hydrate or methylamine at elevated temperature (e.g. at reflux) to give amine derivatives of type **1-21 (A)**.

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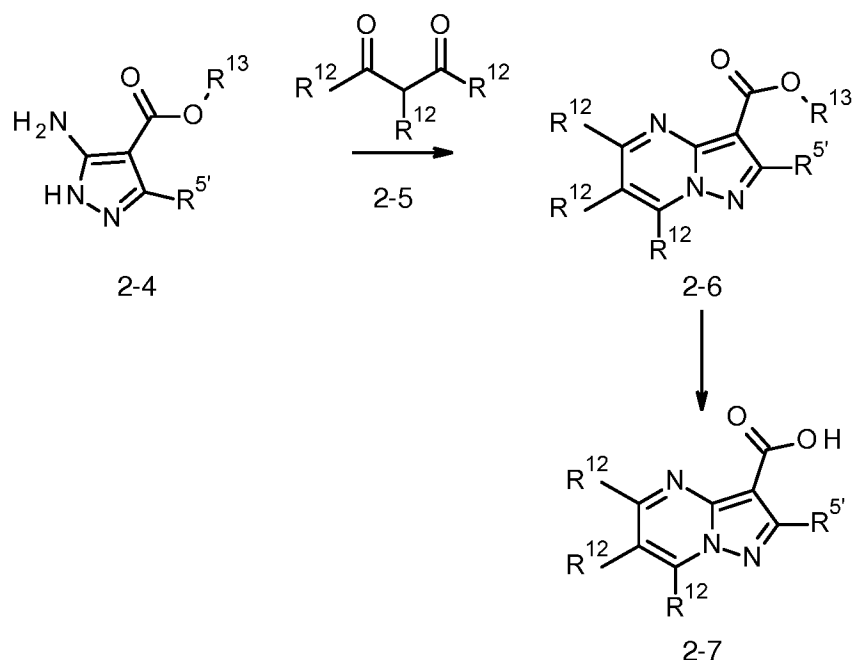
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1.2 Synthesis of heteroaromatic carboxylic acid derivatives



Scheme 6: Synthesis of 3,4 dicarboxylic acid substituted imidazoles, wherein X^1 represents NR^3 and R^2 and R^{20} are as defined herein for the compounds of general formula (I).

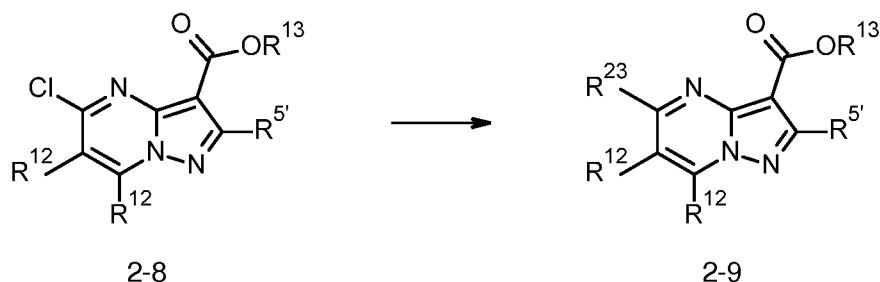
Commercially available benzene-1,2-diamine **2-1** can be reacted with carboxylic acids at elevated temperatures (e.g. up to 200°C) to give compounds of type **2-2**. Treatment of compounds of type **2-2**, for example with hydrogenperoxide under acidic conditions and elevated temperature (e.g. at about 120°C), yields compounds of type **2-3**.



Scheme 7: Synthesis of pyrazolo[1,5-a]pyrimidine-3-carboxylate derivatives, wherein $R^{5'}$, R^{12} and R^{13} are as defined herein for the compounds of general formula (I).

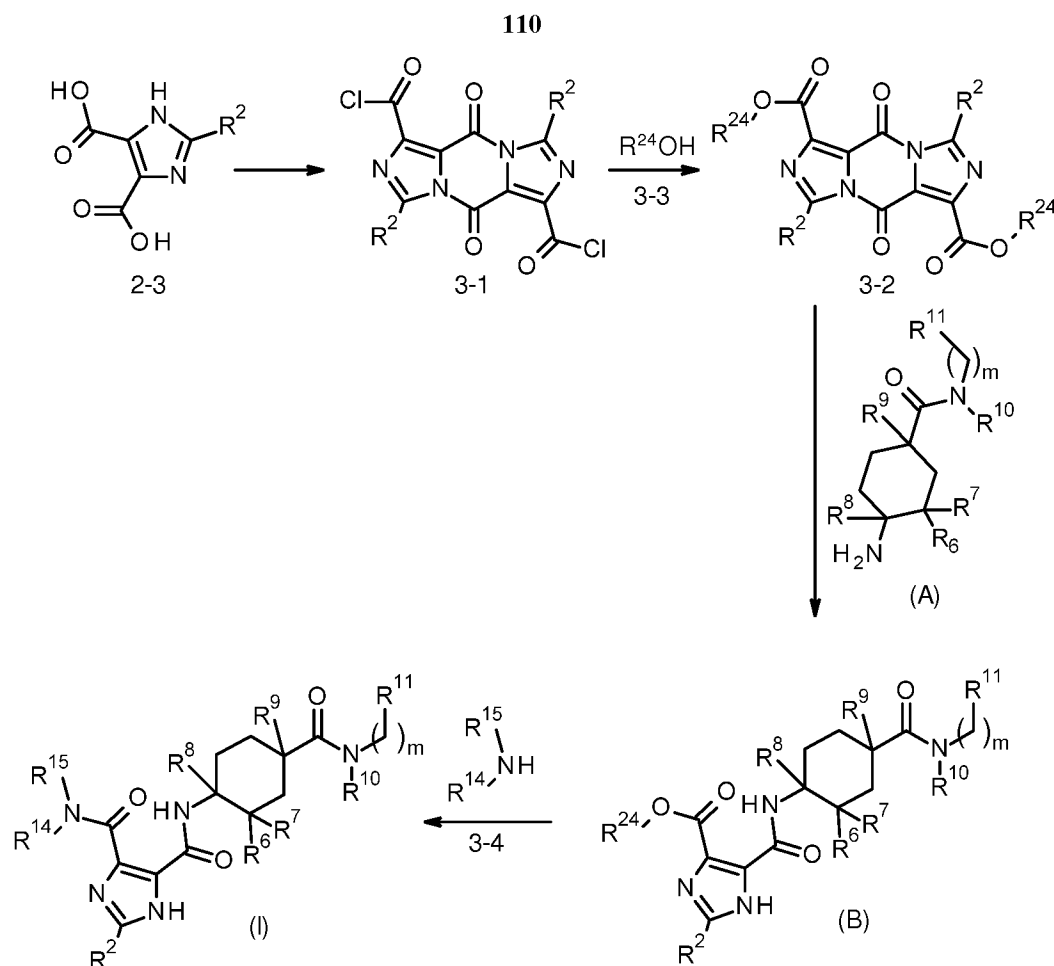
Commercially available, optionally substituted, 5-amino-1H-pyrazole-4-carboxylic acids of type **2-4** can be condensed with dicarbonyl compounds of type **2-5** at elevated temperatures (e.g. about 110°C) in a suitable solvent such as for example acetic acid to give compounds of type **2-6**.

Upon hydrolysis of the ester functionality of compounds of type **2-6** employing standard ester hydrolysis conditions, such as for example, an aqueous inorganic base, such as for example, lithium or sodium hydroxide, carboxylic acids of type **2-7** are obtained.



- 5 **Scheme 8:** Synthesis of pyrazolo[1,5-a]pyrimidine-3-carboxylate derivatives, wherein $R^{5'}$ and R^{12} are as defined herein for the compounds of general formula (I), R^{13} represents hydrogen or R^{13} as defined herein for the compounds of general formula (I), and R^{23} represents C1-C4-alkoxy, C1-C4-haloalkoxy, or $-N(R^{14})R^{15}$.

- 10 Reaction of compounds of type **2-8** with nucleophiles such as alcohols or primary or secondary amines in the presence of suitable base, for example a tertiary amine base, such as for example, N,N-diisopropylethylamine in the case of reaction with secondary amines, in a suitable solvent, such as for example 2-propanol, at elevated temperatures (e.g. at reflux) gives compounds of type **2-9**.



Scheme 9: Synthesis of imidazole derivatives starting from dicarboxylic acid precursors, wherein m , R^2 , R^3 (depicted as H), R^4 (depicted as H), R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} and R^{15} are as defined herein for the compound of general formula (I), R^5 is alkyl, and R^{24} is phenyl or R^{13} .

Starting from the corresponding 1*H*-imidazole-4,5-dicarboxylic acid derivatives of type **2-3**, after treatment with thionylchloride at elevated temperature (e.g. at about 90°C) 5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarbonyl dichlorides of type **3-1** are obtained.

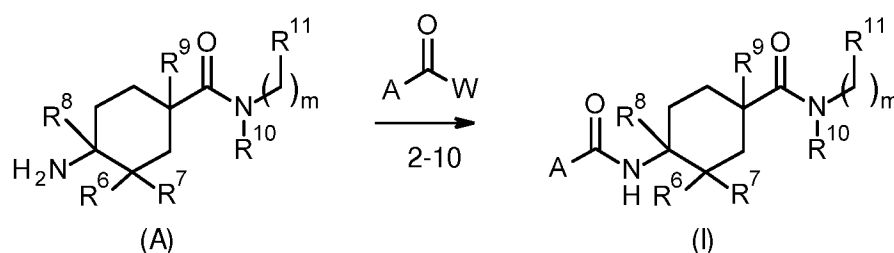
Compounds of type **3-1** can be reacted with alcohols of type **3-3**, such as, for example phenol, in presence of a suitable base, for example *N,N*-diisopropylethylamine or pyridine, to give a compound of general formula **3-2**.

Compounds of type **3-2** can react with intermediates of type (A) to give compounds of type (B). Esters of type (B) can react with nucleophiles of type **3-4**, optionally in presence of a base, such as, for example *N,N*-diisopropylethylamine, or in the presence of reagents such as DABAL, or alternatively in a two-step procedure consisting of ester hydrolysis, for example using sodium hydroxide followed by standard amide bond formation in presence of amines and coupling agents such as HATU or alternatively in a three step procedure after hydrolysis of the

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ester, generation of corresponding acid chloride, for example using thionylchloride and reaction with amines under basic conditions in presence of, for example, N,N-diisopropylethylamine.

- 5 An alternative synthesis route to compounds of the present invention is depicted in scheme 10:



Scheme 10: Synthesis of dicarbonyl compounds starting from amine intermediates of type (A), wherein m, A, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ are as defined herein for the compound of general formula (I), and in which W represents a hydroxyl group or a chloride.

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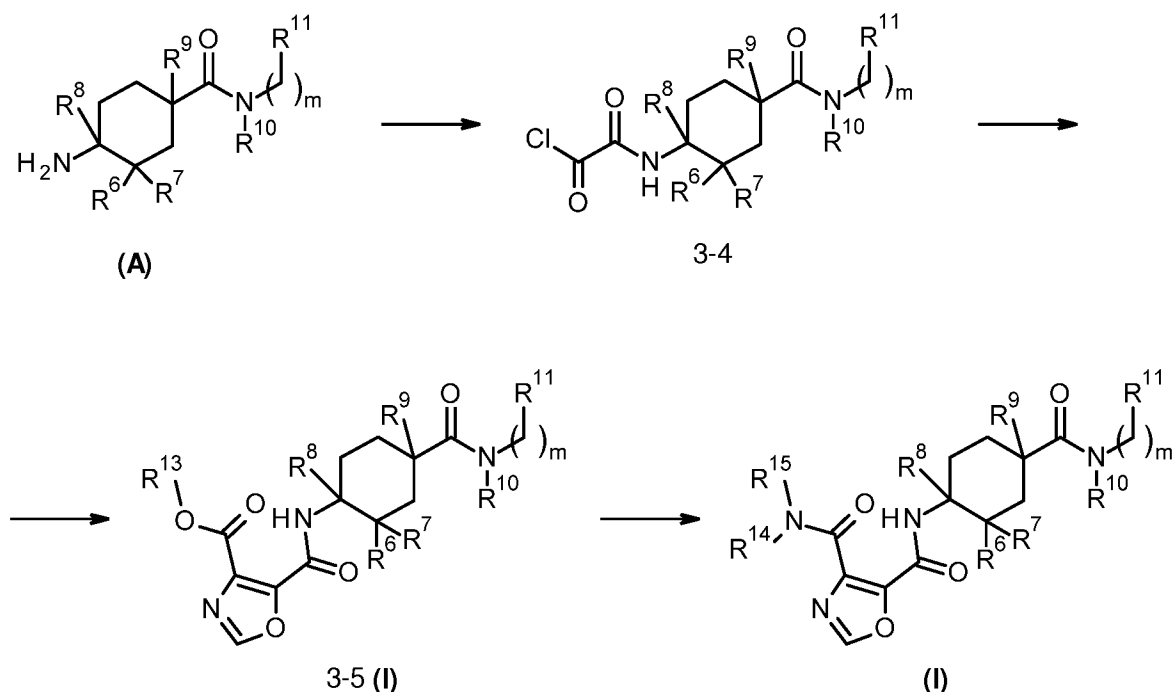
Amines of type (A) can react with carboxylic acids of type 2-10 under standard amide bond forming reaction conditions, for example using a coupling agent such as, for example, PyBOP to give compounds of formula (I). Alternatively, carboxylic acids of type 2-10 can be converted to the corresponding acid chlorides applying chlorinating agents, such as, for example thionyl chloride or 1-chloro-N,N,2-trimethylprop-1-en-1-amine, followed by reaction with amines of type (A) to give compounds of formula (I).

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Yet another possible synthesis route for the compounds of this invention is depicted in schemes 11 and 12.

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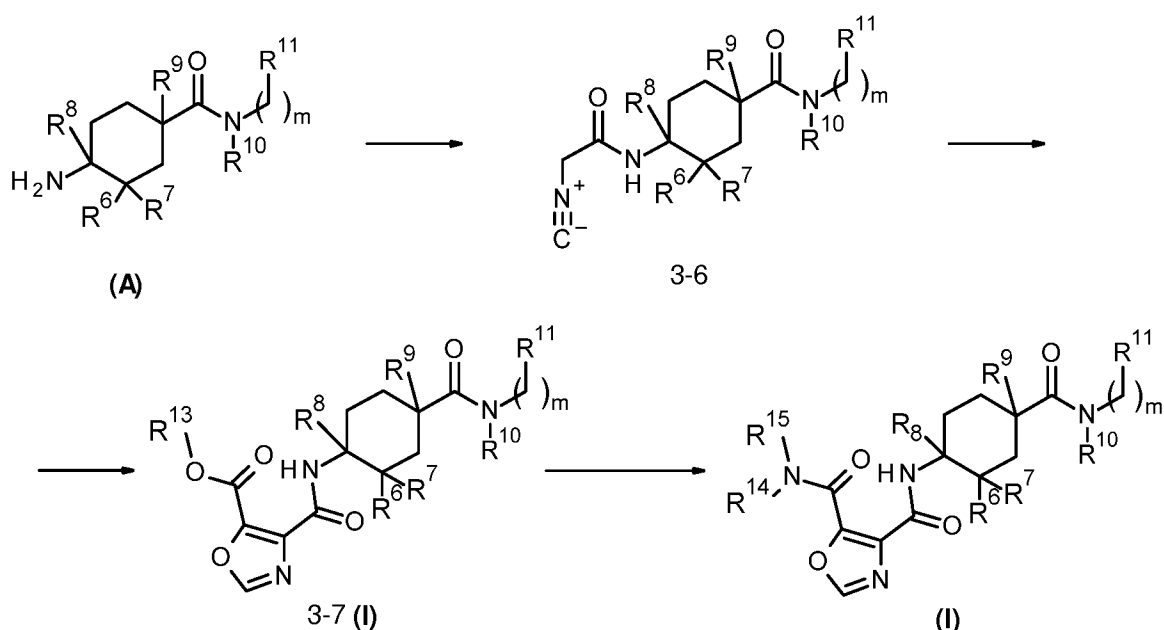
Scheme 11: Synthesis of oxazole derivatives of the present invention, wherein m , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} and R^{15} are as defined herein for the compound of general formula (I).

Compounds of type (A) can be transformed into compounds of type 3-4 by reaction with oxalyl chloride.

Reaction of compounds of type 3-4 with alkyl isocyanoacetates in presence of, for example, imidazole and triethylamine yields esters of general formula (I) as claimed in this invention.

Esters of general formula (I) can be transformed into amides of general formula (I), according to the invention, for example by treatment with different amines of formula $\text{HN}(R^{14})R^{15}$, optionally in presence of a base, such as for example N,N -diisopropylethylamine, or alternatively in a two step procedure consisting of ester hydrolysis, for example using sodium hydroxide followed by standard amide bond formation in presence of amines and coupling agents, such as for example HATU, or alternatively in a three step procedure after hydrolysis of the ester, generation of corresponding acid chloride, for example using thionylchloride, and reaction with amines under basic conditions in presence of, for example N,N -diisopropylethylamine.

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Scheme 12: Synthesis of oxazole derivatives of the present invention, wherein m , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} and R^{15} are as defined herein for the compound of general formula (I).

Compounds of type (A) can be transformed into compounds of type 3-6 by reaction with potassium isocyanacetate in the presence of a suitable base, such as for example N,N-diisopropylethylamine, and HATU.

Reaction of general formula 3-6 with methyl chloro(oxo)acetate in presence of, for example imidazole and trimethylamine, yields esters of general formula (I).

Esters of general formula (I) can be transformed into amides of general formula (I), according to the invention, for example by treatment with different amines of formula $HN(R^{14})R^{15}$, optionally in presence of a base, such as for example N,N-diisopropylethylamine, or alternatively in a two-step procedure consisting of ester hydrolysis, for example using sodium hydroxide followed by standard amide bond formation in presence of amines of formula $HN(R^{14})R^{15}$ and coupling agents such as HATU or alternatively in a three step procedure after hydrolysis of the ester, generation of corresponding acid chloride, for example using thionylchloride and reaction with amines of formula $HN(R^{14})R^{15}$ under basic conditions in presence of, for example N,N-diisopropylethylamine.

2. Experimental section - General Part

Chemical names were generated using ACD/Name Batch. Stereodescriptors were manually adapted as defined above. In case there is discrepancy between the chemical name of a compound and its chemical structure, the chemical structure shall prevail. In some cases generally accepted names of commercially available reagents were used in place of ACD generated names.

- The following table lists the abbreviations used in this paragraph and in the Intermediate Examples and Examples section as far as they are not explained within the text body. A comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears presented in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained therein, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

Abbreviation	Meaning
BOC	<i>tert</i> -butoxycarbonyl-
br.	broad signal (NMR)
DABAL	(μ -1,4-diazabicyclo[2.2.2]octane- κ N1: κ N4) (hexamethyl)dialuminium [CAS No. 137203-34-0]
d	doublet (NMR)
DAD	Diode array detector
dd	doublet of doublet (NMR)
dt	doublet of triplet (NMR)
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ESI	electrospray (ES) ionisation
GC-MS	gas chromatography–mass spectrometry
h, hr (hrs)	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]-pyridinium 3-oxid hexafluorophosphate
HCl	hydrogen chloride, hydrochloric acid
HPLC	high performance liquid chromatography
HRP	horseradish peroxidase
LC-MS	liquid chromatography–mass spectrometry
m	multiplet (NMR)
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

Abbreviation	Meaning
	signal to 2.50 ppm using unless otherwise stated.
NAD ⁺	nicotinamide adenine dinucleotide
PBS	phosphate buffered saline
PG	protecting group
Ph	phenyl
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
q	quartet (NMR)
quin	quintet (NMR)
R _t , Rt	retention time
s	singulet (NMR)
SPA	Scintillation proximity assay
T3P	1-propanephosphonic anhydride
TBAF	tetrabutylammonium fluoride
t	triplet (NMR)
td	triplet of doublet (NMR)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
[³ H]-	tritium
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.

- 5 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. As used herein, "SNAP cartridge" refers to the use of regular silica gel; "SNAP cartridge NH₂ silica" refers to the use of aminophase functionalized silica gel. If reference is made to flash column chromatography or to flash chromatography in the experimental 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.

NMR data:

NMR peak forms are stated as they appear in the spectra, possible higher order effects have not been considered.

The ¹H-NMR data of selected examples are listed in the form of ¹H-NMR peaklists. For each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, a peaklist is described by the general form: δ_1 (intensity₁), δ_2 (intensity₂), ... , δ_i (intensity_i), ... , δ_n (intensity_n).

The intensity of a sharp signal correlates with the height (in cm) of the signal in a printed NMR spectrum. When compared with other signals, this data can be correlated to the real ratios of the signal intensities. In the case of broad signals, more than one peak, or the center of the

signal along with their relative intensity, compared to the most intense signal displayed in the spectrum, are shown. A ^1H -NMR peaklist is similar to a classical ^1H -NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation. Moreover, similar to classical ^1H -NMR printouts, peaklists can show solvent signals, signals derived from stereoisomers of target compounds (also the subject of the invention), and/or peaks of impurities. The peaks of stereoisomers, and/or peaks of impurities are typically displayed with a lower intensity compared to the peaks of the target compounds (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 the reproduction of our manufacturing process on the basis of "by-product fingerprints". An expert who calculates the peaks of the target compounds by known methods (MestReC, ACD simulation, or by use of empirically evaluated expectation values), can isolate the peaks of target compounds as required, optionally using additional intensity filters. Such an operation would be similar to peak-picking in classical ^1H -NMR interpretation. A detailed description of the reporting of NMR data in the form of peaklists can be found in the publication "Citation of NMR Peaklist Data within Patent Applications" (cf. Research Disclosure Database Number 605005, 2014, 01 Aug 2014, or <http://www.researchdisclosure.com/searching-disclosures>). In the peak picking routine, as described in the Research Disclosure Database Number 605005, the parameter "MinimumHeight" can be adjusted between 1% and 4%. 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%.

Analytical HPLC 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 $^{\circ}\text{C}$; 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 $^{\circ}\text{C}$; DAD scan: 210-400 nm.

Method 3:

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;

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gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 4:

Instrument: Waters Acquity UPLCMS SingleQuad; Column: Acquity UPLC BEH C18 1.7
5 50x2.1mm; eluent A: water + 0.1 vol % formic acid (99%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 5:

Instrument: Method 5 1290 UHPLCMS Tof; column: BEH C 18 (Waters) 1.7 µm, 50x2.1mm; eluent A: water + 0.05 Vol-% formic acid (99%), eluent B: acetonitrile + 0.05% formic acid;
10 gradient: 0-1.7 min 98-10% A, 1.7-2.0 min 10% A, 2.0-2.5 min 10-98% A, flow 1.2 ml/min; temperature: 60 °C; DAD scan: 210-400 nm

Preparative HPLC methods:Method 6:

Instrument: Waters Autopurification MS SingleQuad; Column: Waters XBrigde C18 5µ
15 100x30mm; eluent A: water + 0.1 vol % formic acid (99%), eluent B: acetonitrile; gradient eluent A/ eluent B, flow 70 ml/min; temperature: 25 °C; DAD scan: 210-400 nm.

Method 7:

Instrument: Waters Autopurification MS SingleQuad; Colum: Waters XBrigde C18 5µ
20 100x30mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: eluent A / eluent B; flow 70 ml/min; temperature: 25 °C; DAD scan: 210-400 nm.

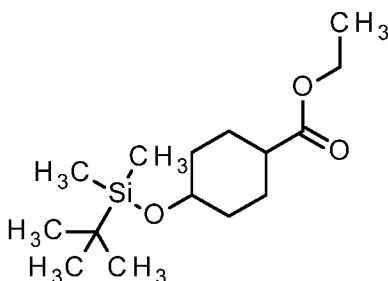
Analytical GC-MS Methods:Method 8

Instruments: Method 5 7890A and Waters GCT Premier; Colum: 29 m HP-5MS, 0.25 mm / 0.25µm; Gas: Helium 1 ml/min, Oven: Start 50°C 1 mi n, linear to 260°C at 10°C/min.

25 **3. Intermediates****Intermediate 1**

ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers)

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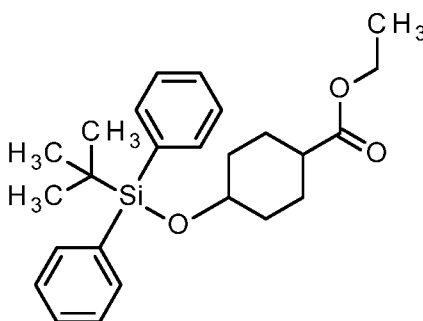


tert-Butyldimethylsilyl chloride (26.3 g, 174 mmol) was added to a solution of ethyl 4-hydroxycyclohexanecarboxylate (25.0 g, 145 mmol, mixture of cis-/trans-isomers, Cas No 17159-80-7) and imidazole (24.7 g, 363 mmol) in DMF (36 ml) and the mixture was stirred over
 5 night at room temperature. For work-up, water was added and the mixture was extracted with tert-butyl methyl ether (3x). The combined organic phases were washed with brine, filtered through a silicone filter and concentrated under reduced pressure to yield ethyl 4-[[*tert*-butyl(dimethyl)silyl]oxy]cyclohexanecarboxylate (43.1 g, 104% yield) which was used in the next step without further purification.

- 10 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$, mixture of isomers): δ [ppm] = 4.10-3.99 (m, 2H), 3.93-3.86 (m, 0.7H), 3.63-3.51 (m, 0.3H), 2.39-2.28 (m, 0.8H), 2.27-2.14 (m, 0.3H), 1.91-1.21 (m, 8H), 1.20-1.13 (m, 3H), 0.89-0.79 (m, 9H), 0.08-0.00 (m, 6H).

Intermediate 2

ethyl 4-[[*tert*-butyl(diphenyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers)



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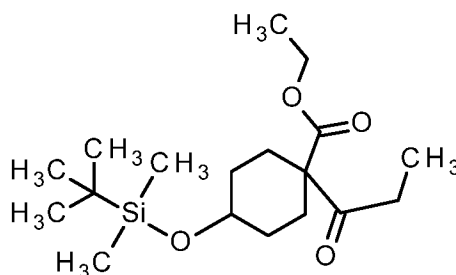
- Tert-butyl(chloro)diphenylsilane (18 ml, 68 mmol, CAS No 58479-61-1) was added drop wise to a mixture of ethyl 4-hydroxycyclohexanecarboxylate (9.4 ml, 57 mmol, CAS No 17159-80-7), 1H-imidazole (9.68 g, 142 mmol, CAS No 16681-56-4) and N,N-dimethylpyridin-4-amine (348 mg, 2.85 mmol, CAS No 1122-58-3) in DMF (81 ml), and the mixture was stirred at room
 20 temperature for 24 h. For work-up, the mixture was poured into water, extracted with ethyl acetate (3x) and the combined organic phases were washed until pH=7 as reached. The organic phase was dried over sodium sulfate and was concentrated under reduced pressure.

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The residue was purified by flash chromatography (340 g SNAP cartridge, hexane/ethyl acetate gradient, 5% -> 30% ethyl acetate) to give the title compound (21 g).

Intermediate 3

ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-propanoylcyclohexanecarboxylate (mixture of cis/trans isomers)

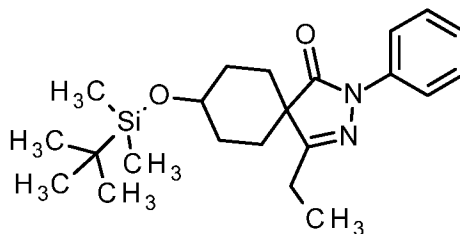


Lithium diisopropylamide (22 ml, 2.0 M in THF, 44 mmol) was added dropwise to a solution of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers) (10.0 g, 34.9 mmol) in THF (40 ml) at -78°C and the mixture was stirred at that temperature for 30 min. propanoyl chloride (4.0 ml, 45 mmol) in THF (10 ml) was added dropwise and the mixture was stirred at -70°C for 2 h. For work-up, water was added and the mixture was extracted with ethyl acetate (3x) and the combined organic phases were washed with brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (340 g SNAP cartridge, hexanes/ethyl acetate gradient, 0%->20% ethyl acetate) to give the title compound in 2 fractions, combined 11.2 g (94% yield) as a mixture of cis/trans-isomers.

¹H-NMR (400 MHz, DMSO-*d*₆, key signals for main isomer): δ [ppm] = 4.14 (q, 2H), 3.71-3.60 (m, 1H), 2.17-2.08 (m, 2H), 1.74-1.62 (m, 4H), 1.40-1.21 (m, 2H), 1.17 (t, 3H), 0.91 (t, 3H), 0.86-0.83 (m, 9H), 0.04-0.01 (m, 6H)

Intermediate 4

8-[[tert-butyl(dimethyl)silyl]oxy]-4-ethyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers)



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A mixture of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-propanoylecyclohexanecarboxylate (mixture of cis-/trans-isomers) (2.87 g, 8.38 mmol) and phenylhydrazine hydrochloride (1.53 g, 95 % purity, 10.1 mmol) in o-xylene (30 ml) was stirred at reflux for 16 h. Upon cooling, the mixture was diluted with ethyl acetate and washed with aqueous hydrochloric acid (1 M), water, saturated aqueous bicarbonate solution and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (100 g SNAP cartridge, hexanes/ethyl acetate gradient, 5%->10% ethyl acetate) to give the title compound 1.98 g (61 % yield).

Major isomer:

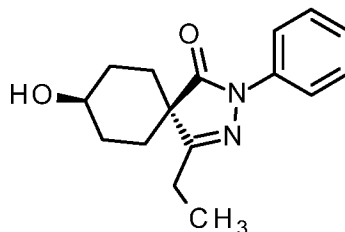
10 LC-MS (Method 2): Rt = 1.83 min; MS (ESIpos): m/z = 387 [M+H]⁺

Minor isomer:

LC-MS (Method 2): Rt = 1.90 min; MS (ESIpos): m/z = 387 [M+H]⁺

Intermediate 5

(cis)-4-ethyl-8-hydroxy-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one



15

TBAF (13 ml, 1.0 M in THF, 13 mmol) was added dropwise to a solution of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-propanoylecyclohexanecarboxylate (mixture of cis-/trans-isomers) (1.98 g, 5.12 mmol) in THF (44 ml) and the mixture was stirred for 20 h at room temperature. For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (50 g SNAP cartridge, hexanes/ethyl acetate gradient, 0%->50% ethyl acetate) to give the title compound a single isomer 731 mg (52% yield).

20

LC-MS (Method 2): Rt = 1.11 min; MS (ESIpos): m/z = 273 [M+H]⁺

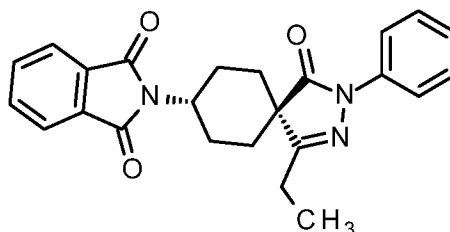
25

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.87-7.83 (m, 2H), 7.45-7.40 (m, 2H), 7.21-7.16 (m, 1H), 4.72 (d, 1H), 3.58-3.49 (m, 1H), 2.41 (q, 2H), 2.04-1.92 (m, 2H), 1.80-1.63 (m, 6H), 1.23-1.17 (m, 4H)

Intermediate 6

122

2-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione



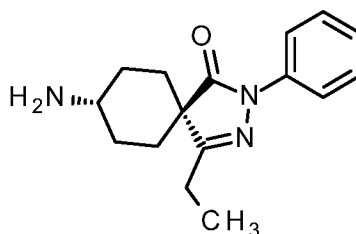
Diisopropyl azodicarboxylate (690 μ l, 3.5 mmol) was added dropwise to a solution of (cis)-4-ethyl-8-hydroxy-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (638 mg, 2.34 mmol), phthalimide (517 mg, 3.51 mmol) and triphenylphosphine (921 mg, 3.51 mmol) in THF (38 ml) and the mixture was stirred at room temperature for 12 h. For work-up, the mixture was concentrated and the residue was purified by flash chromatography (50 g SNAP cartridge, hexanes/ethyl acetate gradient, 0% $\rightarrow$ 20% ethyl acetate) to give the title compound as a single isomer 1.08 g (115 % yield, containing impurities).

LC-MS (Method 2): R_t = 1.44 min; MS (ESIpos): m/z = 402 $[M+H]^+$

1H -NMR (400 MHz, DMSO- d_6 , key signals): δ [ppm] = 7.48-7.42 (m, 2H), 7.23-7.18 (m, 1H), 4.25-4.14 (m, 1H), 2.87 (q, 2H), 1.94-1.78 (m, 6H), 1.34 (t, 3H)

Intermediate 7

(trans)-8-amino-4-ethyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one



15

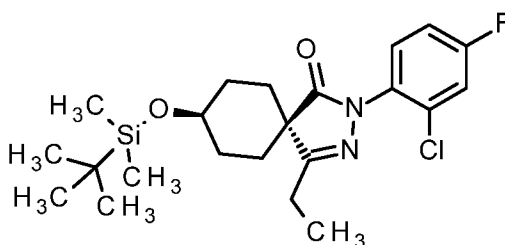
A mixture of 2-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione (980 mg, 2.44 mmol) and hydrazine hydrate (740 μ l, 80 % purity, 12 mmol) in ethanol (21 ml) was stirred for 3 h at 80°C. Upon cooling, the reaction mixture was concentrated and used in the next step without further purification

LC-MS (Method 2): R_t = 1.05 min; MS (ESIpos): m/z = 272 $[M+H]^+$

Intermediate 8

(cis)-8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorophenyl)-4-ethyl-2,3-diazaspiro[4.5]dec-3-en-1-one

123



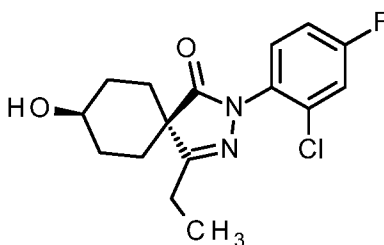
A mixture of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-propanoylecyclohexanecarboxylate (mixture of cis-/trans-isomers) (2.87 g, 8.38 mmol) and (2-chloro-4-fluorophenyl)hydrazine hydrochloride (2.09 g, 95 % purity, 10.1 mmol) in toluene (50 ml) was stirred at reflux for 16 h.

- 5 Upon cooling, the mixture was diluted with ethyl acetate and washed with aqueous hydrochloric acid (1 M), water, saturated aqueous bicarbonate solution and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (100 SNAP cartridge, hexanes/ethyl acetate gradient, 5%→10% ethyl acetate) to give the title compound as single isomer (1.91 g, 52 % yield, containing (2-chloro-4-fluorophenyl)hydrazine as impurity).
- 10

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.65 (dd, 1H), 7.59 (dd, 1H), 7.36 (td, 1H), 3.80-3.71 (m, 1H), 2.39 (q, 2H), 2.06-1.93 (m, 2H), 1.88-1.78 (m, 2H), 1.76-1.62 (m, 4H), 1.11 (t, 2H), 0.88 (s, 9H), 0.08-0.06 (m, 6H)

Intermediate 9

- 15 (cis)-2-(2-chloro-4-fluorophenyl)-4-ethyl-8-hydroxy-2,3-diazaspiro[4.5]dec-3-en-1-one



TBAF (11 ml, 1.0 M in THF, 11 mmol) was added dropwise to a solution of (cis)-8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorophenyl)-4-ethyl-2,3-diazaspiro[4.5]dec-3-en-1-one (1.91 g, 4.35 mmol) in THF (38 ml) and the mixture was stirred for 20 h at room temperature.

- 20 For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (25 g SNAP cartridge, hexanes/ethyl acetate gradient, 0%→50% ethyl acetate) to give the title compound a single isomer (1.18 g, 83 % yield).

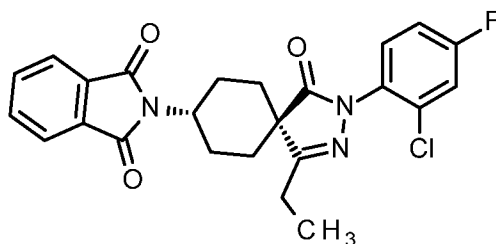
- 25 LC-MS (Method 2): R_t = 1.09 min; MS (ESIpos): m/z = 325 [M+H]⁺

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¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.65 (dd, 1H), 7.59 (dd, 1H), 7.39-7.33 (m, 1H), 4.71 (d, 1H), 3.56-3.47 (m, 1H), 2.38 (q, 2H), 2.00-1.87 (m, 2H), 1.82-1.64 (m, 6H), 1.11 (t, 3H)

Intermediate 10

2-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione



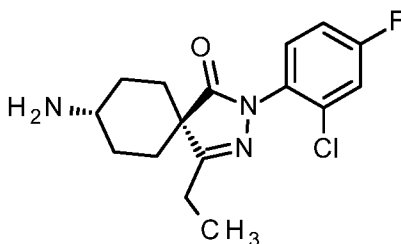
Diisopropyl azodicarboxylate (1.4 ml, 6.9 mmol) was added dropwise to a solution of (cis)-2-(2-chloro-4-fluorophenyl)-4-ethyl-8-hydroxy-2,3-diazaspiro[4.5]dec-3-en-1-one (1.50 g, 4.62 mmol), phthalimide (1.02 g, 6.93 mmol) and triphenylphosphine (1.82 g, 6.9 mmol) in THF (39 ml) and the mixture was stirred at room temperature for 12 h. For work-up, the precipitate was collected by filtration, and washed with THF and then stirred with DMSO. The precipitated was collected by filtration, washed with methanol and dried to give the title compound (1.58 g, 75% yield).

LC-MS (Method 1): *R*_t = 1.42 min; MS (ESIpos): *m/z* = 454 [M+H]⁺

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.89-7.81 (m, 4H), 7.60-7.50 (m, 2H), 7.32 (td, 1H), 4.28-4.18 (m, 1H), 2.83 (q, 2H), 1.98-1.78 (m, 6H), 1.27 (t, 3H)

Intermediate 11

(trans)-8-amino-2-(2-chloro-4-fluorophenyl)-4-ethyl-2,3-diazaspiro[4.5]dec-3-en-1-one



A mixture of 2-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione (1.58 g, 3.47 mmol) and hydrazine hydrate (1.1 ml, 80 % purity, 17 mmol) in ethanol (30 ml) was stirred for 3 h at 80°C. Upon cooling, the reaction mixture was concentrated. The residue was stirred with ethanol, the precipitate was filtered off and the

125

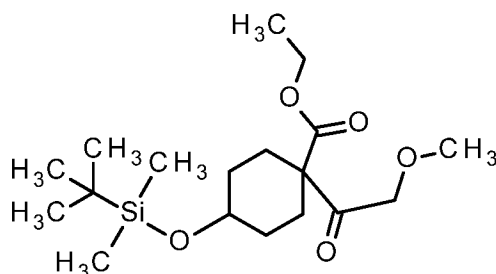
filtrate was concentrated to give the title compound (1.00 g) which was used in the next step without further purification

LC-MS (Method 2): $R_t = 1.02$ min; MS (ESIpos): $m/z = 324$ $[M+H]^+$

1H -NMR (400 MHz, $DMSO-d_6$): δ [ppm] = 7.65 (dd, 1H), 7.57 (dd, 1H), 7.36 (td, 1H), 2.97-2.85 (m, 1H), 2.53 (q, 2H), 2.07-1.91 (m, 4H), 1.58-1.47 (m, 2H), 1.45-1.32 (m, 2H), 1.14 (t, 3H)

Intermediate 12

ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(methoxyacetyl)cyclohexanecarboxylate (mixture of cis-/trans-isomers)



10 Lithium diisopropylamide (22 ml, 2.0 M in THF, 44 mmol) was added dropwise to a solution of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers) (10.0 g, 34.9 mmol) in THF (40 ml) at $-78^\circ C$ and the mixture was stirred at that temperature for 30 min. methoxyacetyl chloride (4.1 ml, 45 mmol) in THF (10 ml) was added dropwise and the mixture was stirred at $-70^\circ C$ for 2 h and then allowed to warm to $4^\circ C$. For work-up, water was

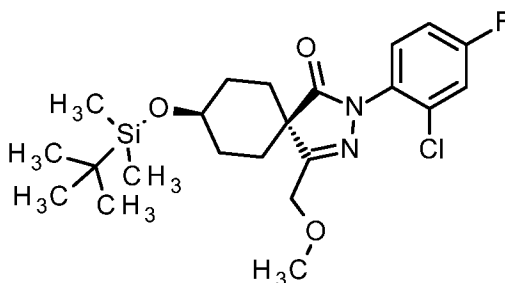
15 added and the mixture was extracted with ethyl acetate (3x) and the combined organic phases were washed with brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (340 g SNAP cartridge, hexanes/ethyl acetate gradient, 20%->30% ethyl acetate) to give the title compound 3.15 g (mixture of cis-/trans-isomers, containing starting material)

20 GC-MS (Method 8): $R_t = 20.97$ min; MS (TOF MS Cl^+): $m/z = 359$ $[M+H]^+$

Intermediate 13

(cis)-8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorophenyl)-4-(methoxymethyl)-2,3-diazaspiro[4.5]dec-3-en-1-one

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A mixture of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(methoxyacetyl)cyclohexanecarboxylate (mixture of cis-/trans-isomers) (3.15 g, 8.79 mmol) and (2-chloro-4-fluorophenyl)hydrazine hydrochloride (2.19 g, 95 % purity, 10.5 mmol) in o-xylene (35 ml) was stirred at reflux for 16 h.

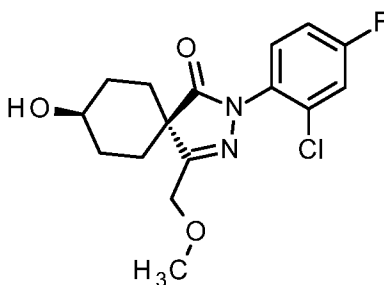
- 5 Upon cooling, the mixture was diluted with ethyl acetate and washed with aqueous hydrochloric acid (1 M), water, saturated aqueous bicarbonate solution and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (100 SNAP cartridge, hexanes/ethyl acetate gradient, 5%→10% ethyl acetate) followed by preparative HPLC (Method 7) to give the title compound as single isomer 117 mg (3 % yield).
- 10 LC-MS (Method 2): $R_t = 1.69$ min; MS (ESIpos): $m/z = 455$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.67 (dd, 1H), 7.62 (dd, 1H), 7.41-7.34 (m, 1H), 4.22 (s, 2H), 3.82-3.71 (m, 1H), 3.29 (s, 3H), 2.02-1.64 (m, 8H), 0.87 (s, 9H), 0.07 (s, 6H)

Intermediate 14

(cis)-2-(2-chloro-4-fluorophenyl)-8-hydroxy-4-(methoxymethyl)-2,3-diazaspiro[4.5]dec-3-en-1-one

15 one



TBAF (510 μl , 1.0 M in THF, 510 μmol) was added dropwise to a solution of (cis)-8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorophenyl)-4-(methoxymethyl)-2,3-diazaspiro[4.5]dec-3-en-1-one (116 mg, 255 μmol) in THF (2.4 ml) and the mixture was stirred for 20 h at room temperature. For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (10 g SNAP cartridge, hexanes/ethyl acetate gradient) to give the title compound single isomer 70.0 mg (81 % yield).

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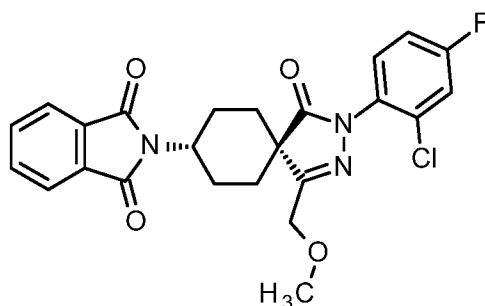
127

LC-MS (Method 2): $R_t = 0.97$ min; MS (ESIpos): $m/z = 341$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.67 (dd, 1H), 7.62 (dd, 1H), 7.41-7.34 (m, 1H), 4.73-4.66 (m, 1H), 4.21 (s, 2H), 3.58-3.46 (m, 1H), 3.29 (s, 3H), 1.98-1.62 (m, 9H)

Intermediate 15

- 5 2-[(trans)-3-(2-chloro-4-fluorophenyl)-1-(methoxymethyl)-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione

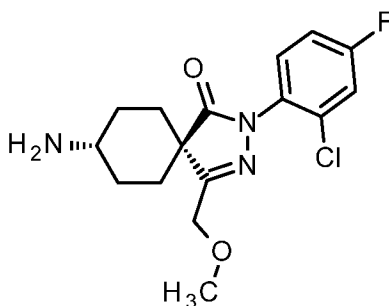


- Diisopropyl azodicarboxylate (59 μl , 300 μmol) was added dropwise at 0°C to a solution of (cis)-2-(2-chloro-4-fluorophenyl)-8-hydroxy-4-(methoxymethyl)-2,3-diazaspiro[4.5]dec-3-en-1-one (68.5 mg, 201 μmol), phthalimide (44.4 mg, 302 μmol) and triphenylphosphine (79.1 mg, 302 μmol) in THF (3.3 ml) and the mixture was stirred at room temperature for 12 h. For work-up, the mixture was concentrated and the residue was triturated with methanol. The precipitate was collected and dried to give the title compound 46.0 mg (49 % yield) and used in the next step without further purification.

- 15 LC-MS (Method 2): $R_t = 1.33$ min; MS (ESIpos): $m/z = 470$ $[M+H]^+$

Intermediate 16

(trans)-8-amino-2-(2-chloro-4-fluorophenyl)-4-(methoxymethyl)-2,3-diazaspiro[4.5]dec-3-en-1-one



- 20 A mixture of 2-[(trans)-3-(2-chloro-4-fluorophenyl)-1-(methoxymethyl)-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione (46.0 mg) and hydrazine hydrate (24

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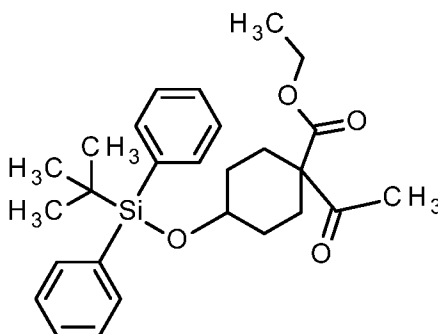
μl , 490 μmol) in ethanol (0.84 ml) was stirred for 3 h at 80°C. Upon cooling, the reaction mixture was concentrated and the residue stirred with ethanol. Solids were filtered off, washed with ethanol and the filtrate was concentrated to give the title compound (23 mg) which was used in the next step without further purification.

- 5 LC-MS (Method 2): $R_t = 0.98$ min; MS (ESIpos): $m/z = 340$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$, key signals): δ [ppm] = 7.67 (dd, 1H), 7.60 (dd, 1H), 7.37 (td, 1H), 4.30 (s, 2H), 2.90-2.83 (m, 1H), 2.53-2.52 (m, 2H), 2.02-1.91 (m, 4H), 1.63-1.52 (m, 2H), 1.49-1.37 (m, 2H)

Intermediate 17

- 10 ethyl 1-acetyl-4-[[tert-butyl(diphenyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers)



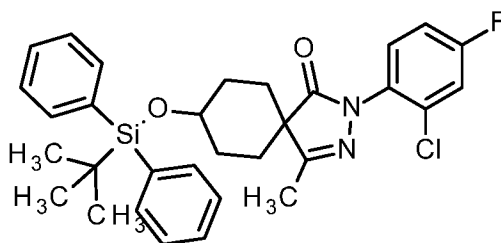
- Lithium diisopropylamide (32 ml, 2.0 M in THF, 64 mmol) was added dropwise to a solution of ethyl 4-[[tert-butyl(diphenyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers) (21.0 g, 51.1 mmol) in THF (60 ml) at -78°C and the mixture was stirred at that temperature for 30 min. Acetyl chloride (4.7 ml, 66 mmol) in THF (15 ml) was added dropwise and the mixture was stirred at -70°C for 2 h. For work-up, water was added and the mixture was extracted with ethyl acetate (3x) and the combined organic phases were washed with brine, filtered through a silicone filter and concentrated. The residue was purified twice by flash chromatography (SNAP cartridge, hexanes/ethyl acetate gradient, 0%→20% ethyl acetate) to give the title compound 16.7 g (72% yield) as mixture of cis-/trans-isomers.
- 20

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$, key signals major isomer): δ [ppm] = 7.64-7.55 (m, 4H), 7.50-7.39 (m, 6H), 4.16 (q, 2H), 3.78-3.67 (m, 1H), 2.07 (s, 3H), 1.66-1.54 (m, 4H), 1.44-1.32 (m, 2H), 1.19 (t, 3H), 1.03-0.97 (m, 9H)

- 25 **Intermediate 18**

8-[[tert-butyl(diphenyl)silyl]oxy]-2-(2-chloro-4-fluorophenyl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one

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A mixture of ethyl 1-acetyl-4-[[tert-butyl(diphenyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers) (5.00 g, 11.0 mmol), (2-chloro-4-fluorophenyl)hydrazine hydrochloride (4.58 g, 95 % purity, 22.1 mmol), triethylamine (3.8 ml, 28 mmol) and ethanol (10 ml) was heated in a microwave reactor for 12 h at 185°C. Upon cooling, the mixture was diluted with ethyl acetate and washed with aqueous hydrochloric acid (1 M), water, saturated aqueous bicarbonate solution and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (100 SNAP cartridge, hexanes/ethyl acetate gradient, 5%→20% ethyl acetate) to give the title compound as major isomer (isomer 1) 4.64 g (76% yield) as well as a minor isomer (isomer 2) (898 mg, 14 % yield, containing impurities).

Major isomer (isomer 1):

LC-MS (Method 1): Rt = 1.79 min; MS (ESIpos): m/z = 549 [M+H]⁺

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.68-7.61 (m, 5H), 7.57 (dd, 1H), 7.51-7.40 (m, 6H), 7.39-7.32 (m, 1H), 3.87-3.77 (m, 1H), 2.17-2.02 (m, 2H), 1.94 (s, 3H), 1.75-1.59 (m, 6H), 1.03 (s, 9H)

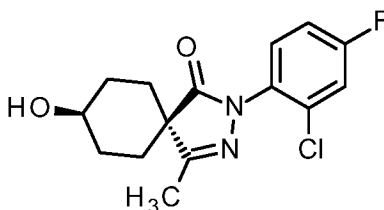
Minor isomer (isomer 2):

LC-MS (Method 1): Rt = 1.84 min; MS (ESIpos): m/z = 549 [M+H]⁺

¹H-NMR (400 MHz, DMSO-*d*₆, significant signals): δ [ppm] = 4.14-4.10 (m, 1H), 2.10 (s, 3H)

Intermediate 19

(cis)-2-(2-chloro-4-fluorophenyl)-8-hydroxy-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one



TBAF (22 ml, 1.0 M in THF, 22 mmol) was added dropwise to a solution of 8-[[tert-butyl(diphenyl)silyl]oxy]-2-(2-chloro-4-fluorophenyl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (Isomer 1) (6.00 g, 10.9 mmol) in THF (110 ml) and the mixture was stirred for 5 h at 80°C. For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The

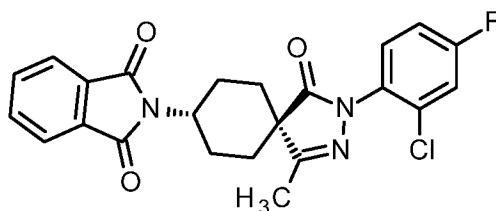
130

combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (100 g SNAP cartridge, hexanes/ethyl acetate gradient, 15%→100% ethyl acetate) to give the title compound a single isomer 2.8 g (82 % yield).

- 5 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.65 (dd, 1H), 7.58 (dd, 1H), 7.36 (td, 1H), 4.72 (d, 1H), 3.56-3.48 (m, 1H), 2.00 (s, 3H), 1.99-1.89 (m, 2H), 1.84-1.65 (m, 6H)

Intermediate 20

2-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione



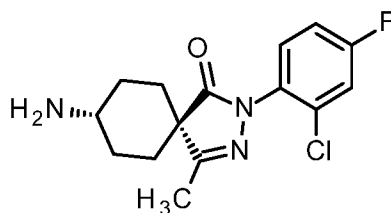
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Diisopropyl azodicarboxylate (2.7 ml, 14 mmol) was added dropwise at 0 °C to a solution of (cis)-2-(2-chloro-4-fluorophenyl)-8-hydroxy-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (2.80 g, 9.01 mmol), phthalimide (2.01 g, 13.5 mmol) and triphenylphosphine (3.58 g, 13.5 mmol) in THF (73 ml) and the mixture was stirred at room temperature for 3 h. For work-up, the mixture

15 was concentrated and the residue was purified by flash chromatography (120 g SNAP cartridge, hexanes/ethyl acetate gradient, 12% →100% ethyl acetate) to give the title compound 2.49 g (62 % yield).

Intermediate 21

(trans)-8-amino-2-(2-chloro-4-fluorophenyl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one



20

- A mixture of 2-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione (1.89 g, 4.30 mmol) and hydrazine hydrate (630 µl, 13 mmol) in ethanol (45 ml) was stirred for 2 h at 80°C. Upon cooling, the reaction mixture was concentrated and purified by flash chromatography (28 g NH₂-SNAP cartridge, dichloromethane/methanol gradient 0% → 10% methanol) to give the title compound (1.10 g,
- 25 82% yield)

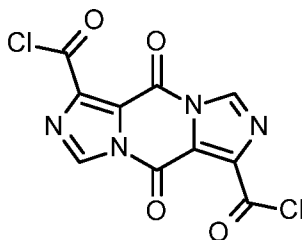
131

LC-MS (Method 1): Rt = 0.66 min; MS (ESIpos): m/z = 310 [M+H]⁺

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 7.64 (dd, 1H), 7.56 (dd, 1H), 7.37-7.32 (m, 1H), 2.96-2.89 (m, 1H), 2.42-2.15 (m, 2H), 2.14 (s, 3H), 2.04-1.91 (m, 4H), 1.61-1.49 (m, 2H), 1.47-1.38 (m, 2H)

5 **Intermediate 22**

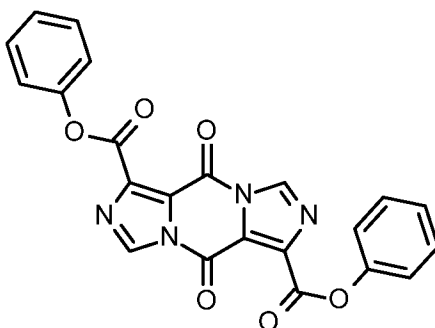
5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarbonyl dichloride



In a dried flask, to 1*H*-imidazole-4,5-dicarboxylic acid (25 g, 157 mmol) in toluene (334 ml), DMF (12.1 ml) and thionyl chloride (94 ml, 1.29 mol) were added. The mixture was stirred for 24 h at 80°C. The mixture was concentrated under reduced pressure. Toluene (100 ml) was added and the mixture was concentrated under reduced pressure to give 35.5 g of the title compound as crude material which was used at the same day without further purification for subsequent steps.

Intermediate 23

15 Diphenyl 5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxylate



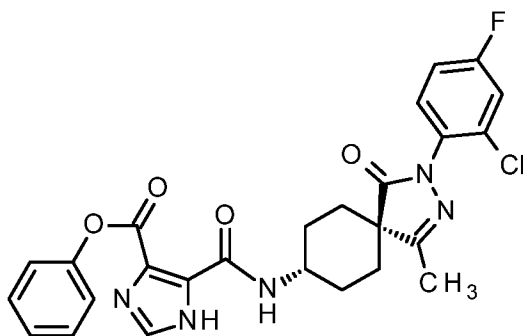
A mixture of 5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarbonyl dichloride (20.0 g, crude product) and phenol (12.6 g, 0.13 mol) was suspended in dichloromethane (380 ml). The resulting mixture was cooled to 0°C and pyridine (and 10.8 ml, 0.13 mol) was added dropwise. The reaction was stirred for 3 h at room temperature. The precipitate was filtered off and washed with dichloromethane. The obtained solid material was dried under vacuum at 50

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°C to give 21.6 g of the title compound as a crude product which was used without further purification in the subsequent steps.

Intermediate 24

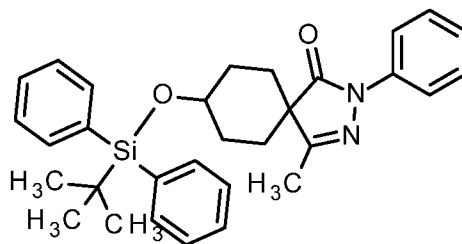
phenyl 5-[[[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]carbamoyl]-1H-imidazole-4-carboxylate



A mixture of diphenyl 5,10-dioxo-5H,10H-diimidazo[1,5-a:1',5'-d]pyrazine-1,6-dicarboxylate (83.0 mg, 194 μ mol), (trans)-8-amino-2-(2-chloro-4-fluorophenyl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (120 mg, 387 μ mol) and triethylamine (54 μ l, 390 μ mol) in dichloromethane (1.5 ml) was stirred for 5 h at room temperature. For work-up, the reaction mixture was concentrated and the residue was purified by flash chromatography (50 g NH₂-SNAP cartridge, dichloromethane/methanol gradient 0% -> 10% methanol) to give the title compound (850 mg, containing impurities).

Intermediate 25

8-[[[tert-butyl(diphenyl)silyl]oxy]-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers)



A mixture of ethyl 1-acetyl-4-[[[tert-butyl(diphenyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers (2.50 g, 5.52 mmol) and phenylhydrazine hydrochloride (958 mg, 6.63 mmol) in o-xylene (30 ml) was stirred at reflux for 16 h. Upon cooling, the mixture was diluted with ethyl acetate and washed with aqueous hydrochloric acid (1 M), water, saturated aqueous bicarbonate solution and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (100 SNAP cartridge, hexanes/ethyl acetate

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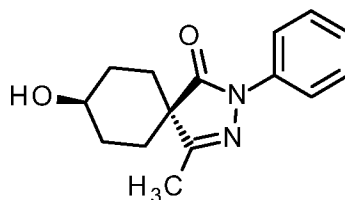
gradient, 0%→20% ethyl acetate) to give the title compound as mixture of cis-/trans-isomers 1.40 g (51 % yield).

LC-MS (Method 2): $R_t = 1.48$ min; MS (ESIpos): $m/z = 497$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$, key signals major isomer): δ [ppm] = 7.85-7.81 (m, 2H), 7.65 (dd, 4H), 7.50-7.36 (m, 9H), 7.22-7.15 (m, 1H), 3.85 (br s, 1H), 2.00 (s, 3H), 1.06-1.00 (m, 9H)

Intermediate 26

(cis)-8-hydroxy-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one



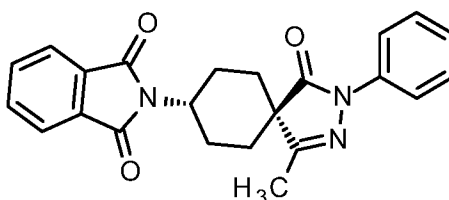
TBAF (7.0 ml, 1.0 M THF, 7.0 mmol) was added dropwise to a solution of 8-[[tert-butyl(diphenyl)silyl]oxy]-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers) (1.40 g, 2.82 mmol) in THF (24 ml) and the mixture was stirred for 20 h at room temperature. TBAF (1.4 ml, 1.0 M THF, 1.5 mmol) was added and the mixture was stirred for 4 h. For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (25 g SNAP cartridge, hexanes/ethyl acetate gradient, 30%→100% ethyl acetate) to give the title compound a single isomer 490 mg (67 % yield).

LC-MS (Method 2): $R_t = 0.96$ min; MS (ESIpos): $m/z = 259$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.86-7.80 (m, 2H), 7.44-7.38 (m, 2H), 7.20-7.15 (m, 1H), 4.72 (d, 1H), 3.59-3.49 (m, 1H), 2.06 (s, 3H), 2.02-1.91 (m, 2H), 1.82-1.62 (m, 6H)

Intermediate 27

2-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione



134

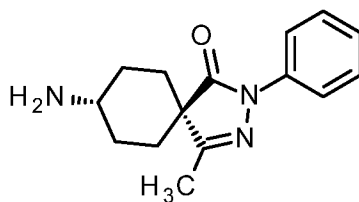
Diisopropyl azodicarboxylate (560 μ l, 2.8 mmol) was added dropwise to a solution of (cis)-8-hydroxy-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (490 mg, 1.90 mmol), phthalimide (419 mg, 2.85 mmol) and triphenylphosphine (746 mg, 2.85 mmol) in THF (31 ml) and the mixture was stirred at room temperature for 12 h. For work-up, the mixture was concentrated and the residue was purified by flash chromatography (SNAP cartridge, hexanes/ethyl acetate 4:1) to give the title compound 323 mg.

LC-MS (Method 2): R_t = 1.35 min; MS (ESIpos): m/z = 387 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.820 (1.88), 1.825 (2.50), 1.853 (1.98), 1.863 (1.14), 1.891 (1.27), 1.902 (1.07), 1.987 (0.65), 2.467 (16.00), 2.518 (1.88), 7.178 (0.85), 7.197 (1.79), 7.215 (1.05), 7.416 (2.28), 7.421 (0.75), 7.434 (2.35), 7.437 (2.81), 7.456 (1.94), 7.815 (12.04), 7.839 (1.29), 7.845 (0.94), 7.849 (1.82), 7.855 (4.55), 7.858 (4.35), 7.861 (6.55), 7.871 (5.75), 7.877 (5.09), 7.880 (2.99), 7.882 (2.25), 7.886 (1.05), 7.893 (1.15).

Intermediate 28

(trans)-8-amino-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one



A mixture of 2-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione (323 mg, 834 μ mol) and hydrazine hydrate (200 μ l, 4.2 mmol) in ethanol (7.1 ml) was stirred for 3 h at 80°C. Upon cooling, solids were filtered off, washed with ethanol and the filtrate was concentrated and dried to give the title compound (173 mg).

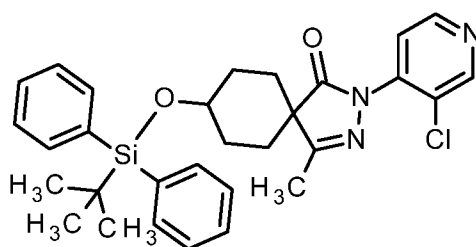
LC-MS (Method 2): R_t = 0.96 min; MS (ESIpos): m/z = 258 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ [ppm] = 7.86-7.80 (m, 2H), 7.45-7.38 (m, 2H), 7.21-7.15 (m, 1H), 2.92-2.82 (m, 1H), 2.21 (s, 3H), 2.03-1.83 (m, 4H), 1.62-1.49 (m, 2H), 1.46-1.35 (m, 2H)

Intermediate 29

8-[[tert-butyl(diphenyl)silyl]oxy]-2-(3-chloropyridin-4-yl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers)

135

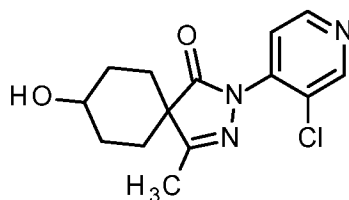


A mixture of ethyl 1-acetyl-4-[[tert-butyl(diphenyl)silyl]oxy]cyclohexanecarboxylate (mixture of cis-/trans-isomers) (985 mg, 2.18 mmol) and 3-chloro-4-hydrazinylpyridine (375 mg, 2.61 mmol) in o-xylene (7.8 ml) was stirred at reflux for 16 h. hydrochloric acid (650 μ l, 4.0 M in dioxane, 2.6 mmol) was added and the mixture was stirred for 20 h at reflux. N-methylpyrrolidone (3.0 ml) was added and the mixture was stirred for 24 h at 160°C. Upon cooling, diluted aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (25 g SNAP cartridge, hexanes/ethyl acetate gradient, 20%→50% ethyl acetate) to give the title compound 180 mg (16 % yield) as mixture of isomers.

LC-MS (Method 2): R_t = 1.52 min; MS (ESIpos): m/z = 532 $[M+H]^+$

Intermediate 30

2-(3-chloropyridin-4-yl)-8-hydroxy-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers)



TBAF (850 μ l, 1.0 M in THF, 850 μ mol) was added dropwise to a solution of 8-[[tert-butyl(diphenyl)silyl]oxy]-2-(3-chloropyridin-4-yl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers) (180 mg, 338 μ mol) in THF (2.9 ml) and the mixture was stirred for 20h at room temperature. For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (10 g SNAP cartridge, hexanes/ethyl acetate 1:1 to ethyl acetate to ethyl acetate/methanol 9:1 gradient) to give the title compound (36.0 mg, 36 % yield) as a mixture of cis-/trans-isomers (ratio: 6:1 by 1H NMR).

LC-MS (Method 2): R_t = 0.84 min; MS (ESI_{neg}): m/z = 292 $[M-H]^-$

136

Major isomer (isomer 1):

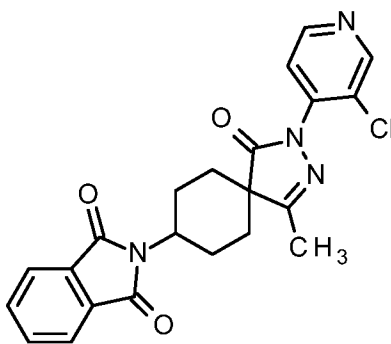
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.77 (s, 1H), 8.61 (d, 1H), 7.57 (d, 1H), 4.73 (d, 1H), 3.60-3.44 (m, 1H), 2.04 (s, 3H), 1.97-1.66 (m, 8H)

Minor isomer (isomer 2):

- 5 ¹H-NMR (400 MHz, DMSO-*d*₆, key signals): δ [ppm] = 4.65 (d, 1H), 3.91-3.81 (m, 1H), 2.11 (s, 3H)

Intermediate 31

2-[3-(3-chloropyridin-4-yl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione (mixture of cis-/trans-isomers)



10

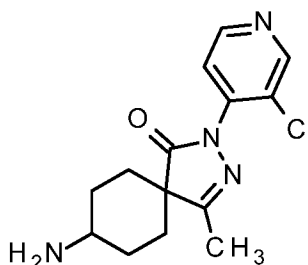
- Diisopropyl azodicarboxylate (34 μl, 170 μmol) was added dropwise to a solution of 2-(3-chloropyridin-4-yl)-8-hydroxy-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers) (34.0 mg, 116 μmol), phthalimide (25.5 mg, 174 μmol) and triphenylphosphine (34 μl, 170 μmol) in THF (1.4 ml) and the mixture was stirred at room temperature for 12 h. For work-
- 15 up, the mixture was concentrated and the residue was purified by flash chromatography (10 g SNAP cartridge, hexanes/ethyl acetate gradient, 0% ->100% ethyl acetate) to give the title compound 59.0 mg (containing impurities).

LC-MS (Method 2): R_t = 1.16 min; MS (ESIpos): m/z = 423 [M+H]⁺

Intermediate 32

- 20 8-amino-2-(3-chloropyridin-4-yl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers)

137

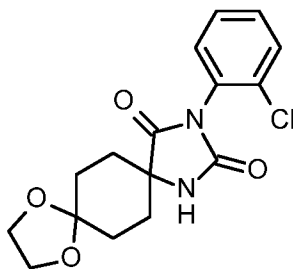


A mixture of 2-[3-(3-chloropyridin-4-yl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-isoindole-1,3(2H)-dione (mixture of cis-/trans-isomers) (58.0 mg, 137 μ mol) and hydrazine hydrate (34 μ l, 690 μ mol) in ethanol (1.2 ml) was stirred for 3 h at 80°C. Upon cooling, solids were filtered off, washed with ethanol and the filtrate was concentrated to give the title compound (61.0 mg, 40% yield), which was used in the next step without further purification

LC-MS (Method 2): R_t = 0.74 min; MS (ESIpos): m/z = 293 $[M+H]^+$

Intermediate 33

3-(2-chlorophenyl)-9,12-dioxaspiro[4.2.4.2]tetradecane-2,4-dione



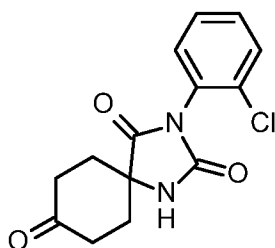
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A mixture of methyl 8-amino-1,4-dioxaspiro[4.5]decane-8-carboxylate hydrochloric acid salt (10.0 g, 39.7 mmol, CAS No: 9017187-99-0) and sodium carbonate (8.42 g, 79.5 mmol) in DMSO (40 ml) was stirred for 2 h at room temperature. The mixture was then cooled to 0°C, 1-chloro-2-isocyanatobenzene (4.8 ml, 40 mmol) was added dropwise and the mixture was stirred at reflux for 2 h. Upon cooling, water was added and the precipitate formed was collected by filtration, washed with water and dried to give the title compound 6.77 g (51 % yield) which was used in the next step without further purification.

Intermediate 34

3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4,8-trione

138

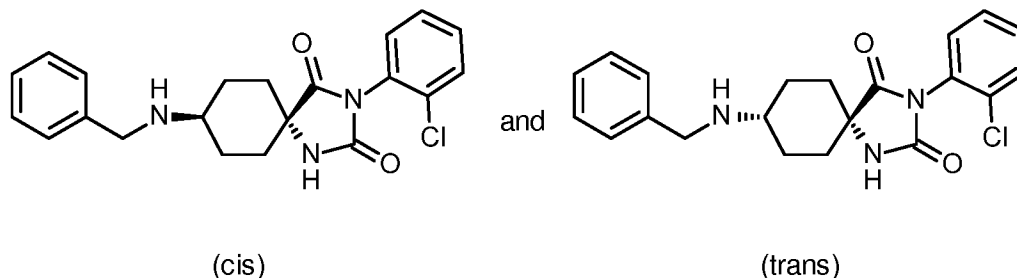


A mixture of 3-(2-chlorophenyl)-9,12-dioxo-1,3-diazadispiro[4.2.4.2]tetradecane-2,4-dione (6.77 g, 20.1 mmol) and hydrochloric acid (13 ml, 4.0 M in water, 50 mmol) in acetone (77 ml) was stirred for 12 h at 60°C. Upon cooling, aqueous sodium bicarbonate was added and the mixture was extracted with dichloromethane. The combined organic phases were washed with aqueous sodium bicarbonate and water, filtered through a silicone filter and concentrated to give the title compound 4.70 g which was used in the next step without further purification.

LC-MS (Method 2): R_t = 0.80 min; MS (ESIpos): m/z = 293 $[M+H]^+$

Intermediate 35

(cis)-8-(benzylamino)-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (major isomer) and (trans)-8-(benzylamino)-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (minor isomer)



A mixture of 3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4,8-trione (800 mg, 2.73 mmol), 1-phenylmethanamine (300 μ l, 2.7 mmol) and sodium triacetoxyborohydride (869 mg, 4.10 mmol) in 1,2-dichloroethane (28 ml) was stirred for 4 h at room temperature. For work-up, water was added and the mixture was extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous sodium bicarbonate and water, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (100 g SNAP cartridge, hexanes/ethyl acetate gradient, 50% $\rightarrow$ 100% ethyl acetate) to give the title compound (200 mg, 19% yield) as a mixture of isomers (cis/trans = 9:1 by 1H NMR).

LC-MS (Method 2): R_t = 1.11 min; MS (ESI_{neg}): m/z = 382 $[M-H]^+$

Major isomer (cis):

139

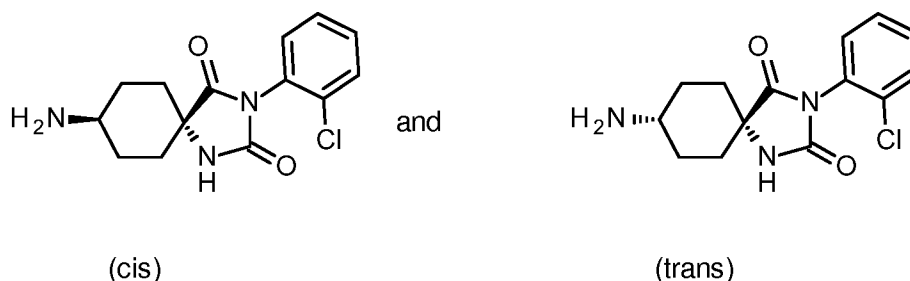
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.88 (s, 1H), 7.70-7.61 (m, 1H), 7.56-7.43 (m, 3H), 7.40-7.29 (m, 4H), 7.27-7.18(m, 1H), 3.75 (br s, 2H), 2.77-2.69 (m, 1H), 2.22-2.09 (m, 2H), 1.84-1.67 (m, 4H), 1.58-1.42 (m, 2H)

Minor Isomer (trans):

- 5 ¹H-NMR (400 MHz, DMSO-*d*₆, key signals): δ [ppm] = 9.07 (s, 1H), 3.78 (br s, 3H)

Intermediate 36

(cis)-8-amino-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (major isomer) and (trans)-8-amino-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (minor isomer)

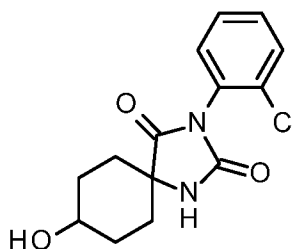


- 10 A mixture of 8-(benzylamino)-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (mixture of cis-/trans-isomers (200 mg, 521 μ mol, Intermediate 35), palladium(II)hydroxide 20% on charcoal (18.3 mg/26.0 μ mol) in methanol (2.8 ml) was stirred under 1 bar hydrogen atmosphere at room temperature. Upon complete conversion of the starting material, the mixture was filtered through a pad of celite, eluted with methanol and the filtrate was
15 concentrated to give the title compound (140 mg) as a mixture of cis-/trans-isomers which was used in the next step without further purification.

LC-MS (Method 2): Rt = 0.73 min; MS (ESI^{neg}): m/z = 292 [M-H]⁻

Intermediate 37

3-(2-chlorophenyl)-8-hydroxy-1,3-diazaspiro[4.5]decane-2,4-dione (mixture of cis-/trans-
20 isomers)



A mixture of 3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4,8-trione (800 mg, 2.73 mmol) and sodium borohydride (114 mg, 3.01 mmol) in ethanol (24 ml) was stirred for 24 h at room

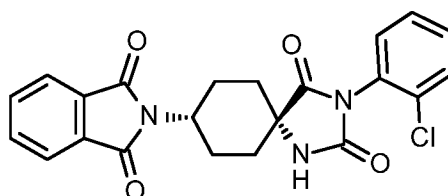
140

temperature. For work-up, water was added and the mixture was extracted with ethyl acetate. The combined organic phases were filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (25 SNAP cartridge, hexanes/ethyl acetate 1:1 to ethyl acetate to ethyl acetate/methanol 4:1 gradient) to give the title compound (500 mg, 57% yield) as a 6:4 mixture of cis-/trans isomers.

LC-MS (Method 2): R_t = 0.71 min (minor isomer); 0.76 major isomer; MS (ESIpos): m/z = 295.1 $[M+H]^+$

Intermediate 38

(trans)-3-(2-chlorophenyl)-8-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1,3-diazaspiro[4.5]decane-2,4-dione



(trans)

Diisopropyl azodicarboxylate (550 μ l, 2.8 mmol) was added dropwise to a solution of 3-(2-chlorophenyl)-8-hydroxy-1,3-diazaspiro[4.5]decane-2,4-dione (mixture of cis-/trans-isomers) (550 mg, 1.87 mmol), phthalimide (412 mg, 2.80 mmol) and triphenylphosphine (734 mg, 2.80 mmol) in THF (22 ml) and the mixture was stirred at room temperature for 3 d. For work-up, the mixture was concentrated and the residue was purified by flash chromatography (50 g SNAP cartridge, hexanes/ethyl acetate gradient, 0% ->50% ethyl acetate) to give (trans)-3-(2-chlorophenyl)-8-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1,3-diazaspiro[4.5]decane-2,4-dione 166 mg (20% yield) as single isomer as well as well as (cis)-3-(2-chlorophenyl)-8-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1,3-diazaspiro[4.5]decane-2,4-dione (505 mg, containing triphenylphosphine oxide as impurity, see intermediate 39)

trans isomer:

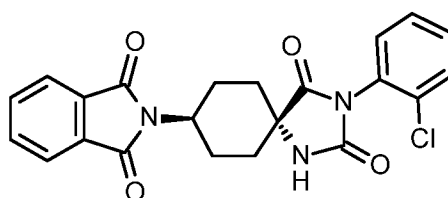
LC-MS (Method 2): R_t = 1.10 min; MS (ESIpos): m/z = 424 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 9.37 (s, 1H), 7.94-7.78 (m, 4H), 7.70-7.64 (m, 1H), 7.59-7.46 (m, 3H), 4.24-4.04 (m, 1H), 2.05-1.74 (m, 6H)

Intermediate 39

(cis)-3-(2-chlorophenyl)-8-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1,3-diazaspiro[4.5]decane-2,4-dione

141



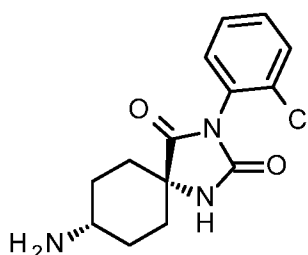
(cis)

Was isolated in the synthesis of (trans)-3-(2-chlorophenyl)-8-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1,3-diazaspiro[4.5]decane-2,4-dione (Intermediate 38).

¹H-NMR (400 MHz, DMSO-*d*₆, key signals): δ [ppm] = 8.51 (s, 1H), 7.91-7.79 (m, 4H), 4.11-4.03 (m, 1H), 2.93-2.73 (m, 2H), 2.29-2.20 (m, 1H), 2.16-2.05 (m, 1H), 1.91-1.58 (m, 6H)

Intermediate 40

(trans)-8-amino-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione

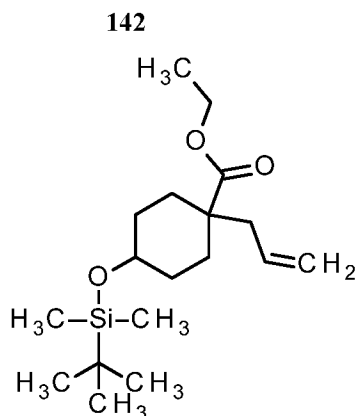


A mixture of (trans)-3-(2-chlorophenyl)-8-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1,3-diazaspiro[4.5]decane-2,4-dione (137 mg, 323 μ mol, Intermediate 38) and hydrazine hydrate (98 μ l, 1.6 mmol) in ethanol (2.8 ml) was stirred for 3 h at 80°C. Upon cooling, solids were filtered off, washed with ethanol and the filtrate was concentrated. The residue was stirred with dichloromethane, solids were filtered off, washed with dichloromethane and the filtrate was concentrated to give the title compound (40 mg)

LC-MS (Method 2): *R*_t = 0.78 min; MS (ESI^{neg}): *m/z* = 292 [M-H]⁻

Intermediate 41

ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(prop-2-en-1-yl)cyclohexanecarboxylate (mixture of cis-/trans-isomers)



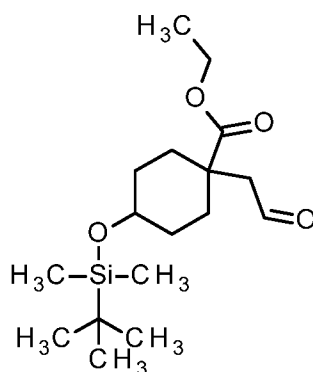
Lithium diisopropylamide (23 ml, 1.8 M in THF, 42 mmol) was added dropwise to a solution of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]cyclohexanecarboxylate (10.0 g, 34.9 mmol, mixture of cis-/trans-isomers) in THF (47 ml) at -78°C and the mixture was stirred at that temperature for 5 30 min. 3-bromoprop-1-ene (4.4 ml, 52 mmol) in THF (47 ml) was added dropwise and the mixture was stirred at -70°C for 1 h and then allowed to warm to room temperature over night. For work-up, water was added and the mixture was extracted with tert-butyl methyl ether (3x) and the combined organic phases were washed with brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (340 g SNAP cartridge, 10 hexanes/ethyl acetate gradient, 0%->10% ethyl acetate) to give the title compound 10.3 g (81 % yield) as a mixture of cis-/trans-isomers.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: -0.007 (0.65), 0.000 (13.85), 0.006 (2.24), 0.812 (1.10), 0.820 (16.00), 0.827 (1.12), 0.835 (0.43), 0.839 (0.30), 0.847 (2.29), 1.129 (0.31), 1.138 (1.69), 1.147 (0.65), 1.156 (3.77), 1.164 (0.42), 1.174 (1.82), 1.185 (0.84), 1.201 (0.38), 1.219 (0.45), 1.658 (0.30), 1.682 (0.47), 1.989 (0.40), 1.994 (0.39), 2.012 (0.23), 2.020 (0.23), 2.134 (0.74), 2.153 (0.77), 2.504 (0.49), 2.509 (0.30), 3.566 (0.18), 4.039 (0.59), 4.056 (1.67), 4.074 (1.62), 4.092 (0.49), 4.961 (0.24), 4.964 (0.26), 4.967 (0.37), 4.979 (0.41), 4.985 (0.29), 5.007 (1.09), 5.590 (0.25), 5.611 (0.18), 5.618 (0.19), 5.630 (0.20), 5.636 (0.17), 5.657 (0.21).

Intermediate 42

20 ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-oxoethyl)cyclohexanecarboxylate (mixture of cis-/trans-isomers)

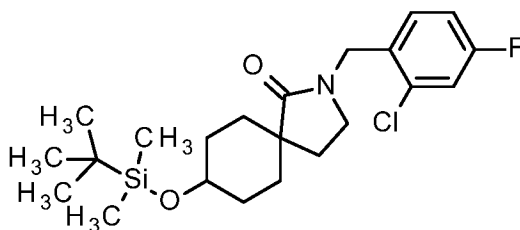
143



Ozone was bubbled through a solution of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(prop-2-en-1-yl)cyclohexanecarboxylate (7.68 g, 23.5 mmol, mixture of cis-/trans isomers) in dichloromethane (340 ml) at -78°C until a blue color persisted. Dimethyl sulfide (17 ml, 240 mmol) was added and the mixture was allowed to warm to room temperature over night. For work-up, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were washed with brine, filtered through a silicone filter and concentrated to give the title compound 8.06 g (104 % yield) which was used in the next step without further purification.

10 **Intermediate 43**

8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorobenzyl)-2-azaspiro[4.5]decan-1-one (mixture of cis-/trans-isomers)

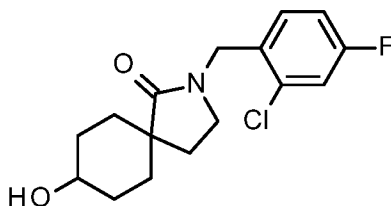


Sodium triacetoxyborohydride (677 mg, 3.20 mmol) was added to a solution of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-oxoethyl)cyclohexanecarboxylate (750 mg, 2.28 mmol, mixture of cis-/trans-isomers), 1-(2-chloro-4-fluorophenyl)methanamine (437 mg, 2.74 mmol) and acetic acid (140 µl, 2.5 mmol) in 1,2-dichloroethane (4.5 ml) and the mixture was stirred for 12 h at room temperature. For work-up, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (SNAP cartridge, hexanes/ethyl acetate-gradient) to give the title compound (521 mg, 54% yield) as a mixture of cis-/trans-isomers.

Intermediate 44

144

2-(2-chloro-4-fluorobenzyl)-8-hydroxy-2-azaspiro[4.5]decan-1-one (mixture of cis-/trans-isomers)



TBAF (3.6 ml, 1.0 M in THF, 3.6 mmol) was added dropwise to a solution of 8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorobenzyl)-2-azaspiro[4.5]decan-1-one (518 mg, 1.22 mmol, mixture of cis-/trans-isomers) in THF (11 ml) and the mixture was stirred for 20 h at room temperature. For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (50 g SNAP cartridge, hexanes to hexanes/ethyl acetate 1:1 to ethyl acetate/methanol 9:1 gradient) to give the title compound (224 mg, 59 % yield) as a mixture of cis-/trans-isomers.

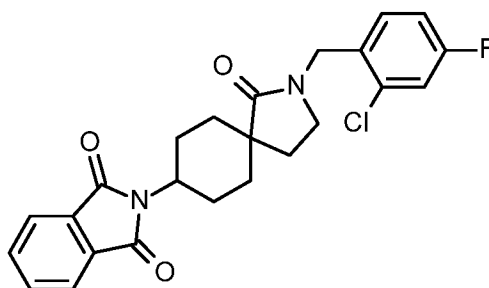
LC-MS (Method 2): $R_t = 1.08$ min; MS (ESIpos): $m/z = 312$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.094 (1.50), 1.109 (4.24), 1.127 (7.00), 1.132 (3.36), 1.145 (4.06), 1.154 (7.40), 1.172 (9.18), 1.190 (4.36), 1.455 (1.45), 1.489 (3.31), 1.517 (3.03), 1.635 (3.24), 1.647 (3.46), 1.669 (2.36), 1.681 (2.06), 1.829 (4.31), 1.847 (8.35), 1.864 (6.07), 1.884 (3.29), 1.893 (3.13), 1.912 (1.88), 1.922 (1.63), 1.988 (14.80), 2.322 (1.10), 2.327 (1.55), 2.331 (1.18), 2.523 (4.76), 2.665 (1.13), 2.669 (1.55), 2.673 (1.15), 3.112 (4.87), 3.129 (8.03), 3.146 (4.84), 3.478 (0.98), 3.712 (2.03), 3.999 (1.38), 4.010 (1.91), 4.017 (3.84), 4.027 (1.93), 4.035 (3.74), 4.053 (1.25), 4.355 (5.62), 4.363 (5.69), 4.420 (16.00), 4.462 (1.13), 4.473 (1.08), 7.205 (0.98), 7.212 (1.03), 7.227 (3.54), 7.233 (3.81), 7.247 (6.80), 7.253 (4.19), 7.263 (4.51), 7.268 (1.68), 7.284 (0.95), 7.458 (3.39), 7.464 (3.41), 7.480 (3.29), 7.486 (3.29).

Intermediate 45

2-[2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]-1H-isoindole-1,3(2H)-dione (mixture of trans-/cis-isomers)

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Diisopropyl azodicarboxylate (210 μ l, 1.1 mmol) was added dropwise to a solution of 2-(2-chloro-4-fluorobenzyl)-8-hydroxy-2-azaspiro[4.5]decan-1-one (220 mg, 706 μ mol, mixture of cis-/trans-isomers), phthalimide (156 mg, 1.06 mmol) and triphenylphosphine (278 mg, 1.1 mmol) in THF (8.4 ml) and the mixture was stirred at room temperature for 12 h. For work-up, the mixture was concentrated and the residue was purified by flash chromatography (SNAP cartridge, hexanes/ethyl acetate gradient) to give the title compound (155 mg, 50 % yield) as mixture of trans-/cis-isomers (ratio by LC-MS ca. 10:1)

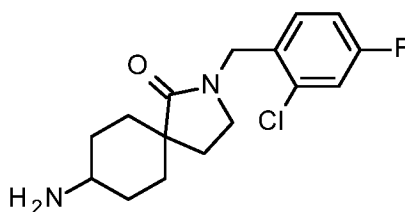
LC-MS (Method 2): R_t = 1.40 min (major isomer), 1.45 min (minor isomer); MS (ESIpos): m/z =

441 $[M+H]^+$

1H -NMR (400 MHz, DMSO- d_6) δ [ppm]: 1.154 (2.30), 1.172 (5.20), 1.185 (2.37), 1.190 (2.72), 1.254 (1.20), 1.270 (1.11), 1.552 (1.13), 1.586 (3.67), 1.604 (2.61), 1.628 (2.08), 1.637 (2.81), 1.665 (3.30), 1.700 (2.19), 1.988 (8.92), 2.006 (5.22), 2.024 (3.12), 2.181 (1.88), 2.192 (1.79), 2.212 (1.64), 2.224 (1.64), 2.323 (0.93), 2.327 (1.31), 2.332 (0.93), 2.518 (4.29), 2.523 (3.05), 2.665 (0.93), 2.669 (1.33), 2.673 (0.93), 3.186 (3.36), 3.204 (5.40), 3.221 (3.19), 3.980 (0.86), 3.999 (1.17), 4.010 (1.46), 4.017 (2.24), 4.034 (1.93), 4.052 (0.82), 4.447 (1.17), 4.461 (11.29), 7.213 (1.08), 7.219 (1.22), 7.234 (2.85), 7.241 (3.08), 7.256 (2.08), 7.262 (2.30), 7.281 (3.01), 7.296 (3.14), 7.302 (1.93), 7.318 (1.68), 7.469 (3.10), 7.475 (3.14), 7.491 (3.16), 7.497 (3.10), 7.815 (1.37), 7.819 (1.20), 7.825 (2.19), 7.827 (3.01), 7.832 (5.51), 7.836 (15.93), 7.841 (16.00), 7.846 (6.57), 7.851 (2.79), 7.859 (1.00), 7.863 (1.28).

Intermediate 46

8-amino-2-(2-chloro-4-fluorobenzyl)-2-azaspiro[4.5]decan-1-one (mixture of trans-/cis-isomers)



A mixture of 2-[2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]-1H-isoindole-1,3(2H)-dione (153 mg, 347 μ mol, mixture of trans-/cis-isomers) and hydrazine hydrate (86 μ l,

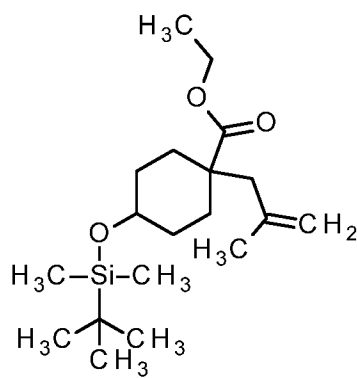
146

1.7 mmol) in ethanol (3.0 ml) was stirred for 3 h at 80°C. Upon cooling, solids were filtered off, washed with ethanol and the filtrate was concentrated to give the title compound (132 mg) as mixture of trans-/cis-isomers which was used in the next step without further purification.

¹H-NMR (400 MHz, DMSO-*d*₆, key signals major isomer): δ [ppm] = 7.48 (dd, 1H), 7.29-7.20 (m, 2H), 4.43 (s, 2H), 3.15 (t, 2H), 1.90-1.84 (m, 2H), 1.73-1.63 (m, 2H), 1.58-1.48 (m, 2H), 1.43-1.34 (m, 2H)

Intermediate 47

ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-methylprop-2-en-1-yl)cyclohexanecarboxylate (mixture of cis-/trans-isomers)



10

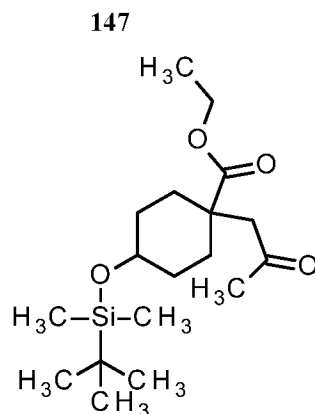
Lithium diisopropylamide (21 ml, 2.0 M in THF, 42 mmol) was added dropwise to a solution of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]cyclohexanecarboxylate (10.0 g, 34.9 mmol, mixture of cis-/trans-isomers) in THF (47 ml) at -78°C and the mixture was stirred at that temperature for 30 min. 3-bromo-2-methylprop-1-ene (5.4 ml, 52 mmol) was added dropwise and the mixture was stirred at -70°C for 1 h at that temperature and then allowed to warm to room temperature over night. For work-up, water was added and the mixture was extracted with ethyl acetate (3x) and the combined organic phases were washed with brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (340 g SNAP cartridge, hexanes/ethyl acetate gradient, 0%->10% ethyl acetate) to give the title compound as mixture of cis-/trans-isomers (9.53 g, 80 % yield).

20

GC-MS (Method 8): *R*_t = 19.66 min; MS (CI⁺): *m/z* = 431.2 [M+H]⁺

Intermediate 48

ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-oxopropyl)cyclohexanecarboxylate (isomer 1)

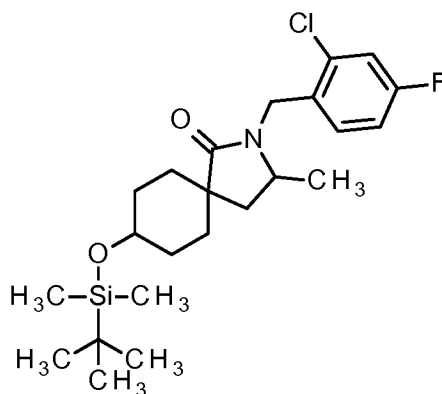


Was prepared in analogy to the synthesis of ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-oxoethyl)cyclohexanecarboxylate (mixture of cis-/trans-isomers) using ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-methylprop-2-en-1-yl)cyclohexanecarboxylate (6.45 g, 18.9 mmol, mixture of cis-/trans-isomers) as starting material. Upon purification by flash chromatography (100 SNAP cartridge, hexanes/ethyl acetate-gradient 0% -> 100% ethyl acetate), the title compound (1.47 g, 23% yield) was isolated as single isomer (by ¹H NMR).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 4.02 (q, 2H), 3.69-3.62 (m, 1H), 2.73 (s, 2H), 2.03 (s, 3H), 2.02-1.95 (m, 2H), 1.64-1.56 (n, 2H), 1.43-1.27 (m, 4H), 1.12 (t, 3H), 0.84 (s, 9H), 0.02 (s, 6H)

Intermediate 49

(3RS)-8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorobenzyl)-3-methyl-2-azaspiro[4.5]decan-1-one (isomer 1 at cyclohexane ring)



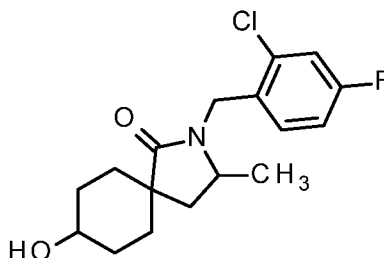
Was prepared in analogy to the synthesis of 8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorobenzyl)-2-azaspiro[4.5]decan-1-one (mixture of cis-/trans-isomers) using ethyl 4-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-oxopropyl)cyclohexanecarboxylate (594 mg, 1.73 mmol, isomer 1) as starting material to give the title compound (404 mg, 48% yield) as single isomer at cyclohexane ring.

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¹H-NMR (400 MHz, DMSO-*d*₆, key signals): δ [ppm] = 7.46 (dd, 1H), 7.26-7.19 (m, 2H), 4.63 (d, 1H), 4.22 (d, 1H), 3.97-3.90 (m, 1H), 3.46-3.36 (m, 1H), 2.22 (dd, 1H), 1.09 (d, 3H), 0.90-0.83 (m, 9H), 0.04 (s, 6H)

Intermediate 50

- 5 (3RS)-2-(2-chloro-4-fluorobenzyl)-8-hydroxy-3-methyl-2-azaspiro[4.5]decan-1-one (isomer 1 at cyclohexane ring)



- TBAF (2.3 ml, 1.0 M in THF, 2.3 mmol) was added dropwise to a solution of (3RS)-8-[[tert-butyl(dimethyl)silyl]oxy]-2-(2-chloro-4-fluorobenzyl)-3-methyl-2-azaspiro[4.5]decan-1-one (404 mg, 918 μmol, isomer 1 at cyclohexane ring) in THF (7.9 ml) and the mixture was stirred for 20 h at room temperature. For work-up, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, filtered through a silicone filter and concentrated. The residue was purified by flash chromatography (25 g SNAP cartridge, hexanes/ethyl acetate gradient, 50%->100% ethyl acetate) to give the title compound as single isomer at cyclohexane ring (219 mg, 73 % yield).

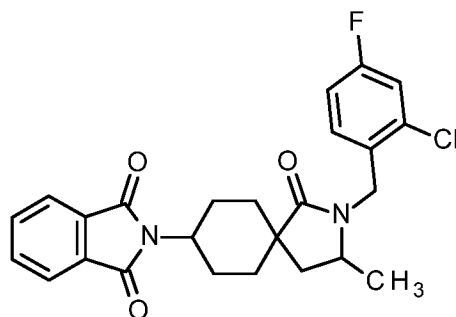
LC-MS (Method 2): *R*_t = 1.14 min; MS (ESIpos): *m/z* = 326 [M+H]⁺

- ¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 1.082 (7.04), 1.097 (7.22), 1.172 (1.17), 1.372 (0.97), 1.391 (0.97), 2.075 (16.00), 2.155 (0.96), 2.174 (1.10), 2.188 (1.01), 2.205 (0.93), 2.518 (4.29), 2.523 (2.93), 3.410 (1.10), 3.426 (1.10), 4.202 (1.86), 4.242 (2.15), 4.358 (2.04), 4.366 (2.08), 4.609 (1.69), 4.648 (1.44), 7.218 (1.56), 7.224 (1.83), 7.231 (2.15), 7.238 (1.74), 7.244 (2.60), 7.247 (2.31), 7.444 (1.41), 7.450 (1.46), 7.466 (1.34), 7.471 (1.32).

Intermediate 51

- 2-[(3RS)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]-1H-isoin-
25 1,3(2H)-dione (isomer 1 at cyclohexane ring)

149

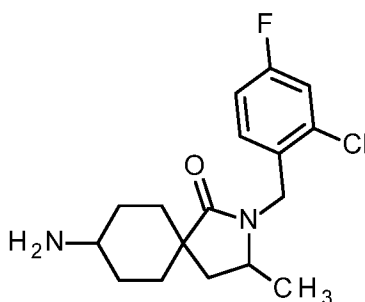


Was prepared in analogy to the synthesis of 2-[2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]-1H-indole-1,3(2H)-dione (mixture of trans-/cis-isomers) using (3RS)-2-(2-chloro-4-fluorobenzyl)-8-hydroxy-3-methyl-2-azaspiro[4.5]decan-1-one (139 mg, 427 μ mol, isomer 1 at cyclohexane ring) as starting material to give the title compound as single isomer at cyclohexane ring (61.0 mg).

LC-MS (Method 3): R_t = 1.38 min; MS (ESIpos): m/z = 455 $[M+H]^+$

Intermediate 52

(3RS)-8-amino-2-(2-chloro-4-fluorobenzyl)-3-methyl-2-azaspiro[4.5]decan-1-one (isomer 1 at cyclohexane ring)



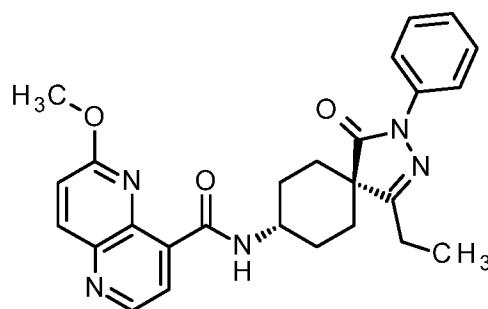
A mixture of 2-[(3RS)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]-1H-indole-1,3(2H)-dione (61.0 mg, 134 μ mol, isomer 1 at cyclohexane ring) and hydrazine hydrate (33 μ l, 670 μ mol) in ethanol (1.9 ml) was stirred for 3 h at 80°C. Upon cooling, solids were filtered off, washed with ethanol and the filtrate was concentrated to give the title compound (132 mg) as single isomer at cyclohexane which was used in the next step without further purification.

4. Examples

Example 1

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N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-6-methoxy-1,5-naphthyridine-4-carboxamide



- PyBOP (240 mg, 461 μ mol) was added to a mixture of (trans)-8-amino-4-ethyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (100 mg, 369 μ mol), 6-methoxy-1,5-naphthyridine-4-carboxylic acid (94.1 mg, 461 μ mol) and N,N-diisopropylethylamine (320 μ l, 1.8 mmol) in DMF (1.2 ml) and the mixture was stirred for 12 h at room temperature. For work-up, the reaction mixture was concentrated and the residue was stirred with methanol. The precipitate was collected by filtration, washed with water and methanol and then dried to give the title compound 93.5 mg (55 % yield).

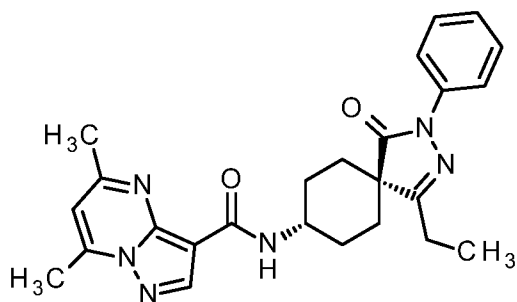
LC-MS (Method 2): R_t = 1.36 min; MS (ESI^{neg}): m/z = 456 [M-H]⁻

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.80 (d, 1H), 8.95 (d, 1H), 8.43 (d, 1H), 8.13 (d, 1H), 7.90-7.86 (m, 2H), 7.46-7.40 (m, 3H), 7.22-7.17 (m, 1H), 4.21-4.11 (m, 1H), 4.10 (s, 3H), 2.62 (q, 2H), 2.28-2.19 (m, 2H), 1.95-1.73 (m, 6H), 1.24 (t, 3H)

- The following examples were prepared in analogy to the synthesis of N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-6-methoxy-1,5-naphthyridine-4-carboxamide. In some cases the final products were purified by preparative HPLC (Method 6 or 7).

Example	Structure
	IUPAC-Name
	LC-MS (method): Retention time; Mass found
	¹ H-NMR

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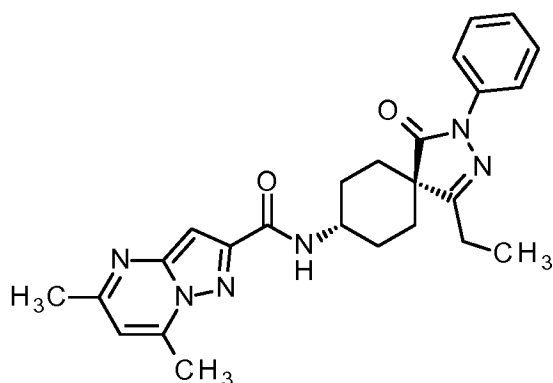
N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide

2

LC-MS (Method 2): $R_t = 1.35$ min; MS (ESIpos): $m/z = 445$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.229 (3.07), 1.248 (7.50), 1.265 (3.12), 1.725 (1.92), 1.737 (1.24), 1.751 (2.55), 1.918 (0.73), 1.931 (0.56), 1.945 (1.27), 1.971 (0.68), 2.312 (0.59), 2.323 (0.98), 2.327 (1.12), 2.332 (1.29), 2.336 (1.24), 2.363 (0.52), 2.371 (0.52), 2.465 (0.47), 2.518 (3.16), 2.523 (2.23), 2.530 (1.03), 2.540 (1.31), 2.549 (2.95), 2.567 (2.81), 2.585 (0.82), 2.665 (16.00), 2.758 (9.07), 2.760 (9.30), 4.239 (0.54), 7.167 (3.00), 7.169 (3.09), 7.176 (0.91), 7.179 (0.54), 7.195 (1.83), 7.210 (0.63), 7.214 (1.15), 7.216 (0.63), 7.417 (2.30), 7.422 (0.80), 7.436 (2.44), 7.439 (2.79), 7.452 (0.70), 7.457 (2.11), 7.858 (2.72), 7.860 (3.12), 7.863 (1.69), 7.875 (0.84), 7.879 (2.83), 7.882 (2.32), 8.422 (1.17), 8.441 (1.12), 8.529 (7.05).

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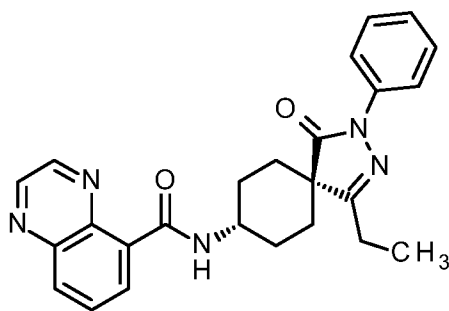
3

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-2-carboxamide

LC-MS (Method 3): $R_t = 1.25$ min; MS (ESIpos): $m/z = 445$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.270 (3.06), 1.287 (7.28), 1.305 (3.12), 1.728 (0.48), 1.751 (0.91), 1.758 (0.93), 1.763 (0.83), 1.780 (0.93), 1.793 (0.89), 1.851 (1.55), 1.860 (1.34), 1.891 (1.74), 1.921 (0.97), 1.953 (1.59), 1.964 (1.36), 1.974 (0.76), 1.986 (0.58), 1.998 (0.43), 2.332 (0.89), 2.518 (6.08), 2.524 (16.00), 2.673 (0.91), 2.679 (0.43), 2.711 (0.87), 2.729 (2.91), 2.748 (2.91), 2.766 (11.56), 2.768 (11.51), 4.018 (0.48), 4.027 (0.45), 4.040 (0.45), 6.924 (7.75), 7.026 (3.53), 7.028 (3.41), 7.173 (0.54), 7.176 (0.89), 7.179 (0.54), 7.195 (1.96), 7.210 (0.68), 7.213 (1.22), 7.216 (0.70), 7.419 (2.46), 7.423 (0.87), 7.438 (2.65), 7.440 (3.02), 7.454 (0.76), 7.459 (2.13), 7.874 (2.87), 7.877 (3.43), 7.891 (0.93), 7.896 (3.12), 7.898 (2.44), 8.416 (1.41), 8.437 (1.39).

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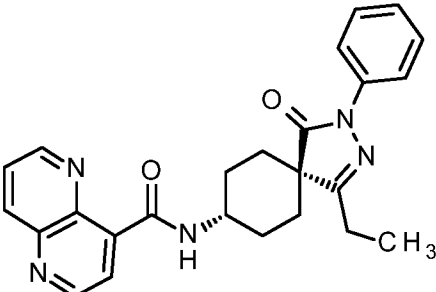
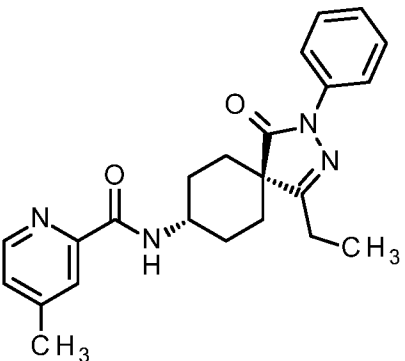
N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide

LC-MS (Method 2): $R_t = 1.34$ min; MS (ESIpos): $m/z = 428$ $[M+H]^+$

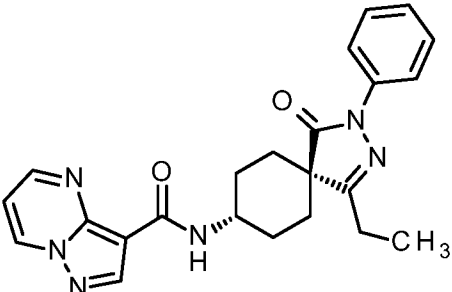
4

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.239 (6.58), 1.258 (16.00), 1.275 (6.86), 1.678 (0.85), 1.690 (1.66), 1.703 (1.33), 1.712 (1.18), 1.726 (2.04), 1.737 (1.42), 1.776 (0.71), 1.789 (1.28), 1.799 (1.42), 1.822 (1.56), 1.834 (1.42), 1.998 (1.18), 2.008 (1.28), 2.026 (1.61), 2.034 (2.41), 2.060 (1.37), 2.069 (1.09), 2.318 (1.89), 2.323 (1.99), 2.327 (2.70), 2.332 (1.99), 2.337 (1.42), 2.344 (1.80), 2.352 (1.80), 2.368 (0.80), 2.378 (0.99), 2.518 (6.44), 2.523 (4.64), 2.553 (1.94), 2.570 (6.34), 2.589 (6.20), 2.607 (1.66), 2.665 (1.23), 2.669 (1.70), 2.674 (1.18), 4.303 (1.04), 5.758 (0.99), 7.175 (0.95), 7.178 (1.85), 7.181 (0.99), 7.196 (3.88), 7.212 (1.37), 7.214 (2.27), 7.218 (1.33), 7.420 (4.59), 7.425 (1.66), 7.439 (5.02), 7.442 (5.73), 7.456 (1.42), 7.461 (4.45), 7.465 (0.66), 7.861 (0.76), 7.867 (5.59), 7.869 (6.96), 7.883 (1.66), 7.888 (6.20), 7.891 (4.69), 7.983 (3.50), 8.002 (3.79), 8.004 (4.12), 8.022 (3.93), 8.278 (4.07), 8.282 (4.36), 8.299 (3.64), 8.303 (3.55), 8.444 (4.02), 8.448 (4.02), 8.463 (3.83), 8.466 (3.41), 9.113 (2.89), 9.119 (15.81), 9.124 (2.70), 10.050 (2.13), 10.069 (2.08).

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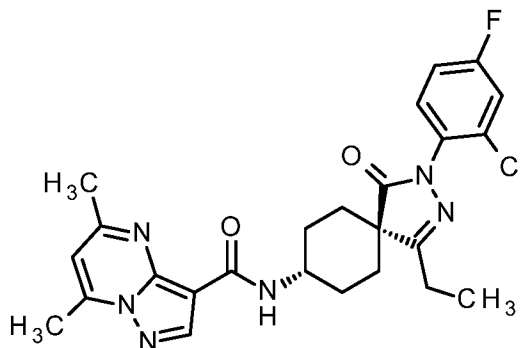
5	 N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1,5-naphthyridine-4-carboxamide LC-MS (Method 2): $R_t = 1.31$ min; MS (ESI^{neg}): $m/z = 426$ [M-H]⁻ ¹H-NMR (400 MHz, DMSO-<i>d</i>₆): δ [ppm] = 10.67 (d, 1H), 9.21-9.15 (m, 2H), 8.63 (dd, 1H), 8.28 (d, 1H), 7.97 (dd, 1H), 7.90-7.86 (m, 2H), 7.47-7.41 (m, 2H), 7.22-7.17 (m, 1H), 4.36-4.29 (m, 1H), 2.58 (q, 2H), 2.43-2.32 (m, 2H), 2.09-1.99 (m, 2H), 1.86-1.68 (m, 4H), 1.26 (t, 3H)
6	 N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-methylpyridine-2-carboxamide LC-MS (Method 2): $R_t = 1.36$ min; MS (ESI^{neg}): $m/z = 389$ [M-H]⁻ ¹H-NMR (400 MHz, DMSO-<i>d</i>₆): δ [ppm] = 8.83 (d, 1H), 8.52 (d, 1H), 7.91-7.86 (m, 3H), 7.46-7.41 (m, 3H), 7.22-7.16 (m, 1H), 4.05-3.95 (m, 1H), 2.73 (q, 2H), 2.42 (s, 3H), 2.01-1.67 (m, 8H), 1.27 (t, 3H)

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7	 N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide LC-MS (Method 2): $R_t = 1.10$ min; MS (ESI^{neg}): $m/z = 415.3$ $[M-H]^-$ 1H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.35 (dd, 1H), 8.86 (dd, 1H), 8.60 (s, 1H), 8.27 (d, 1H), 7.90-7.85 (m, 2H), 7.44 (t, 2H), 7.31 (dd, 1H), 7.22-7.17 (m, 1H), 4.25-4.17 (m, 1H), 2.63 (q, 2H), 2.32-2.22 (m, 2H), 2.01-1.89 (m, 2H), 1.80-1.69 (m, 4H), 1.28 (t, 3H)
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Example 8

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide



5

PyBOP (201 mg, 386 μ mol) was added to a mixture of (trans)-8-amino-2-(2-chloro-4-fluorophenyl)-4-ethyl-2,3-diazaspiro[4.5]dec-3-en-1-one (100 mg, 309 μ mol), 5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxylic acid (73.8 mg, 386 μ mol) and N,N-diisopropylethylamine (270 μ l, 1.5 mmol) in DMF (1.2 ml) and the mixture was stirred for 12 h at room temperature. For work-up, the reaction mixture was concentrated and the residue was stirred with methanol. The precipitate was collected by filtration, washed with water and methanol and then dried to give the title compound 114 mg (72 % yield).

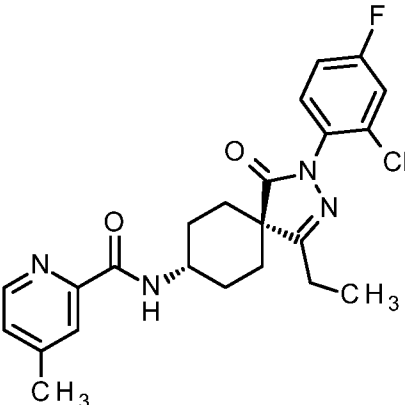
10

LC-MS (Method 2): $R_t = 1.28$ min; MS (ESI^{pos}): $m/z = 497$ $[M+H]^+$

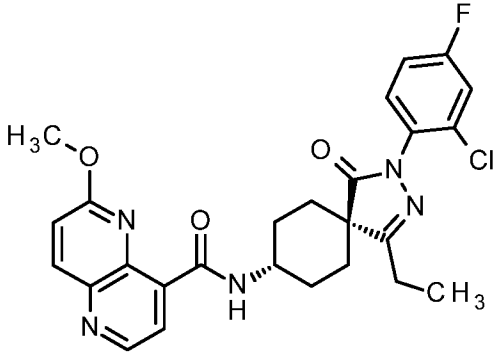
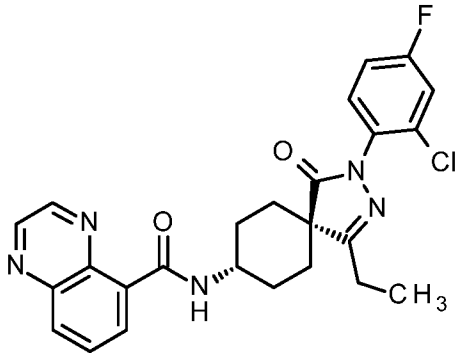
156

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.53 (s, 1H), 8.46 (d, 1H), 7.67 (dd, 1H), 7.62 (dd, 1H), 7.40-7.34 (m, 1H), 7.17 (d, 1H), 4.29-4.22 (m, 1H), 2.76 (d, 3H), 2.67 (s, 3H), 2.55-2.52 (m, 2H), 2.37-2.27 (m, 2H), 2.05-1.90 (m, 2H), 1.82-1.67 (m, 4H), 1.15 (t, 3H)

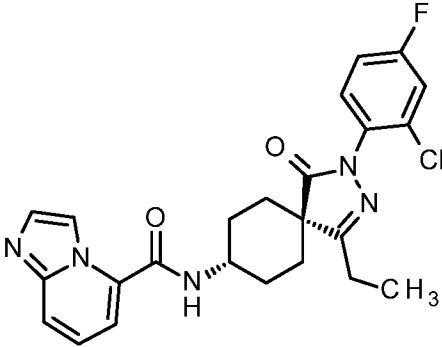
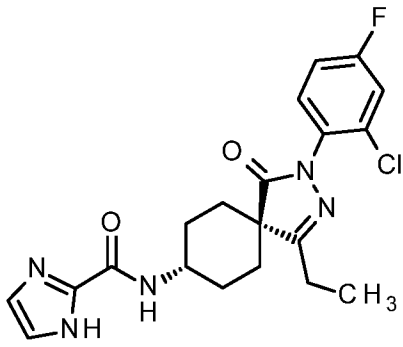
- The following examples were prepared in analogy to the synthesis of N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide. In some cases the final products were purified by preparative HPLC (Method 6 or 7).

Example	Structure IUPAC-Name LC-MS (method): Retention time; Mass found ¹H-NMR
9	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-methylpyridine-2-carboxamide LC-MS (Method 2): R_t = 1.32 min; MS (ESIpos): m/z = 443.6 [M+H]⁺ ¹H-NMR (400 MHz, DMSO-<i>d</i>₆): δ [ppm] = 8.81 (d, 1H), 8.52 (d, 1H), 7.91-7.88 (m, 1H), 7.66 (dd, 1H), 7.59 (dd, 1H), 7.46-7.42 (m, 1H), 7.37 (td, 1H), 4.06-3.96 (m, 1H), 2.72-2.64 (m, 2H), 2.42 (s, 3H), 2.03-1.83 (m, 6H), 1.81-1.65 (m, 2H), 1.17 (t, 3H)

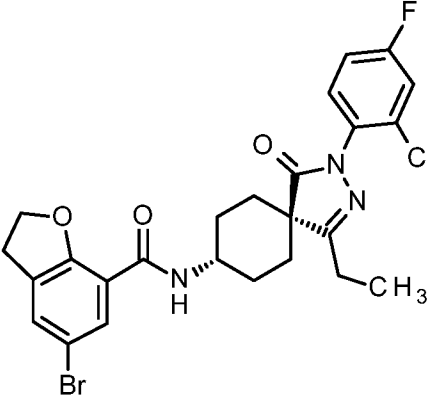
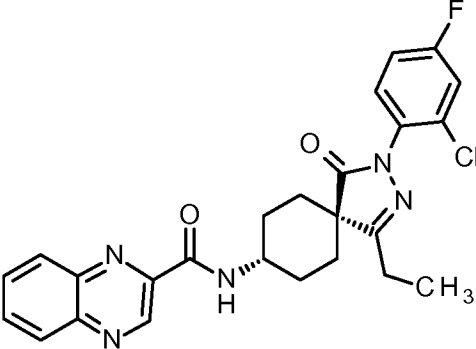
157

10	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-6-methoxy-1,5-naphthyridine-4-carboxamide LC-MS (Method 2): $R_t = 1.30$ min; MS (ESI^{neg}): $m/z = 508$ [M-H]⁻ ¹H-NMR (400 MHz, DMSO-<i>d</i>₆): δ [ppm] = 9.76 (d, 1H), 8.94 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.66 (dd, 1H), 7.59 (dd, 1H), 7.42 (d, 1H), 7.40-7.34 (m, 1H), 4.21-4.12 (m, 1H), 4.10 (s, 3H), 2.57 (q, 2H), 2.30-2.19 (m, 2H), 1.99-1.89 (m, 2H), 1.89-1.70 (m, 4H), 1.13 (t, 3H)
11	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide LC-MS (Method 2): $R_t = 1.27$ min; MS (ESI^{pos}): $m/z = 480$ [M+H]⁺ ¹H-NMR (400 MHz, DMSO-<i>d</i>₆): δ [ppm] = 10.12 (d, 1H), 9.13 (s, 2H), 8.47 (dd, 1H), 8.30 (dd, 1H), 8.01 (dd, 1H), 7.67 (dd, 1H), 7.62 (dd, 1H), 7.38 (td, 1H), 4.35-4.28 (m, 1H), 2.57-2.52 (m, 2H), 2.38-2.27 (m, 2H), 2.11-2.02 (m, 2H), 1.87-1.76 (m, 2H), 1.76-1.65 (m, 2H), 1.16 (t, 3H)

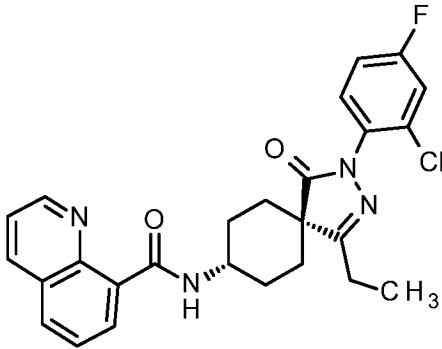
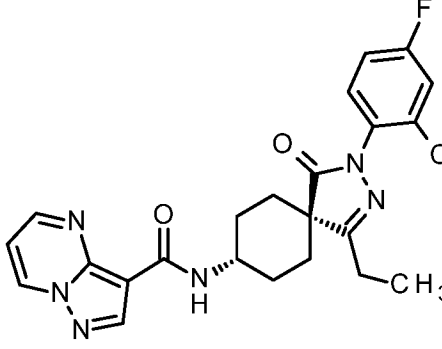
158

12	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-a]pyridine-5-carboxamide LC-MS (Method 3): $R_t = 1.06$ min; MS (ESIpos): $m/z = 468$ $[M+H]^+$ $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 9.12-9.10 (m, 1H), 8.46 (d, 1H), 8.10-8.08 (m, 1H), 7.68-7.57 (m, 5H), 7.37 (td, 1H), 4.09-4.00 (m, 1H), 2.65 (q, 2H), 2.15-2.06 (m, 2H), 2.03-1.93 (m, 2H), 1.87-1.65 (m, 4H), 1.18 (t, 3H)
13	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-imidazole-2-carboxamide LC-MS (Method 3): $R_t = 1.07$ min; MS (ESIpos): $m/z = 418$ $[M+H]^+$ $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 13.00 (br s, 1H), 8.50 (d, 1H), 7.68-7.56 (m, 2H), 7.39-7.32 (m, 1H), 7.16 (br s, 2H), 4.02-3.93 (m, 1H), 2.70-2.64 (m, 2H), 2.00-1.82 (m, 6H), 1.77-1.64 (m, 2H), 1.16 (t, 3H)

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14	 5-bromo-N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-2,3-dihydro-1-benzofuran-7-carboxamide LC-MS (Method 2): $R_t = 1.44$ min; MS (ESIpos): $m/z = 548$ $[M+H]^+$ 1H-NMR (400 MHz, $DMSO-d_6$): δ [ppm] = 7.97 (d, 1H), 7.67-7.58 (m, 4H), 7.37 (td, 1H), 4.79 (t, 2H), 4.14-4.07 (m, 1H), 3.29 (t, 2H), 2.54 (q, 2H), 2.23-2.13 (m, 2H), 1.97-1.86 (m, 2H), 1.77-1.63 (m, 4H), 1.17 (t, 3H)
15	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-2-carboxamide LC-MS (Method 3): $R_t = 1.29$ min; MS (ESI_{neg}): $m/z = 478$ $[M-H]^-$ 1H-NMR (400 MHz, $DMSO-d_6$): δ [ppm] = 9.48 (s, 1H), 9.12 (d, 1H), 8.29-8.19 (m, 2H), 8.03-7.98 (m, 2H), 7.67 (dd, 1H), 7.60 (dd, 1H), 7.38 (td, 1H), 4.15-4.06 (m, 1H), 2.73 (q, 2H), 2.06-1.89 (m, 6H), 1.84-1.72 (m, 2H), 1.20 (t, 3H)

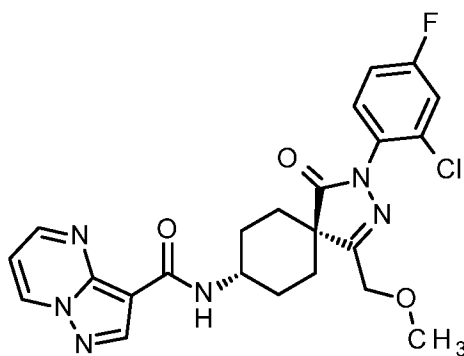
160

16	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoline-8-carboxamide LC-MS (Method 2): $R_t = 1.37$ min; MS (ESI^{neg}): $m/z = 477$ [M-H]⁻ ¹H-NMR (400 MHz, DMSO-<i>d</i>₆): δ [ppm] = 11.40 (d, 1H), 9.13 (dd, 1H), 8.65-8.58 (m, 2H), 8.24 (dd, 1H), 7.81-7.71 (m, 2H), 7.70-7.61 (m, 2H), 7.41-7.35 (m, 1H), 4.39-4.33 (m, 1H), 2.56 (q, 2H), 2.42-2.32 (m, 2H), 2.14-2.00 (m, 2H), 1.90-1.71 (m, 4H), 1.17 (t, 3H)
17	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide LC-MS (Method 2): $R_t = 1.15$ min; MS (ESI^{pos}): $m/z = 469.3$ [M+H]⁺ ¹H-NMR (400 MHz, DMSO-<i>d</i>₆): δ [ppm] = 9.36 (dd, 1H), 8.87 (dd, 1H), 8.61 (s, 1H), 8.32 (d, 1H), 7.67 (dd, 1H), 7.62 (dd, 1H), 7.38 (td, 1H), 7.35-7.30 (m, 1H), 4.27-4.19 (m, 1H), 2.59 (q, 2H), 2.32-2.22 (m, 2H), 2.06-1.93 (m, 2H), 1.81-1.69 (m, 4H), 1.19 (t, 3H)

Example 18

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-(methoxymethyl)-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

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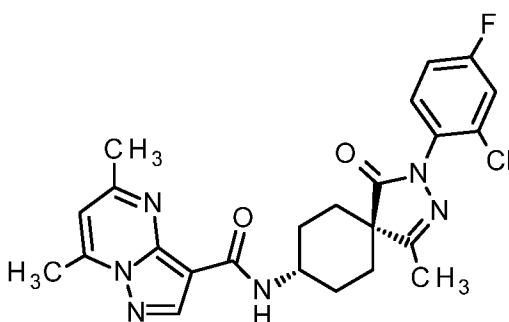
PyBOP (37.1 mg, 71.2 μmol) was added to a mixture of pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (13.2 mg, 80.9 μmol), (trans)-8-amino-2-(2-chloro-4-fluorophenyl)-4-(methoxymethyl)-2,3-diazaspiro[4.5]dec-3-en-1-one (22.0 mg, 64.7 μmol) and N,N-diisopropylethylamine (56 μl , 320 μmol) in DMF (1.0 ml) and the mixture was stirred for 12 h at room temperature. For work-up, the reaction mixture was concentrated and the residue purified by preparative HPLC to give the title compound 12.0 mg (29 % yield).

LC-MS (Method 2): R_t = 1.08 min; MS (ESIpos): m/z = 485 $[\text{M}+\text{H}]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$): δ [ppm] = 9.35 (dd, 1H), 8.87 (dd, 1H), 8.60 (s, 1H), 8.24 (d, 1H), 7.71-7.62 (m, 2H), 7.39 (td, 1H), 7.31 (dd, 1H), 4.36 (s, 2H), 4.22-4.11 (m, 1H), 2.28-2.18 (m, 2H), 2.14-2.03 (m, 2H), 1.87-1.70 (m, 4H)

Example 19

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide



PyBOP (256 mg, 492 μmol) was added to a mixture of 5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxylic acid (90.0 mg, 447 μmol), (trans)-8-amino-2-(2-chloro-4-fluorophenyl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (152 mg, 492 μmol) and N,N-diisopropylethylamine (310 μl , 1.8 mmol) in DMF (4.5 ml) and the mixture was stirred for 5 h at room temperature. For work-up, the reaction mixture was concentrated and the residue purified by flash chromatography

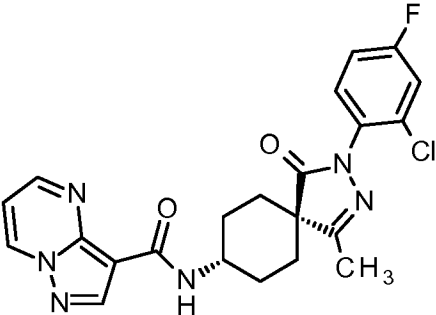
162

(25 g SNAP cartridge, dichloromethane/methanol gradient 0%->10% methanol) followed by trituration from methanol to give the title compound (167 mg, 77 %).

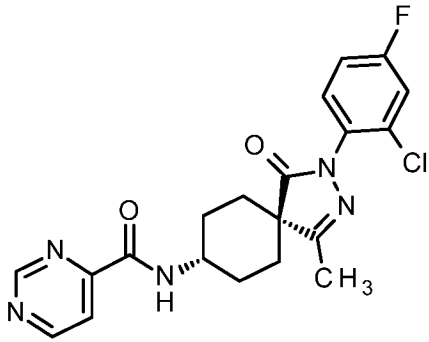
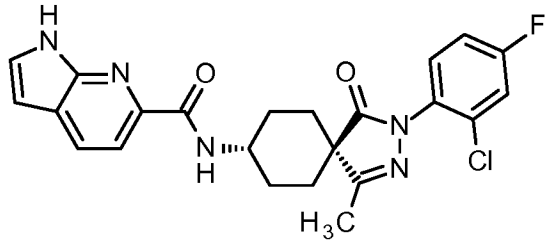
LC-MS (Method 1): Rt = 1.17 min; MS (ESIpos): m/z = 483 [M+H]⁺

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 8.58 (s, 1H), 8.36 (br d, 1H), 7.36-7.33 (m, 1H), 7.20-7.17 (m, 1H), 7.04-6.96 (m, 1H), 6.69-6.67 (m, 1H), 4.41-4.34 (m, 1H), 2.77-2.74 (m, 3H), 2.63-2.59 (m, 3H), 2.51-2.42 (m, 2H), 2.14-2.09 (m, 3H), 2.00-1.78 (m, 6H)

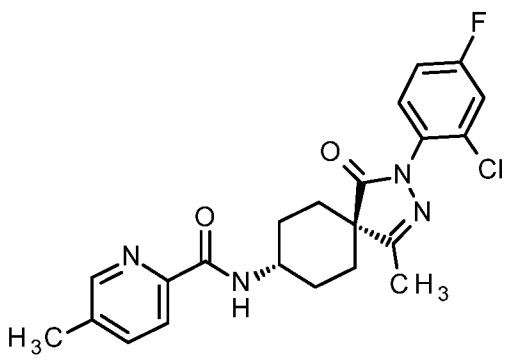
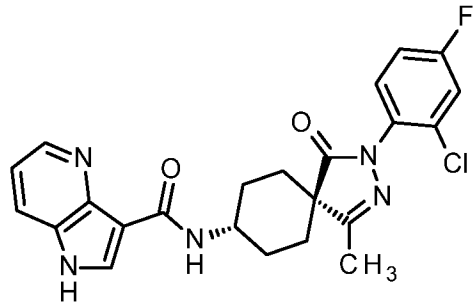
The following examples were prepared in analogy to the synthesis of N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide. In some cases the final products were purified using modified conditions for flash chromatography and/or crystallization.

Example	Structure IUPAC-Name LC-MS (method): Retention time; Mass found ¹H-NMR
20	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide LC-MS (Method 5): Rt = 1.00 min; MS (ESIpos): m/z = 455 [M+H]⁺ ¹H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.000 (2.56), 1.522 (1.44), 1.788 (0.61), 1.797 (0.81), 1.804 (0.78), 1.812 (2.24), 1.819 (1.36), 1.835 (1.99), 1.845 (1.22), 1.862 (0.61), 1.913 (0.54), 1.929 (0.82), 1.946 (1.11), 1.954 (1.40), 1.979 (0.66), 1.987 (0.44), 2.163 (16.00), 2.405 (0.68), 2.414 (0.71), 2.429 (0.75), 2.438 (1.16), 2.453 (0.43), 2.462 (0.47), 2.816 (0.42), 2.890 (0.51), 4.376 (0.48), 6.954 (1.54), 6.964 (1.51), 6.972 (1.55), 6.982 (1.76), 6.987 (0.94), 6.999 (0.87), 7.002 (0.92), 7.006 (0.93), 7.009 (1.02), 7.021 (0.87), 7.028 (0.95), 7.171 (1.50), 7.178 (1.46), 7.320 (1.56), 7.334 (1.58), 7.342 (1.41), 7.355 (1.38), 8.120 (0.66), 8.140 (0.65), 8.582 (1.81), 8.586 (1.98), 8.592 (1.73), 8.597 (1.81), 8.649 (5.53), 8.747 (1.88), 8.750 (1.76), 8.764 (1.87), 8.768 (1.80).

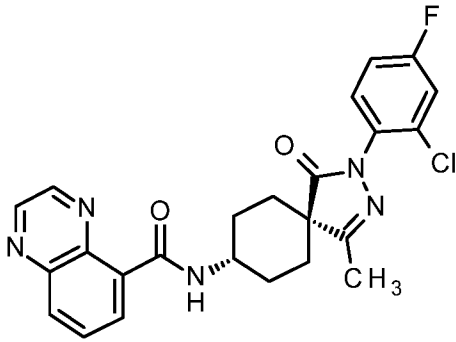
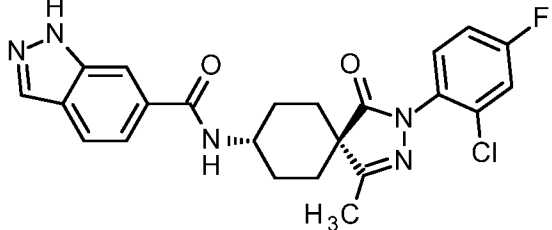
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21	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrimidine-4-carboxamide LC-MS (Method 2): Rt = 1.04 min; MS (ESIpos): m/z = 416 [M+H]⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 9.36 (d, 1H), 9.16-9.02 (m, 2H), 8.04 (dd, 1H), 7.66 (dd, 1H), 7.58 (dd, 1H), 7.36 (td, 1H), 4.11-3.96 (m, 1H), 2.28 (s, 3H), 2.04-1.84 (m, 6H), 1.81-1.65 (m, 2H)
22	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-pyrrolo[2,3-b]pyridine-6-carboxamide LC-MS (Method 2): Rt = 1.12 min; MS (ESIpos): m/z = 454 [M+H]⁺ ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.190 (2.83), 1.206 (2.85), 1.221 (0.60), 1.239 (2.56), 1.254 (2.75), 1.268 (1.53), 1.737 (0.41), 1.746 (0.42), 1.773 (1.44), 1.800 (1.14), 1.865 (0.91), 1.888 (2.78), 1.914 (2.29), 1.940 (0.69), 2.074 (1.40), 2.084 (1.11), 2.095 (1.02), 2.115 (0.63), 2.276 (16.00), 2.323 (0.54), 2.327 (0.76), 2.332 (0.54), 2.518 (3.37), 2.523 (2.12), 2.665 (0.53), 2.669 (0.75), 2.673 (0.54), 4.009 (0.58), 4.021 (0.58), 4.030 (0.57), 5.759 (3.16), 6.557 (2.08), 6.561 (2.29), 6.565 (2.33), 6.570 (2.13), 7.344 (0.85), 7.351 (0.96), 7.366 (1.41), 7.373 (1.50), 7.386 (1.02), 7.393 (1.09), 7.575 (1.89), 7.590 (1.96), 7.597 (1.73), 7.612 (1.53), 7.653 (1.83), 7.660 (1.92), 7.674 (3.24), 7.681 (4.25), 7.687 (2.07), 7.785 (4.17), 7.806 (4.40), 8.102 (3.02), 8.123 (2.66), 8.452 (1.76), 8.473 (1.70), 11.792 (1.68).

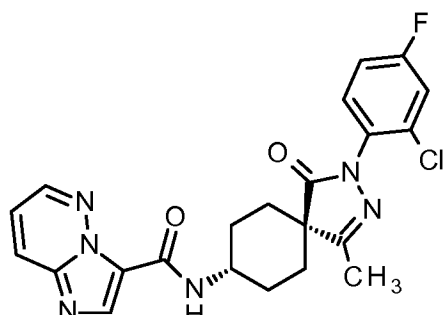
164

23	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5-methylpyridine-2-carboxamide LC-MS (Method 2): $R_t = 1.21$ min; MS (ESIpos): $m/z = 429$ $[M+H]^+$ 1H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.77 (d, 1H), 8.50 (s, 1H), 7.95 (d, 1H), 7.81 (dd, 1H), 7.66 (dd, 1H), 7.58 (dd, 1H), 7.36 (td, 1H), 4.00 (dt, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 2.00-1.83 (m, 6H), 1.80-1.67 (m, 2H).
24	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-pyrrolo[3,2-b]pyridine-3-carboxamide LC-MS (Method 1): $R_t = 1.02$ min; MS (ESIpos): $m/z = 454$ $[M+H]^+$ 1H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 11.99 (br s, 1H), 9.37 (br d, 1H), 8.53 (d, 1H), 8.20 (d, 1H), 7.96 (d, 1H), 7.77-7.53 (m, 2H), 7.37 (td, 1H), 7.29 (dd, 1H), 4.30 (br s, 1H), 2.37-2.26 (m, 2H), 2.19 (s, 3H), 2.05 (br t, 2H), 1.74 (br d, 4H)

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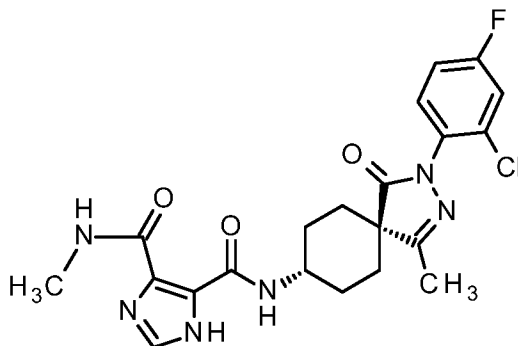
25	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide LC-MS (Method 2): $R_t = 1.16$ min; MS (ESIpos): $m/z = 466$ $[M+H]^+$ 1H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 10.15 (d, 1H), 9.13 (dd, 2H), 8.48 (dd, 1H), 8.29 (dd, 1H), 8.01 (dd, 1H), 7.67 (dd, 1H), 7.61 (dd, 1H), 7.37 (td, 1H), 4.31 (br s, 1H), 2.40-2.28 (m, 2H), 2.15 (s, 3H), 2.12-1.99 (m, 2H), 1.90-1.66 (m, 4H)
26	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-indazole-6-carboxamide LC-MS (Method 2): $R_t = 1.04$ min; MS (ESIpos): $m/z = 454$ $[M+H]^+$ 1H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 13.36 (s, 1H), 8.50 (d, 1H), 8.15 (s, 1H), 8.04 (s, 1H), 7.84 (d, 1H), 7.67 (dd, 1H), 7.62-7.51 (m, 2H), 7.37 (td, 1H), 4.04 (dt, 1H), 3.17 (d, 1H), 2.25 (s, 3H), 2.13-1.92 (m, 4H), 1.90-1.66 (m, 4H)

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27	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-b]pyridazine-3-carboxamide LC-MS (Method 5): Rt = 0.97 min; MS (ESIpos): m/z = 455 [M+H]⁺ ¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 8.79 (br d, 1H), 8.58 (s, 1H), 8.56 (dd, 1H), 8.21 (dd, 1H), 7.43 (dd, 1H), 7.33-7.29 (m, 1H), 7.27 (d, 1H), 7.10 (ddd, 1H), 4.57-4.43 (m, 1H), 2.61-2.46 (m, 2H), 2.25 (s, 3H), 2.07-1.84 (m, 6H)
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Example 28

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-methyl-1H-imidazole-4,5-dicarboxamide



5

A mixture of phenyl 5-[[trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]carbonyl]-1H-imidazole-4-carboxylate (100 mg, 191 μmol) and methanamine (480 μl, 2.0 M in THF, 950 μmol) in THF (3.1 ml) was stirred over night at room temperature. For work-up, the reaction mixture was concentrated and the residue was purified by flash chromatography (24 g SNAP cartridge, dichloromethane/methanol gradient, 0%→10% methanol) followed by trituration from diethyl ether to give the title compound 61.7 mg (70% yield).

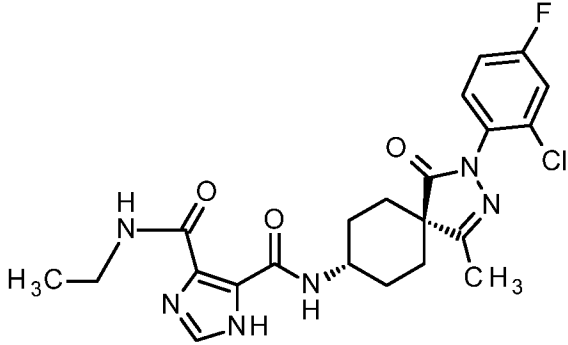
10

LC-MS (Method 2): Rt = 1.03 min; MS (ESIpos): m/z = 461 [M+H]⁺

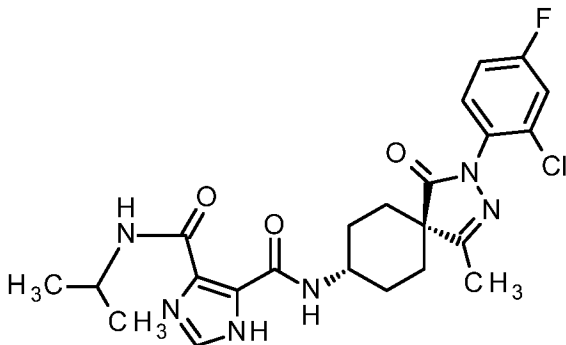
167

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 13.26 (br s, 1H), 11.75 (br s, 1H), 8.72 (br s, 1H), 7.83 (s, 1H), 7.66 (dd, 1H), 7.60 (dd, 1H), 7.36 (td, 1H), 4.26 (br s, 1H), 2.84 (d, 3H), 2.35-1.99 (m, 7H), 1.80-1.5066 (m, 4H)

- 5 The following compounds were prepared in analogy to the synthesis of N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-methyl-1H-imidazole-4,5-dicarboxamide.

Example	Structure IUPAC-Name LC-MS (method): Retention time; Mass found ¹H-NMR
29	 N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-ethyl-1H-imidazole-4,5-dicarboxamide LC-MS (Method 5): Rt = 1.11 min; MS (ESIpos): m/z = 475 [M+H]⁺ ¹H-NMR (400 MHz, CHLOROFORM-<i>d</i>) δ [ppm]: 0.000 (1.05), 1.124 (0.99), 1.141 (2.04), 1.158 (0.91), 1.200 (3.47), 1.217 (7.90), 1.236 (3.78), 1.239 (2.01), 1.258 (0.78), 1.578 (2.14), 1.679 (0.84), 1.689 (0.60), 1.717 (2.05), 1.732 (0.63), 1.745 (0.95), 1.755 (0.77), 1.765 (0.42), 1.863 (0.43), 1.878 (0.59), 2.119 (0.49), 2.127 (0.56), 2.169 (16.00), 2.184 (0.78), 2.460 (0.42), 2.468 (0.52), 2.483 (0.59), 2.491 (0.82), 2.524 (0.46), 3.381 (0.49), 3.385 (0.42), 3.400 (1.59), 3.403 (1.30), 3.414 (1.75), 3.417 (1.75), 3.420 (1.41), 3.433 (1.69), 3.438 (0.65), 3.444 (0.41), 3.450 (0.67), 4.438 (0.46), 4.448 (0.49), 4.458 (0.44), 6.978 (0.72), 6.985 (0.77), 6.998 (0.89), 7.000 (0.95), 7.005 (0.98), 7.007 (1.04), 7.020 (0.79), 7.027 (0.88), 7.169 (1.47), 7.176 (1.42), 7.330 (1.42), 7.344 (1.45), 7.352 (1.26), 7.366 (1.22), 7.547 (1.04), 7.556 (4.86), 7.597 (0.41), 7.611 (0.76), 11.782 (0.76), 11.802 (0.75), 11.901 (0.55).

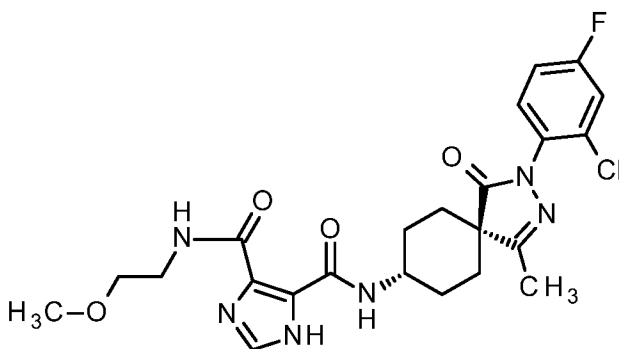
30

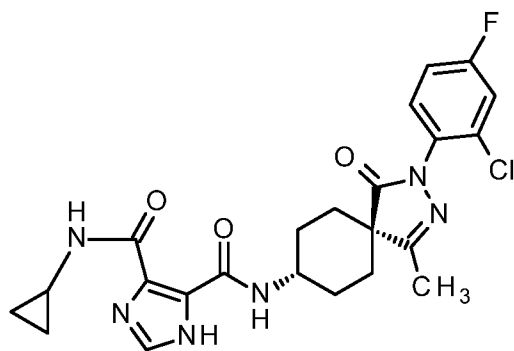


N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(propan-2-yl)-1H-imidazole-4,5-dicarboxamide

LC-MS (Method 5): Rt = 1.20 min; MS (ESIpos): m/z = 489 [M+H]⁺

¹H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.000 (1.19), 1.124 (2.45), 1.142 (4.59), 1.159 (2.66), 1.224 (13.95), 1.240 (14.81), 1.264 (3.51), 1.542 (4.35), 1.675 (2.40), 1.710 (5.39), 1.738 (2.87), 1.878 (1.24), 2.128 (1.71), 2.164 (16.00), 2.359 (0.44), 2.462 (1.48), 2.490 (2.38), 3.387 (0.90), 3.403 (2.33), 3.421 (2.31), 3.439 (0.92), 4.119 (0.88), 4.135 (1.35), 4.152 (1.47), 4.168 (1.09), 4.444 (1.50), 5.078 (0.92), 6.754 (0.81), 6.774 (0.91), 6.858 (0.47), 6.984 (1.19), 7.004 (2.05), 7.021 (1.24), 7.175 (3.80), 7.329 (1.74), 7.344 (1.94), 7.364 (1.38), 7.425 (1.64), 7.444 (1.64), 7.544 (4.51), 11.519 (1.58), 11.769 (1.65), 11.788 (1.60).

31	 N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(2-methoxyethyl)-1H-imidazole-4,5-dicarboxamide LC-MS (Method 5): Rt = 1.06 min; MS (ESIpos): m/z = 505 [M+H]⁺ ¹H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.000 (0.77), 1.124 (4.76), 1.141 (9.06), 1.158 (4.92), 1.572 (1.07), 1.677 (0.71), 1.687 (0.53), 1.714 (1.79), 1.729 (0.55), 1.741 (0.78), 1.752 (0.64), 2.097 (0.42), 2.106 (0.48), 2.138 (0.87), 2.155 (10.96), 2.170 (1.87), 2.461 (0.45), 2.476 (0.50), 2.485 (0.69), 3.345 (16.00), 3.361 (2.60), 3.385 (1.56), 3.402 (4.38), 3.420 (4.65), 3.438 (1.50), 3.500 (0.56), 3.504 (0.66), 3.515 (1.94), 3.527 (1.72), 3.552 (1.05), 3.564 (1.63), 3.578 (1.12), 4.436 (0.42), 6.978 (0.62), 6.985 (0.68), 6.997 (0.69), 7.000 (0.78), 7.004 (0.78), 7.007 (0.87), 7.019 (0.67), 7.026 (0.72), 7.168 (1.19), 7.175 (1.14), 7.327 (1.12), 7.341 (1.16), 7.349 (1.06), 7.363 (0.99), 7.546 (0.59), 7.563 (3.76), 7.875 (0.68), 11.663 (0.68), 11.684 (0.74).
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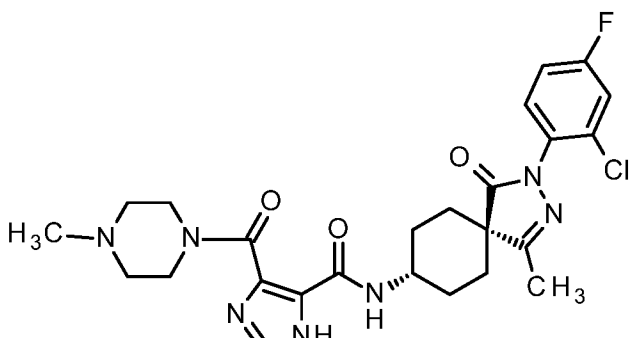
N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-cyclopropyl-1H-imidazole-4,5-dicarboxamide

LC-MS (Method 5): Rt = 1.12 min; MS (ESIpos): m/z = 487 [M+H]⁺

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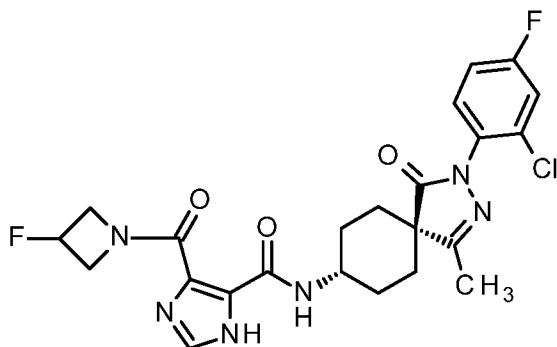
¹H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.000 (4.11), 0.599 (0.65), 0.616 (2.29), 0.621 (2.46), 0.626 (2.35), 0.639 (0.97), 0.654 (0.52), 0.773 (0.84), 0.790 (2.69), 0.804 (2.77), 0.821 (0.75), 1.124 (3.47), 1.141 (6.89), 1.158 (3.54), 1.569 (2.20), 1.690 (1.43), 1.700 (1.25), 1.726 (3.61), 1.752 (1.61), 1.762 (1.33), 1.855 (0.60), 1.869 (0.85), 2.136 (0.82), 2.145 (0.94), 2.163 (3.80), 2.177 (1.77), 2.199 (16.00), 2.458 (0.72), 2.466 (0.86), 2.489 (1.39), 2.513 (0.56), 2.522 (0.73), 2.787 (0.52), 2.797 (0.81), 2.806 (1.15), 2.814 (1.13), 2.823 (0.80), 2.832 (0.50), 3.385 (1.17), 3.403 (3.36), 3.420 (3.34), 3.438 (1.11), 4.434 (0.78), 4.444 (0.85), 4.453 (0.76), 6.979 (0.82), 6.986 (0.89), 7.000 (1.29), 7.006 (1.37), 7.020 (0.92), 7.027 (0.95), 7.169 (1.76), 7.176 (1.72), 7.323 (0.42), 7.331 (1.78), 7.344 (1.84), 7.353 (1.45), 7.366 (1.35), 7.536 (4.34), 7.546 (1.04), 7.631 (1.45), 7.639 (1.41), 11.707 (1.27), 11.727 (1.24), 11.835 (0.96).

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33	 N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-imidazole-5-carboxamide LC-MS (Method 2): Rt = 0.88 min; MS (ESIpos): m/z = 530 [M+H]⁺ ¹H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.009 (5.85), 1.193 (0.49), 1.677 (1.00), 1.695 (1.27), 1.713 (1.86), 1.729 (1.13), 1.740 (0.87), 2.022 (0.60), 2.030 (0.67), 2.062 (1.09), 2.087 (0.67), 2.099 (0.47), 2.150 (16.00), 2.221 (8.90), 2.293 (12.57), 2.453 (3.08), 2.466 (4.33), 2.478 (3.73), 2.502 (0.48), 2.511 (0.59), 2.841 (1.40), 2.853 (2.38), 2.866 (1.39), 3.768 (1.31), 4.183 (1.18), 4.401 (0.54), 4.411 (0.59), 4.420 (0.53), 6.745 (0.50), 6.747 (0.59), 6.766 (0.66), 6.769 (0.54), 6.985 (0.72), 6.993 (0.81), 7.005 (0.90), 7.007 (0.99), 7.012 (1.03), 7.014 (1.08), 7.027 (0.81), 7.034 (0.92), 7.157 (0.46), 7.175 (2.02), 7.183 (1.59), 7.196 (2.22), 7.329 (1.55), 7.343 (1.58), 7.351 (1.42), 7.365 (1.38), 7.590 (6.50), 10.849 (0.72), 10.870 (0.72).
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Example 34

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-[(3-fluoroazetidin-1-yl)carbonyl]-1H-imidazole-5-carboxamide



5

A mixture of phenyl 5-[[[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]carbonyl]-1H-imidazole-4-carboxylate (90.0 mg, 172 μmol), and

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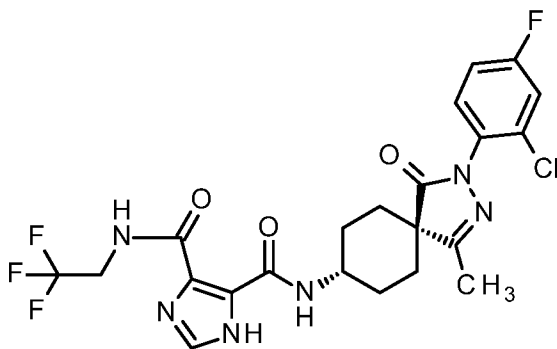
3-fluoroazetidine hydrochloride (38.3 mg, 344 μ mol) and triethylamine (72 μ l, 520 μ mol) in THF (2.8 ml) was stirred for 4 h at room temperature. For work-up, the reaction mixture was concentrated and the residue was purified by flash chromatography (24 g SNAP cartridge, dichloromethane/methanol gradient, 0%→10% methanol) followed by trituration from diethyl ether to give the title compound (57.1 mg, 66% yield).

LC-MS (Method 5): Rt = 1.09 min; MS (ESIpos): m/z = 505 [M+H]⁺

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 11.73 (br d, 1H), 11.58 (br s, 1H), 7.66 (s, 1H), 7.43 (dd, 1H), 7.26 (d, 1H), 7.14-7.01 (m, 1H), 5.58-5.26 (m, 1H), 5.47-5.25 (m, 1H), 5.17-5.01 (m, 1H), 4.95-4.74 (m, 1H), 4.59-4.42 (m, 2H), 4.38-4.19 (m, 1H), 3.50 (q, 1H), 2.67-2.46 (m, 2H), 2.27-2.12 (m, 5H), 1.93-1.73 (m, 4H), 1.23 (t, 1H)

Example 35

N⁵-[[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(2,2,2-trifluoroethyl)-1H-imidazole-4,5-dicarboxamide



A mixture of phenyl 5-[[[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]carbonyl]-1H-imidazole-4-carboxylate (100 mg, 191 μ mol), 2,2,2-trifluoroethanamine hydrochloride (155 mg, 1.15 mmol) in pyridine (3.4 ml) was heated for 4 h at 170°C in a microwave reactor. Upon cooling, the reaction mixture was concentrated and the residue was purified by flash chromatography (24 g SNAP cartridge, dichloromethane/methanol gradient, 0%→10% methanol) followed by trituration from hexanes/diethyl ether to give the title compound (51.4 mg, 51% yield).

LC-MS (Method 1): Rt = 1.25 min; MS (ESIpos): m/z = 559 [M+H]⁺

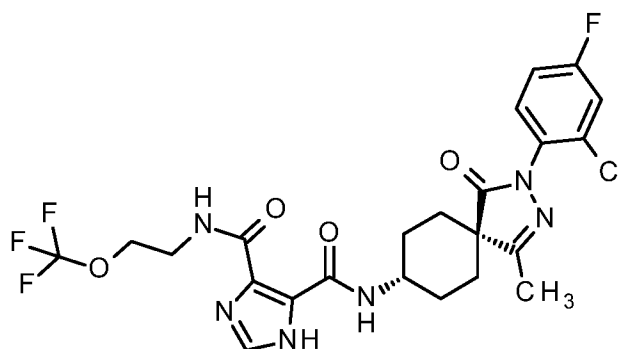
¹H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.000 (0.58), 0.813 (0.67), 1.195 (0.63), 1.552 (3.26), 1.685 (2.74), 1.721 (6.22), 1.754 (3.51), 1.877 (2.54), 2.076 (1.89), 2.122 (16.00), 2.165 (5.08), 2.372 (0.79), 2.484 (1.68), 2.510 (2.66), 4.004 (2.46), 4.024 (3.54), 4.044 (3.00), 4.197 (0.50), 4.448 (1.72), 4.985 (1.04), 6.751 (1.28), 6.770 (1.40), 6.859 (0.76), 6.877 (0.48), 6.987 (1.52), 7.006 (2.61), 7.021 (1.62), 7.175 (4.89), 7.328 (2.22), 7.344 (2.38), 7.365 (1.54), 7.595

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(6.60), 7.719 (0.63), 7.740 (0.64), 7.959 (2.09), 11.250 (1.90), 11.268 (1.88), 11.658 (0.43), 11.822 (1.79).

Example 36

5 N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-[2-(trifluoromethoxy)ethyl]-1H-imidazole-4,5-dicarboxamide



A mixture of phenyl 5-[[[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]carbamoyl]-1H-imidazole-4-carboxylate (50.0 mg, 95.4 μ mol), 2-(trifluoromethoxy)ethanamine hydrochloride (94.8 mg, 573 μ mol) and triethylamine (80 μ l, 570 μ mol) in THF (1.9 ml) was stirred for 6 h at room temperature. For work-up, the reaction mixture was concentrated and the residue was purified by flash chromatography (24 g SNAP cartridge, dichloromethane/methanol gradient, 0%→10% methanol) followed by trituration from diethyl ether to give the title compound (36.8 mg, 53% yield).

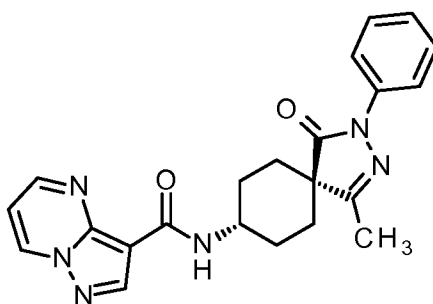
LC-MS (Method 1): Rt = 1.25 min; MS (ESIpos): m/z = 559 [M+H]⁺

15 ¹H-NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.000 (4.52), 1.124 (7.19), 1.141 (16.00), 1.159 (7.84), 1.536 (2.34), 1.687 (0.93), 1.697 (0.83), 1.710 (1.29), 1.721 (2.25), 1.734 (0.91), 1.745 (1.07), 1.755 (0.88), 1.861 (0.58), 1.876 (0.76), 2.070 (0.55), 2.079 (0.61), 2.111 (1.05), 2.135 (14.07), 2.158 (0.79), 2.166 (3.40), 2.462 (0.48), 2.472 (0.55), 2.494 (0.91), 2.528 (0.51), 3.385 (2.36), 3.403 (7.59), 3.421 (7.29), 3.438 (2.19), 3.682 (0.64), 3.696 (1.74), 3.711 (1.91),
20 3.723 (0.90), 4.082 (2.07), 4.096 (3.57), 4.101 (1.35), 4.109 (1.79), 4.115 (0.54), 4.425 (0.53), 4.435 (0.58), 4.444 (0.52), 6.980 (0.72), 6.987 (0.80), 6.999 (0.98), 7.002 (0.99), 7.006 (1.07), 7.009 (1.02), 7.021 (0.81), 7.028 (0.89), 7.170 (1.49), 7.177 (1.48), 7.327 (1.50), 7.341 (1.48), 7.349 (1.39), 7.363 (1.28), 7.569 (1.38), 7.577 (5.54), 7.886 (0.45), 7.902 (0.88), 7.918 (0.44), 11.408 (0.98), 11.427 (0.94).

25 **Example 37**

N-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

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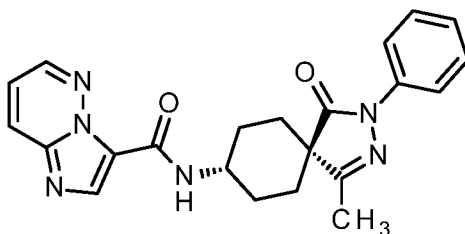
PyBOP (209 mg, 401 μ mol) was added to a mixture of (trans)-8-amino-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (86.0 mg, 334 μ mol), pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (68.1 mg, 418 μ mol) and N,N-diisopropylethylamine (290 μ l, 1.7 mmol) in DMF (4.0 ml) and the mixture was stirred over night at room temperature. For work-up, water was added and the precipitate was collected by filtration, washed with methanol and water and dried to give the title compound 95.0 mg (69 % yield).

LC-MS (Method 2): R_t = 1.08 min; MS (ESI^{neg}): m/z = 401 [M-H]⁻

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.35 (dd, 1H), 8.87 (dd, 1H), 8.60 (s, 1H), 8.26 (d, 1H), 7.85 (dd, 2H), 7.46-7.40 (m, 2H), 7.30 (dd, 1H), 7.22-7.17 (m, 1H), 4.23-4.16 (m, 1H), 2.31-2.18 (m, 5H), 2.00-1.89 (m, 2H), 1.85-1.67 (m, 4H)

Example 38

N-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-b]pyridazine-3-carboxamide



PyBOP (206 mg, 396 μ mol) was added to a mixture of (trans)-8-amino-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-en-1-one (85.0 mg, 330 μ mol), imidazo[1,2-b]pyridazine-3-carboxylic acid (67.4 mg, 413 μ mol) and N,N-diisopropylethylamine (290 μ l, 1.7 mmol) in DMF (4.0 ml) and the mixture was stirred over night at room temperature. For work-up, the reaction mixture was concentrated and the residue was stirred with methanol. The precipitate was collected by filtration, washed with water and methanol and then dried to give the title compound 93.6 mg (70 % yield).

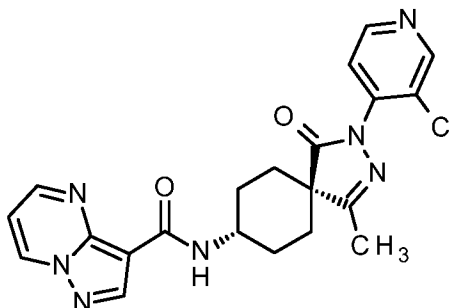
LC-MS (Method 2): R_t = 1.05 min; MS (ESI^{neg}): m/z = 401 [M-H]⁻

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¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.88-8.82 (m, 2H), 8.38 (dd, 1H), 8.33 (s, 1H), 7.87-7.83 (m, 2H), 7.50 (dd, 1H), 7.47-7.40 (m, 2H), 7.22-7.17 (m, 1H), 4.28-4.21 (m, 1H), 2.34-2.23 (m, 5H), 1.99-1.91 (m, 2H), 1.86-1.70 (m, 4H)

Example 39

- 5 N-[(trans)-3-(3-chloropyridin-4-yl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide



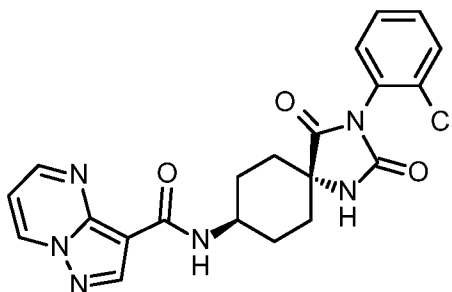
- PyBOP (75.9 mg, 146 μmol) was added to a mixture of 8-amino-2-(3-chloropyridin-4-yl)-4-methyl-2,3-diazaspiro[4.5]dec-3-en-1-one (mixture of cis-/trans-isomers) (38.8 mg, 133 μmol),
 10 pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (27.1 mg, 166 μmol) and N,N-diisopropylethylamine (120 μl, 660 μmol) in DMF (1.5 ml) and the mixture was stirred over night at room temperature. For work-up, the reaction mixture was concentrated and the residue was purified by preparative HPLC (Method 7) followed by trituration from ethanol to give the title compound 14.5 mg (25 % yield).

- 15 LC-MS (Method 2): Rt = 0.89 min; MS (ESI^{neg}): m/z = 436 [M-H]⁻

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.35 (dd, 1H), 8.87 (dd, 1H), 8.79 (s, 1H), 8.63 (d, 1H), 8.61 (s, 1H), 8.31 (d, 1H), 7.60 (d, 1H), 7.33-7.29 (m, 1H), 4.26-4.19 (m, 1H), 2.30-2.20 (m, 5H), 2.06-1.94 (m, 2H), 1.83-1.72 (m, 4H)

Example 40

- 20 N-[(cis)-3-(2-chlorophenyl)-2,4-dioxo-1,3-diazaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide



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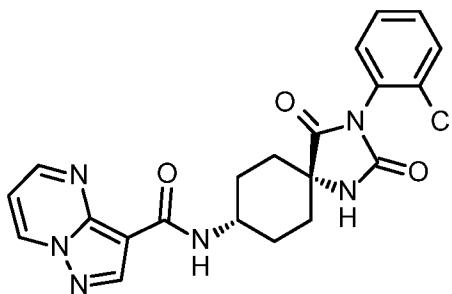
PyBOP (298 mg, 572 μ mol) was added to a mixture of 8-amino-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (mixture of cis-/trans-isomers) (140 mg, 477 μ mol, Intermediate 36), pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (97.2 mg, 596 μ mol) and N,N-diisopropylethylamine (420 μ l, 2.4 mmol) in DMF (1.7 ml) and the mixture was stirred over night at room temperature. For work-up, water was added and the mixture was extracted with ethyl acetate. The combined organic phases were filtered through a silicone filter and concentrated. The residue was purified by preparative HPLC to give the title compound 45.0 mg (21 % yield).

LC-MS (Method 2): R_t = 0.88 min; MS (ESI^{neg}): m/z = 437 [M-H]⁻

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.34-9.31 (m, 1H), 8.93 (s, 1H), 8.82 (dd, 1H), 8.59 (s, 1H), 8.11 (d, 1H), 7.68-7.64 (m, 1H), 7.56-7.45 (m, 3H), 7.29-7.25 (m, 1H), 4.14-4.04 (m, 1H), 2.23-1.67 (m, 8H)

Example 41

N-[(trans)-3-(2-chlorophenyl)-2,4-dioxo-1,3-diazaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide



PyBOP (85.0 mg, 163 μ mol) was added to a mixture of (trans)-8-amino-3-(2-chlorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (40.0 mg, 136 μ mol, intermediate 40), pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (27.8 mg, 170 μ mol) and N,N-diisopropylethylamine (120 μ l, 680 μ mol) in DMF (480 μ l) and the mixture was stirred over night at room temperature. For work-up, water was added and the precipitate was collected by filtration washed with 2-propanol and dried to give the title compound 22.0 mg (35 % yield).

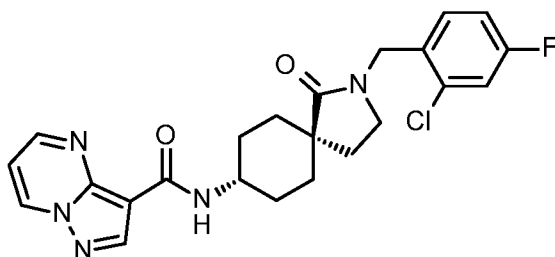
LC-MS (Method 2): R_t = 0.87 min; MS (ESI^{neg}): m/z = 437 [M-H]⁻

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.34 (dd, 1H), 9.19 (s, 1H), 8.84 (dd, 1H), 8.60 (s, 1H), 7.81 (d, 1H), 7.68-7.61 (m, 1H), 7.55-7.45 (m, 3H), 7.29 (dd, 1H), 4.06-3.91 (m, 1H), 2.08-1.84 (m, 5H), 1.82-1.66 (m, 3H)

Example 42

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N-[(trans)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide



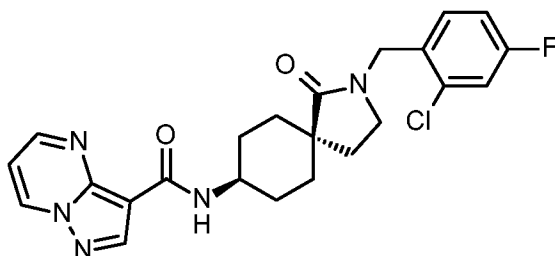
PyBOP (272 mg, 523 μ mol) was added to a mixture of 8-amino-2-(2-chloro-4-fluorobenzyl)-2-azaspiro[4.5]decan-1-one (130 mg, 418 μ mol, mixture of trans-/cis-isomers, intermediate 46), pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (85.3 mg, 523 μ mol) and N,N-diisopropylethylamine (360 μ l, 2.1 mmol) in DMF (4.6 ml) and the mixture was stirred over night at room temperature. For work-up, the reaction mixture was concentrated and the residue was stirred with methanol. The precipitate was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC [Instrument: Waters Autopurificationsystem SQD; column: Waters XBrigde C18 5 μ 100x30mm; eluent A: water + 0.2% vol. ammonia (32%), eluent B: acetonitrile; gradient: 0,00–0,50 min 33% B (25–>70mL/min), 0,51–5,50 min 53% B (70mL/min), temperature: room temperature; DAD scan: 210-400 nm; MS ESIPos., scan range 160-1000 m/z] to give N-[(trans)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (85 mg, 44% yield) and N-[(cis)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (9.0 mg, 5% yield, see example 43)

LC-MS (Method 2): Rt = 1.13 min; MS (ESIpos): m/z = 456 [M+H]⁺

¹H-NMR (500 MHz, DMSO-d₆): δ [ppm] = 9.31 (dd, 1H), 8.81 (dd, 1H), 8.56 (s, 1H), 7.79 (d, 1H), 7.46 (dd, 1H), 7.31-7.21 (m, 3H), 4.46 (s, 2H), 3.87-3.79 (m, 1H), 3.21-3.16 (m, 2H), 2.01-1.90 (m, 4H), 1.71-1.61 (m, 2H), 1.55-1.49 (m, 2H), 1.49-1.36 (m, 2H)

Example 43

N-[(cis)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide



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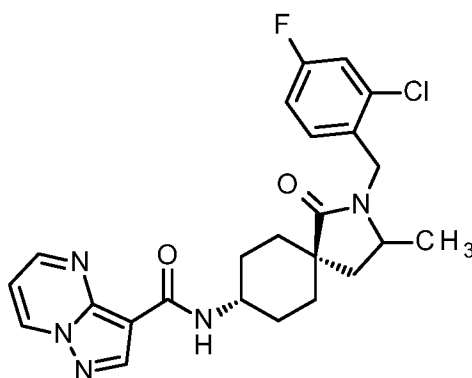
Was isolated as side product in the synthesis of N-[(trans)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (example 42) (9.0 mg).

LC-MS (Method 2): Rt = 1.15 min; MS (ESIpos): m/z = 456 [M+H]⁺

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 9.33 (dd, 1H), 8.85 (dd, 1H), 8.58 (s, 1H), 8.07 (br d, 1H), 7.49 (dd, 1H), 7.33-7.22 (m, 3H), 4.45 (s, 2H), 4.09-4.01 (m, 1H), 3.21-3.15 (m, 2H), 1.95-1.72 (m, 8H), 1.50-1.37 (m, 2H)

Example 44

N-[(3RS,trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide



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Was prepared in analogy to the synthesis of N-[(trans)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide, using (3RS)-8-amino-2-(2-chloro-4-fluorobenzyl)-3-methyl-2-azaspiro[4.5]decan-1-one (49.0 mg, 151 μmol, isomer 1 at cyclohexane ring, intermediate 52) as starting material to give the title compound (38.5 mg, 54 % yield).

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LC-MS (Method 2): Rt = 1.19 min; MS (ESIpos): m/z = 470 [M+H]⁺

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 9.31 (dd, 1H), 8.81 (dd, 1H), 8.57 (s, 1H), 7.80 (d, 1H), 7.47 (dd, 1H), 7.29-7.20 (m, 3H), 4.67 (d, 1H), 4.25 (d, 1H), 3.87-3.77 (m, 1H), 3.52-3.41 (m, 1H), 2.40-2.33 (m, 1H), 2.00-1.88 (m, 2H), 1.83 (td, 1H), 1.58-1.33 (m, 6H), 1.13 (d, 3H)

The title compound (34.0 mg) was separated into enantiomers using preparative chiral HPLC to give enantiomer 1 (13.4 mg, see example 45) and enantiomer 2 (13.2 mg, see example 46).

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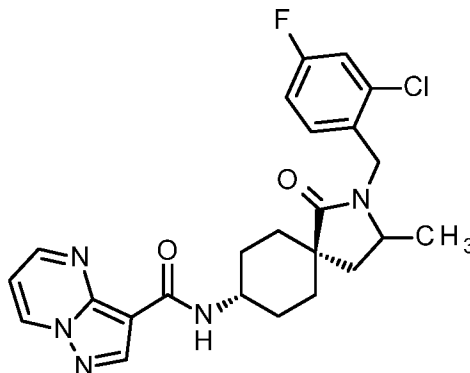
Preparative chiral HPLC method: Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000, column: Chiralpak IA 5μ 250x30mm; eluent A: acetonitrile + 0.1 vol-% diethylamine (99%); eluent B: methanol; isocratic: 50%A+50%B; flow 40.0 ml/min; UV 254 nm

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Analytical chiral HPLC method: Instrument: Method 5 HPLC 1260; column: Chiralpak IA 3 μ 100x4,6mm; eluent A: acetonitrile + 0.1 vol-% diethylamine (99%); eluent B: methanol; isocratic: 50%A+50%B; flow 1.4 ml/min; temperature: 25 °C; DAD 254 nm

Example 45

- 5 N-[(trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (enantiomer 1)

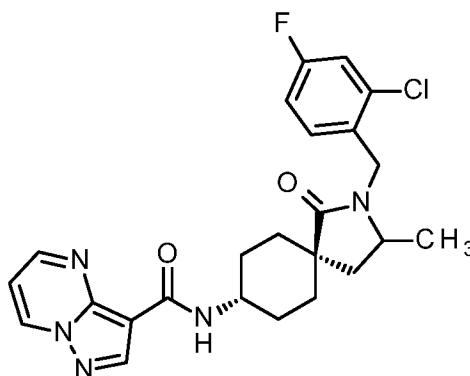


- Synthesis and separation of enantiomers and chiral HPLC methods see N-[(3RS,trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (example 44) .
- 10

Chiral HPLC: Rt = 1.61 min; ee >99.9%

Example 46

- N-[(trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (enantiomer 2)



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- Synthesis and separation of enantiomers and chiral HPLC methods see N-[(3RS,trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (example 44) .

Chiral HPLC: $R_t = 2.25$ min; ee 97.6%

Further, the compounds of formula (I) of the present invention can be converted to any salt as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of 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.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatine type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet

granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavouring and colouring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more colouring agents; one or more flavouring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavouring and colouring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or

interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using

suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable

delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as
5 necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5),
10 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the
15 composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid) ;

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium
20 carbonate, sodium hydroxide, triethanolamine, triethylamine) ;

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal) ;

aerosol propellants (examples include but are not limited to carbon dioxide, CCl₂F₂, F₂ClC-CClF₂ and CClF₃)

25 **air displacement agents** (examples include but are not limited to nitrogen and argon) ;

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate) ;

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol,
30 phenylethyl alcohol, phenylmercuric nitrate and thimerosal) ;

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite) ;

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binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers) ;

5 **buffering agents** (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

10 **chelating agents** (examples include but are not limited to edetate disodium and edetic acid)

colourants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red) ;

clarifying agents (examples include but are not limited to bentonite) ;

15 **emulsifying agents** (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate) ;

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

20 **flavourants** (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin) ;

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol) ;

levigating agents (examples include but are not limited to mineral oil and glycerin) ;

25 **oils** (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil) ;

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment) ;

30 **penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerol) ;

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation) ;

- 5 **stiffening agents** (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax) ;

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures)) ;

- 10 **surfactants** (examples include but are not limited to benzalkonium chloride, nonoxynol 10, octoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate) ;

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum) ;

- 15 **sweetening agents** (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose) ;

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc) ;

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch) ;

- 20 **tablet and capsule diluents** (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch) ;

- 25 **tablet coating agents** (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac) ;

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate) ;

- 30 **tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch) ;

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc) ;

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate) ;

tablet/capsule opaquants (examples include but are not limited to titanium dioxide) ;

tablet polishing agents (examples include but are not limited to carnuba wax and white wax) ;

5 **thickening agents** (examples include but are not limited to beeswax, cetyl alcohol and paraffin) ;

tonicity agents (examples include but are not limited to dextrose and sodium chloride) ;

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth) ; and

10 **wetting agents** (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

15 Sterile IV Solution: A 5 mg/ml solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over about 60 min.

20 Lyophilised powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/ml sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/ml, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/ml, and is administered either IV bolus or by IV infusion over 15 – 60 min.

25 Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/ml of the desired, water-insoluble compound of this invention

5 mg/ml sodium carboxymethylcellulose

4 mg/ml TWEEN 80

9 mg/ml sodium chloride

30 9 mg/ml benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Combination therapies

The term "combination" in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or 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 the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a "fixed combination" is a pharmaceutical composition wherein the said first active ingredient and the said second 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 the said first active ingredient and the said second 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 the said first active ingredient and the said second 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 said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination or kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. The present invention relates also to such combinations. For example, the compounds of this invention can be combined with known chemotherapeutic agents or anti-cancer agents, e.g. anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof. Other indication agents include, but are not limited to, anti-angiogenic agents, mitotic inhibitors, alkylating agents, anti-metabolites, DNA-intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, or anti-hormones.

The term “chemotherapeutic anti-cancer agents”, includes but is not limited to

131I-chTNT, abarelix, abiraterone, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, anectim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, blinatumomab, bortezomib, buserelin, bosutinib, brentuximab vedotin, 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 diftotox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab,

edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, 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, 5 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, 10 ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, 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, 15 lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine 20 sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neridronic acid, netupitant/palonosetron, nivolumab, pentetretotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nintedanib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, osimertinib, 25 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, 30 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, 35 refametinib, regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, rucaparib, samarium (153Sm) lexidronam, sargramostim, 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, tetrafosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib, valrubicin, vandetanib, vaporeotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

The compounds of the invention may also be administered in combination with protein therapeutics. Such protein therapeutics suitable for the treatment of cancer or other angiogenic disorders and for use with the compositions of the invention include, but are not limited to, an interferon (e.g., interferon .alpha., .beta., or .gamma.) supraagonistic monoclonal antibodies, Tuebingen, TRP-1 protein vaccine, Colostrinin, anti-FAP antibody, YH-16, gemtuzumab, infliximab, cetuximab, trastuzumab, denileukin diftitox, rituximab, thymosin alpha 1, bevacizumab, mecasermin, mecasermin rinfabate, oprelvekin, natalizumab, rhMBL, MFE-CP1 + ZD-2767-P, ABT-828, ErbB2-specific immunotoxin, SGN-35, MT-103, rinfabate, AS-1402, B43-genistein, L-19 based radioimmunotherapeutics, AC-9301, NY-ESO-1 vaccine, IMC-1C11, CT-322, rhCC10, r(m)CRP, MORAb-009, aviscumine, MDX-1307, Her-2 vaccine, APC-8024, NGR-hTNF, rhH1.3, IGN-311, Endostatin, volociximab, PRO-1762, lexatumumab, SGN-40, pertuzumab, EMD-273063, L19-IL-2 fusion protein, PRX-321, CNTO-328, MDX-214, tigapotide, CAT-3888, labetuzumab, alpha-particle-emitting radioisotope-linked lintuzumab, EM-1421, HyperAcute vaccine, tucotuzumab celmoleukin, galiximab, HPV-16-E7, Javelin - prostate cancer, Javelin - melanoma, NY-ESO-1 vaccine, EGF vaccine, CYT-004-MelQbG10, WT1 peptide, oregovomab, ofatumumab, zalutumumab, cintredekin besudotox, WX-G250, Albuferon, aflibercept, denosumab, vaccine, CTP-37, efungumab, or 131I-chTNT-1/B. Monoclonal antibodies useful as the protein therapeutic include, but are not limited to, muromonab-CD3, abciximab, edrecolomab, daclizumab, gentuzumab, alemtuzumab, ibritumomab, cetuximab, bevicizumab, efalizumab, adalimumab, omalizumab, muromomab-CD3, rituximab, daclizumab, trastuzumab, palivizumab, basiliximab, and infliximab.

A compound of general formula (I) as defined herein can optionally be administered in combination with one or more of the following: ARRY-162, ARRY-300, ARRY-704, AS-703026, AZD-5363, AZD-8055, BEZ-235, BGT-226, BKM-120, BYL-719, CAL-101, CC-223, CH-5132799, deforolimus, E-6201, enzastaurin, GDC-0032, GDC-0068, GDC-0623, GDC-0941, GDC-0973, GDC-0980, GSK-2110183, GSK-2126458, GSK-2141795, MK-2206, novolimus,

OSI-027, perifosine, PF-04691502, PF-05212384, PX-866, rapamycin, RG-7167, RO-4987655, RO-5126766, selumetinib, TAK-733, trametinib, triciribine, UCN-01, WX-554, XL-147, XL-765, zotarolimus, ZSTK-474.

- 5 Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:
- (1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor 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,
 - 15 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 tumor progression, and/or
 - 20 (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.

Methods of Sensitizing Cells to Radiation

- 25 In a distinct embodiment of the present invention, a compound of the present invention may be used to sensitize a cell to radiation. That is, 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 invention. In one aspect, the cell is treated with at least one compound of the invention.
- 30

Thus, the present invention also provides a method of killing a cell, wherein a cell is administered one or more compounds of the 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 the 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 the 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 one embodiment, a cell is killed by treating the cell with at least one DNA damaging agent. That is, after treating a cell with one or more compounds of the 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.*, cisplatinum), ionizing radiation (X-rays, ultraviolet radiation), carcinogenic agents, and mutagenic agents.

In another embodiment, 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 the 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 the 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 the 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*.

As mentioned *supra*, the compounds of the present invention have surprisingly been found to effectively inhibit tankyrases and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses are affected by inhibition of tankyrases, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, *e.g.*

leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin
5 tumours, and sarcomas, and/or metastases thereof.

In accordance with another aspect therefore, the present invention covers a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as
10 described and defined herein, for use in the treatment or prophylaxis of a disease, as mentioned *supra*.

Another particular aspect of the present invention is therefore the use of a compound of general formula (I), described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a
15 solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

Another particular aspect of the present invention is therefore the use of a compound of general formula (I) described *supra* or a stereoisomer, a tautomer, an N-oxide, a hydrate, a
20 solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same. for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease.

Another aspect of the present invention is the use of a compound of formula (I) or a
25 stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described herein, in the manufacture of a medicament for the treatment or prophylaxis of a disease.

The diseases referred to in the three preceding paragraphs are diseases of uncontrolled cell
30 growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant

lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

5

The term “inappropriate” within the context of the present invention, in particular in the context of “inappropriate cellular immune responses, or inappropriate cellular inflammatory responses”, as used herein, is to be understood as meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said

10 diseases.

Preferably, the use is in the treatment or prophylaxis of diseases, wherein the diseases are haematological tumours, solid tumours and/or metastases thereof.

- 15 Diseases further included in the context of the present invention are metabolic diseases (e.g. diabetes and obesity), fibrosis (e.g. lung fibrogenesis) and viral infection.

Method of treating hyper-proliferative disorders

- The present invention relates to a method for using the compounds of the present invention
- 20 and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis. 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 ; etc. which is
- 25 effective to treat the disorder. Hyperproliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, 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 lymphomas, sarcomas, and leukaemias.
- 30 Examples of breast cancer 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 hypophtalamic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

5 Tumours of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumours of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumours of the digestive tract include, but are not limited to anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

10 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.

15 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.

20 Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocyoma, lymphosarcoma, and rhabdomyosarcoma.

25 Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

30 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, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Methods of treating angiogenic disorders

The present invention also provides methods of treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

5 Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480 ; Peer et al. Lab. Invest. **1995**, 72, 638], age-related macular degeneration [AMD ; see, Lopez et al. Invest. Ophthalmol. Vis. Sci. 10 **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumour enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumour provides an escape route 15 for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell 20 types.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the 25 treatment of hyper-proliferative disorders and angiogenic 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 medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount 30 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 35 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to

about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about
5 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 of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The
10 average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

15 Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a
20 compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Preferably, the diseases of said method are haematological tumours, solid tumour and/or
25 metastases thereof.

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.

30

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The example testing experiments described herein serve to illustrate the present invention and
35 the invention is not limited to the examples given.

Pharmacol. Toxicol. Methods 2002 47:137] and using a BMG Pherastar MTP reader [BMG-Labtech, Offenburg, Germany].

TNKS1 Assay B

The potency of selected compounds according to the invention was assessed applying a modified in vitro inhibition assay. Here, the TNKS1 catalyzed NAD⁺-dependent ribosylation of the enzyme itself (auto-parsylation) was detected using [³H]-NAD⁺ as substrate and applying the scintillation proximity assay (SPA) method to detect tritium-labeled, parsylated TNKS1. The intensity of the readout signal is proportional to the incorporated [³H]-NAD⁺. Inhibition of TNKS1 leads to a decreased incorporation of [³H]-NAD⁺ and consequently to a lower readout signal intensity. The concentration of a test compound which inhibits the enzyme activity by 50% (corresponds to half of the normed readout signal intensity) is reported as IC₅₀.

Protocol Auto-Parsylation Assay

The assay was conducted in a 96 well MTP format with the identical TNKS1 enzyme sample and NAD⁺ sample as in the histone ribosylation assay with the following modifications: TNKS1 enzyme sample was diluted with a modified assay buffer (50 mM MES pH 7.0, 1 mM DTT, 0.01% Triton X-100) to a final concentration of 6 nM TNKS1 and 10x NAD⁺ solution was diluted with the modified assay buffer (s. above) to a final 0.445x NAD⁺ solution doped with 100 Bq/μl [³H]-NAD⁺ [Catalog #NET443H050UC, Perkin Elmer, Waltham, Massachusetts, USA]. Substrate solution (10 μl) was incubated with different test compound concentrations (2.5 μl in 10 % DMSO in modified assay buffer) or control (2.5 μl 10 % DMSO in modified assay buffer only) and enzyme (10 μl) over night at room temperature. Incorporated tritium was measured after addition of 50 μl SPA beads (1 mg/ml) [Catalog #RPNQ0095 20 mg/ml, Perkin Elmer, Waltham, Massachusetts, USA; diluted 1:10 with Dulbecco's phosphate buffered saline, PBS Catalog #D8537, Sigma-Aldrich, Steinheim, Germany] and detection of the photon emission with a beta count plate reader [Wallac MicroBeta®, Perkin Elmer, Waltham, Massachusetts, USA].

6.2 TNKS2 Assays

TNKS2 Assay A

The potency of the compounds according to the invention was assessed applying an *in vitro* inhibition assay. The TNKS2 catalyzed NAD⁺-dependent ribosylation of a suitable protein substrate was detected using a commercially available biotin/streptavidin binding based assay format [TNKS2 Histone Ribosylation Assay Kit (Biotin-labeled NAD⁺), Catalog #80572; BPS Bioscience, San Diego, USA]. Here, the incorporation of a biotin-labeled NAD⁺ during the TNKS2 catalyzed ribosylation reaction was detected with a streptavidin-HRP coupled chemi-luminescent readout. The intensity of the readout signal is proportional to the incorporated

NAD⁺. Inhibition of TNKS2 leads to a decreased incorporation of NAD⁺ and consequently to a lower readout signal intensity. The concentration of a test compound which inhibits the enzyme activity by 50% (corresponds to half of the normed readout signal intensity) is reported as IC₅₀.

Protocol

- 5 The assay was conducted in a 384 well MTP format according to the manufacturer's protocol [<http://www.bpsbioscience.com/poly-adp-ribose-polymerase/assay-kit/tnks2-histone-ribosylation-assay-kit-biotin-labeled-nad-80572> referencing: Brown, J.A., Marala, R.B. J. Pharmacol. Toxicol. Methods 2002 47:137]. and using a BMG Pherastar MTP reader [BMG-Labtech, Offenburg, Germany].

10

TNKS2 Assay B

- The potency of selected compounds according to the invention was assessed applying a modified in vitro inhibition assay. Here, the TNKS2 catalyzed NAD⁺-dependent ribosylation of the enzyme itself (auto-parsylation) was detected using [³H]-NAD⁺ as substrate and applying
15 the scintillation proximity assay (SPA) method to detect tritium-labeled, parsylated TNKS2. The intensity of the readout signal is proportional to the incorporated [³H]-NAD⁺. Inhibition of TNKS2 leads to a decreased incorporation of [³H]-NAD⁺ and consequently to a lower readout signal intensity. The concentration of a test compound which inhibits the enzyme activity by 50% (corresponds to half of the normed readout signal intensity) is reported as IC₅₀.

20 Protocol Auto-Parsylation Assay

- The assay was conducted in a 96 well MTP format with the identical TNKS2 enzyme sample and NAD⁺ sample as in the histone ribosylation assay with the following modifications: TNKS2 enzyme sample was diluted with a modified assay buffer (50 mM MES pH 7.0, 1 mM DTT, 0.01% Triton X-100) to a final concentration of 6 nM TNKS2 and 10x NAD⁺ solution was diluted
25 with the modified assay buffer (s. above) to a final 0.445x NAD⁺ solution doped with 100 Bq/μl [³H]-NAD⁺ [Catalog #NET443H050UC, Perkin Elmer, Waltham, Massachusetts, USA]. Substrate solution (10 μl) was incubated with different test compound concentrations (2.5 μl in 10 % DMSO in modified assay buffer) or control (2.5 μl 10 % DMSO in modified assay buffer only) and enzyme (10 μl) over night at room temperature. Incorporated tritium was measured
30 after addition of 50 μl SPA beads (1 mg/ml) [Catalog #RPNQ0095 20 mg/ml, Perkin Elmer, Waltham, Massachusetts, USA; diluted 1:10 with Dulbecco's phosphate buffered saline, PBS Catalog #D8537, Sigma-Aldrich, Steinheim, Germany] and detection of the photon emission with a beta count plate reader [Wallac MicroBeta®, Perkin Elmer, Waltham, Massachusetts, USA].

35 6.3 PARP1 Assay

The potency of the compounds according to the invention was assessed using a commercially available biotin/streptavidin binding assay kits from BPS Bioscience, San Diego, USA (Catalog #80551). The incorporation of a biotin-labeled NAD⁺ during the PARP1 catalyzed ribosylation of a suitable protein substrate was detected using with a streptavidin-HRP coupled chemi-luminescent readout. The intensity of the readout signal is proportional to the incorporated NAD⁺. Inhibition of PARP1 leads to a decreased incorporation of NAD⁺ and consequently to a lower readout signal intensity. The concentration of a test compound that inhibits the enzyme activity by 50% (corresponds to half of the normed readout signal intensity) is reported as IC₅₀.

Protocol

- 10 The assay was conducted in a 96 well MTP format according to the manufacturer's protocol (Catalog No. 80551) and using a BMG Pherastar MTP reader [BMG-Labtech, Offenburg, Germany].

6.4 PARP2 Assay

- 15 The potency of the compounds according to the invention was assessed using a commercially available biotin/streptavidin binding assay kits from BPS Bioscience, San Diego, USA (Catalog #80551). The incorporation of a biotin-labeled NAD⁺ during the PARP2 catalyzed ribosylation of a suitable protein substrate was detected using with a streptavidin-HRP coupled chemi-luminescent readout. The intensity of the readout signal is proportional to the incorporated NAD⁺. Inhibition of PARP2 leads to a decreased incorporation of NAD⁺ and consequently to a lower readout signal intensity. The concentration of a test compound that inhibits the enzyme activity by 50% (corresponds to half of the normed readout signal intensity) is reported as IC₅₀.

Protocol

- 25 The assay was conducted in a 96 well MTP format according to the manufacturer's protocol (Catalog No. 80552) and using a BMG Pherastar MTP reader [BMG-Labtech, Offenburg, Germany].

7 Cellular Assays

7.1 Measurement of the inhibitory activity of selected compounds on the Wildtype Wnt signaling cascade: HEK293 TOP/FOP Assay

- 30 In order to discover and characterize small molecules which inhibit the wildtype Wnt pathway, a cellular reporter assay was employed. The corresponding assay cell was generated by transfection of the mammalian cell line HEK293 (ATCC, #CRL-1573) with the Super TopFlash vector (Morin, Science 275, 1997, 1787-1790; Molenaar et al., Cell 86 (3), 1996, 391-399). The HEK293 cell line is cultivated at 37°C and 5% CO₂ in DMEM (Life Technologies, #41965-039), supplemented with 2 mM glutamine, 20 mM HEPES, 1.4 mM pyruvate, 0.15% Na-bicarbonate

and 10% foetal bovine serum (GIBCO, #10270). Stable transfectants were generated by selection with 300 µg/ml Hygromycin.

In a parallel approach, HEK293 cells were cotransfected with the FOP control vector and pcDNA3. The FOP vector is identical to the TOP construct, but it contains instead of functional TCF elements a randomized, non-functional sequence. For this transfection a stable transfected cell line was generated as well, based on selection with Geneticin (1 mg/ml).

In preparation of the assay, the two cell lines were plated 24 h before beginning the test at 10000 cells per well in a 384 micro titre plate (MTP) in 30 µl growth medium. Before compound testing a dose response curve for the Wnt dependent luciferase expression was recorded by stimulating the assay cell line with human recombinant Wnt-3a (R&D, #5036-WN-010) at different concentrations for 16 h at 37°C and 5% CO₂ followed by subsequent luciferase measurement, to determine the Wnt-3a EC₅₀ for the HEK293 TOP cell line on the day of testing. The recombinant human Wnt-3a was thereby applied between 2500 and 5 ng/ml in two-fold dilution steps.

Selective inhibitory activity for small molecules on the wildtype Wnt pathway was determined after parallel incubation of both (TOP and FOP) HEK293 reporter cell lines with a compound dilution series from 50 µM to 15 nM in steps of 3.16-fold dilutions in CAFTY buffer (130 mM sodium chloride, 5 mM potassium chloride, 20 mM HEPES, 1 mM magnesium chloride, 5 mM sodium bicarbonate, pH 7.4) containing 2 mM Ca²⁺ and 0.01% BSA.

The compounds were thereby serially prediluted in 100% DMSO and thereafter 50 fold into the CAFTY compound dilution buffer (described above). From this dilution 10 µl were added in combination with the EC₅₀ concentration of recombinant Wnt3a to the cells in 30 µl growth medium and incubated for 16 hours at 37°C and 5% CO₂. Thereafter luciferase assay buffer (1: 1 mixture of luciferase substrate buffer (20 mM Tricine, 2.67 mM magnesium sulfate, 0.1 mM EDTA, 4 mM DTT, 270 µM Coenzyme A, 470 µM Luciferin, 530 µM ATP, pH adjusted to pH 7.8 with a sufficient volume of 5M sodium hydroxide) and Triton buffer (30 ml Triton X-100, 115 ml glycerol, 308 mg Dithiothreitol, 4.45 g disodium hydrogen phosphate dihydrate, 3.03 g Tris . HCl, ad 1l H₂O, pH 7.8) was added in an equal volume to determine luciferase expression as a measure of Wnt signaling activity in a luminometer. The Wnt inhibitory activity was determined as IC₅₀ of resulting dose response curves.

7.2 Axin Stabilization Assay

The in vitro and in vivo effect of Tankyrase inhibition on the stabilization of cellular Axin was assessed using Peggy Simple Western assay with size-based separation and immunodetection of Axin2. SW403 cells (but not limited to) were seeded at 50000 cells per well in 96-well plates. After overnight incubation, cells were treated with testing compounds

and vehicle at 37 °C for 24 hours. Thereafter, cells were washed with PBS and then lysed in 15 µl of lysis buffer (M-PER buffer, Thermo Scientific # 78505) with complete proteinase and phosphatase inhibitors (Roche, #11836153001 and # 04906837001). The lysates were centrifuged and the supernatants were harvested for analysis. Tumor xenografts from in vivo studies were homogenized in a 2 ml tubes of Precellys®24 (Bertin Technologies, Villeurbanne, France) following with centrifugation to obtain tumor lysates. Capillary electrophoresis-based Simple Western assays were carried out with Peggy Sue™ NanoPro 1000 (ProteinSimple, California, USA). The protein amounts of Axin2 (but not limited to) were detected using anti-Axin2 antibody (Cell Signaling, Catalog #2151), quantified using the area under the curve, and normalized against GAPDH (anti-GAPDH, Zytomed Systems GmbH, Catalog #RGM2-6C5, Berlin, Germany).

7.3 Real-time RT-PCR for quantitative analysis of gene transcription

Real-time RT-PCR using a TaqMan fluorogenic detection system is a simple and sensitive assay for quantitative analysis of gene transcription. The TaqMan fluorogenic detection system can monitor PCR in real time using a dual-labeled fluorogenic hybridization probe (TaqMan probe) and a polymerase with 5'-3' exonuclease activity.

Cells from different cancer cell lines (as HCT116, but not limited to) were grown at 500-1000 cells/well in 384 well cell culture plates. For cell lysis the cell medium was carefully removed. The cells were washed carefully once with 50 µl/well PBS. Then 9.75 µl/well cell lysis buffer (50 mM Tris HCl pH 8,0, 40 mM sodium chloride, 1,5 mM magnesium chloride, 0,5 % IGEPAL CA 630, 50mM Guanidium thiocyanate) and 0.25 µl RNaseOUT (40 U/µl, Invitrogen, 10777-019)) per well were added. The plate was incubated for 5 min at room temperature. Then 30 µl DNase/RNase-free water per well was added and the lysates mixed. Isolation of total RNA from tumor tissues was conducted using InviTrap® Spin Tissue RNA Mini Kit (#1062100300, STRATEC MOLECULAR).

For the One-Step RT-PCR 2 µl lysate (each) was transferred to a 384 well PCR plate. The PCR reaction was composed by 5 µl 2x One Step RT qPCR MasterMix Plus, 0.05 µl Euroscript RT/RNase Inhibitor (50 U/µl, 20 U/µl) and 200 nM of the appropriate Primer/Hydrolysis Probe mix (primer sequences of forward, reverse and probe are given below for each analysed gene of interest or house keeping gene). 10 µl water were added per well. The plate was sealed with an adhesive optical film. The RT-PCR protocol was setup with 30 min 48°C, then 10 min 95°C followed by 50 cycles of 15 sec 95°C/1 min 60°C and a cooling step of 40°C for 30 sec using a Lightcycler LS440 from Roche. Relative expression was calculated using CP values from the gene of interest (e.g. AXIN2, but not limited to) and a house keeping gene (L32).

Used primers

205

L32 (forward primer: AAGTTCATCCGGCACCAGTC (SEQ ID NO. 1); reverse primer: TGGCCCTTGAATCTTCTACGA (SEQ ID NO. 2); probe: CCCAGAGGCATTGACAACAGGG (SEQ ID NO. 3))

AXIN2 (forward primer: AGGCCAGTGAGTTGGTTGTC (SEQ ID NO. 4); reverse primer: AGCTCTGAGCCTTCAGCATC (SEQ ID NO. 5); probe: TCTGTGGGGAAGAAATTCCATACCG (SEQ ID NO. 6))

8 In vivo Efficacy in xenograft models

Subcutaneous xenograft models in immunocompromised mice were used to evaluate in vivo anti-tumor efficacy of the compounds.

8.1 Maximum tolerable dose (MTD) studies

Prior to efficacy studies, the maximal tolerable dose (MTD) was determined by the following protocol: Female nude mice (NMRI (nu/nu), Taconic M&B A/S) received a defined oral dose of the test compound daily or bi-daily for 7 consecutive days followed by a 7 day observation period without dosing. Individual body weight and lethality were monitored daily.

The MTD is defined as the maximal applicable dose with a) no animal losing more than 10% body weight compared to initial body weight and b) no lethality during treatment phase.

8.2 In vivo efficacy studies

To measure anti-tumor efficacy, the test compounds were analysed in xenograft models on mice. Test compounds were dosed orally at their respective MTD as well as at sub-MTD dosages. In case the MTD could not be determined in previous MTD studies, the compounds were dosed at a maximum daily dose of 200 mg/kg (applied either in one single dose or split in 2 doses at 100 mg/kg).

Compounds were primarily analyzed in an ovarian teratocarcinoma model (PA-1) and in various colorectal cancer models on female immunocompromised mice.

For this purpose, $1-5 \times 10^6$ tumor cells (suspended in 0.1 ml of 50% cell culture medium/50% Matrigel) were subcutaneously injected into the flank of each animal. Animals were randomized into treatment groups when tumors had reached an average area of 20-30 mm² and treatment was started. Body weight and tumor area of each animal were measured 2-3 times weekly, depending on tumor growth. Studies were terminated, when animals in the control groups (receiving only compound vehicle solutions) or treatment groups reached tumor areas ~150 mm². At that time point, all groups in the study were terminated, tumors were isolated and weighed.

As primary parameter for anti-tumor efficacy the Treatment/Control (T/C) ratio of the final tumor weights were calculated (mean tumor weight of treatment group divided by mean tumor weight of vehicle group).

8.3 In vivo Mode of Action studies

- 5 To determine in vivo Mode of Action (MoA) of the test compounds, the same in vivo models as described under 8.2 were utilized. Tumor-bearing animals were treated for at least 3 days at MTD and also sub-MTD dosages. At study end, tumors were isolated and snap frozen in liquid nitrogen. Total RNA and protein were isolated from tumor samples following standard protocols.
- 10 Wnt/ β -catenin target gene expression and Axin2 protein abundance were measured by standard qRT-PCR and Western blotting methods (see 7.2 and 7.3).

Table 1: IC₅₀ values for selected examples in cellular HEK293 TOP and FOP assay as well as in TNKS1 and TNKS 2 biochemical assay

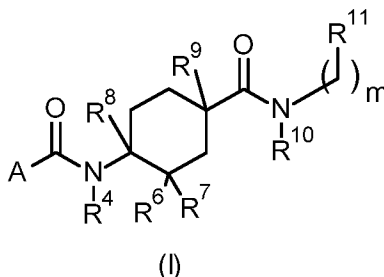
Example	HEK293 TOP IC ₅₀ [μ M]	HEK293 FOP IC ₅₀ [μ M]	TNKS1 Assay B IC ₅₀ [μ M]	TNKS2 Assay B IC ₅₀ [μ M]
1	0.25	50		7.2
2	0.39	50		0.49
3	14	40		> 10
4	0.27	8.4		0.53
5	0.28	50		0.79
6	9.0	50		7.8
7	0.15	50		0.97
8	0.021	50		0.0051
9	0.10	35		0.090
10	0.0025	50		0.0032
11	0.047	19		0.0042
12	0.18	50		0.23
13	0.34	50		0.32
14	2.0	50		>10
15	0.059	2.3		0.091
16	0.094	9.5		0.015
17	0.0080	50		0.011
18	0.0025	50		0.016

Example	HEK293 TOP IC50 [μ M]	HEK293 FOP IC50 [μ M]	TNKS1 Assay B IC50 [μ M]	TNKS2 Assay B IC50 [μ M]
19	0.0010	0.50	0.016	0.0036
20	0.0023	25	0.0096	0.0045
21	0.12	50		0.17
22	0.033	50		0.084
23	0.16	50		0.15
24	0.021	9.4		0.032
25	0.0015	3.2		0.0062
26	0.10	50		0.20
27	0.0024	0.50	0.032	0.012
28	0.0032	4.1	0.0082	0.0052
29	0.0031	0.50	0.0068	0.0059
30	0.0067	50	0.015	0.014
31	0.0039	0.50		0.0068
32	0.0051	0.50		0.0053
33	0.12	50		0.22
34	0.0032	25	0.0088	0.0035
35	0.0022	0.50		0.012
36	0.0050	50		0.011
37	0.21	50		1.5
38	0.51	50		2.1
39	0.0017	50		0.011
40	0.10	50		0.47
41	0.031	50		0.024
42	0.094	50	0.89	0.69
43	50	50	10	10
44	0.37	50		
45	2.6	50		3.4
46	0.59	24		1.4

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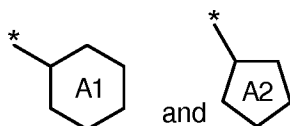
CLAIMS

1. A compound of formula (I) :

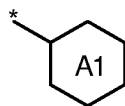


in which,

5 A represents a ring group selected from:



wherein * indicates the point of attachment of said groups with the rest of the molecule,
and wherein said point of attachment is a carbon atom ;



10 ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,

15 whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

20 c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

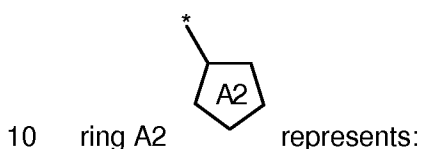
wherein said rings are fused with ring A1,

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said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

or,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;



- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms, or
- a 5-membered heterocyclic ring, optionally partially unsaturated, which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two carbon atoms of the heterocyclic ring are optionally replaced by a heteroatom-containing group selected from (C=O), N, NR^{20} , O, S, S(=O) and S(=O)₂;

said 5-membered heteroaryl and 5-membered heterocyclic rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

- a) a phenyl ring,
- b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or
- c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,

wherein said rings are fused with ring A2,

said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R^5 ;

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or

whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;

R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R^{14}) R^{15} , phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , OR¹³;

$R^{5'}$ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R^{14}) R^{15} , phenyl and 6-membered heteroaryl which contains one or two nitrogen atoms,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , OR¹³;

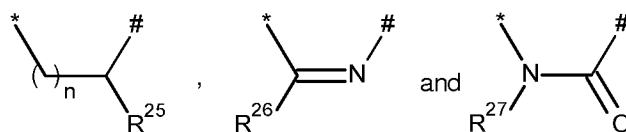
R^6 represents hydrogen, halogen, hydroxy, C₁-C₃-alkyl or C₁-C₃-alkoxy;

R^7 represents hydrogen; or

R^6 , R^7 represent, independently of each other, halogen;

R^8 represents hydrogen, or C₁-C₃-alkyl,

R^9 and R^{10} together represent a group selected from:



wherein * indicates the point of attachment of said group to the rest of the molecule at R^9 ,

and # indicates the point of attachment of said group to the rest of the molecule at R^{10} ;

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R¹¹ represents a group selected from :

aryl, and heteroaryl ,

wherein aryl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

- 5 C₁-C₆-alkyl , C₁-C₃-alkoxy , C₁-C₃-hydroxyalkyl , C₃-C₆-cycloalkyl, C₃-C₆-cycloalkoxy, C₁-C₃-haloalkyl , C₁-C₃-haloalkoxy, halogen , cyano, nitro, hydroxy, (C₁-C₆-alkyl)-S-, (C₁-C₆-alkyl)-S(=O)-, (C₁-C₆-alkyl)-S(=O)₂-,
 -S(=O)(=NR²¹)R²², -N(R¹⁴)R¹⁵, R¹⁴(R¹⁵)N-(C₁-C₆-alkyl)-,
 10 R¹⁴(R¹⁵)N-(C₂-C₆-alkoxy)-, phenyl, phenoxy, -N(R¹⁶)C(=O)R¹⁷, -C(=O)OH, -C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

whereby two substituents of said aryl group, when they are in ortho-position to one another, can be linked to one another in such a way that they jointly form methanediylbisoxo, ethane-1,2-diylbisoxo, propane-1,3-diyl, or butane-1,4-diyl,

R¹³ represents a group selected from :

- 15 C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₂-C₆-hydroxyalkyl-, and (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)-,

R¹⁴ and R¹⁵ are, independently of each other, selected from :

- hydrogen, C₁-C₆-alkyl , C₃-C₆-cycloalkyl , (C₃-C₆-cycloalkyl)-(C₁-C₆-alkyl)- ,
 20 C₂-C₆-hydroxyalkyl , (C₁-C₃-alkoxy)-(C₂-C₆-alkyl)- , (C₁-C₃-haloalkoxy)-(C₂-C₆-alkyl)-, C₁-C₆-haloalkyl ,
 H₂N-(C₂-C₆-alkyl)-, (C₁-C₃-alkyl)N(H)(C₂-C₆-alkyl)-,
 (C₁-C₃-alkyl)₂N(C₂-C₆-alkyl)- , HOC(=O)-(C₁-C₆-alkyl)-,
 R¹³OC(=O)-(C₁-C₆-alkyl)-, 4- to 6-membered heterocycloalkyl,
 (4- to 6-membered heterocycloalkyl)-(C₁-C₆-alkyl)- , aryl, heteroaryl,
 25 aryl-(C₁-C₆-alkyl)-, and heteroaryl-(C₁-C₆-alkyl)-,

wherein 4- to 6-membered heterocycloalkyl groups are optionally substituted with one, two, three or four substituents, which are independently of each other selected from :

- 30 C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -NH₂, -NH(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)₂, hydroxy, a halogen atom, and cyano,
 and,

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wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

5 C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy,
C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, -C(=O)OH,
-C(=O)OR¹³, and -C(=O)N(R¹⁶)₂,

or,

10 R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, O, S, S(=O) and S(=O)₂, and in which one additional ring atom is optionally replaced by C(=O),

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two, three or four groups, which are independently of each other selected from :

C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom, and cyano,

15 whereby when two substituents are attached to the same ring carbon atom, together with the carbon atom to which they are attached, can be linked to one another in such a way that they jointly form a cyclobutane, cyclopentane, azetidine, pyrrolidine, oxetane, tetrahydrofuran, thietane, tetrahydrothiophene, thietane 1-oxide, tetrahydrothiophene 1-oxide, thietane 1,1-dioxide or tetrahydrothiophene 1,1-dioxide group;

20 R¹⁶ represents, independently of each other, hydrogen, or C₁-C₃-alkyl,

R¹⁷ represents hydrogen, C₁-C₆-alkyl, C₁-C₆-hydroxyalkyl, C₃-C₆-cycloalkyl, C₁-C₆-haloalkyl, (C₁-C₃-alkoxy)-(C₁-C₆-alkyl)-, aryl, or heteroaryl,

wherein aryl and heteroaryl groups are optionally substituted with one or two substituents, which are independently of each other selected from :

25 C₁-C₃-alkyl, C₃-C₆-cycloalkyl, C₁-C₃-alkoxy, C₃-C₆-cycloalkoxy,
C₁-C₃-haloalkyl, C₁-C₃-haloalkoxy, halogen, cyano, and hydroxy,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, C₃-C₄-cycloalkyl, -C(=O)C₁-C₄-alkyl, -C(=O)OC₁-C₄-alkyl and phenyl,

30 R²¹ represents hydrogen, cyano, (C₁-C₃-alkyl)-C(=O)-, or (C₁-C₃-haloalkyl)-C(=O)-,

R²² represents C₁-C₄-alkyl, or C₃-C₄-cycloalkyl,

R²⁵ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-,

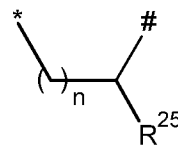
213

R²⁶ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-,

R²⁷ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-,

5 n is 1 or 2,

m is 0, 1 or 2,

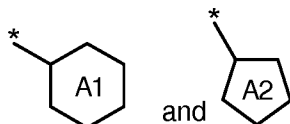


with the proviso that when R⁹ and R¹⁰ together represent a group or 2,

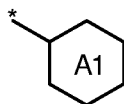
10 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. The compound of formula (I) according to claim 1, wherein:

A represents a group selected from:



15 wherein * indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom ;



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

20 said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,

whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

25 b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

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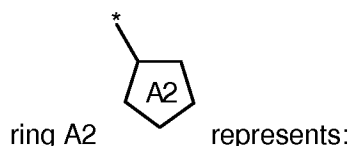
c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

5 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R⁵;

or,

whereby two substituents R⁵ when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in
10 which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR²⁰, O, S, S(=O) and S(=O)₂;



15 - a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR²⁰, O and S, in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R⁵,

20 whereby two substituents R⁵ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, or

25 c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR²⁰, O and S, in which one ring carbon atoms is optionally further replaced by a nitrogen atom,

wherein said rings are fused with ring A2,

30 said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, two or three times, independently from each other, with R⁵;

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or

whereby two substituents $R^{5'}$ when they are in adjacent positions of the ring A2, can be linked to one another in such a way that they jointly form a methylenedioxy, ethylenedioxy, ethyleneoxy, trimethyleneoxy, trimethylene or tetramethylene group, in which one carbon atom of said groups is optionally replaced by a heteroatom-containing group selected from (C=O), NR^{20} , O, S, S(=O) and S(=O)₂;

R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, and -N(R^{14}) R^{15} ,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , and OR¹³;

$R^{5'}$ represents, independently of each other, a group selected from :

halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R^{14}) R^{15} , phenyl and a 6-membered heteroaryl which contains one or two nitrogen atoms,

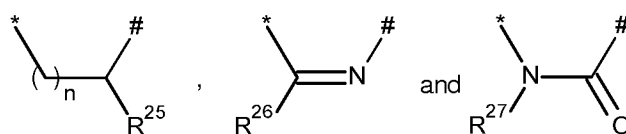
wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R^{14}) R^{15} , and OR¹³;

R^6 represents hydrogen;

R^7 represents hydrogen;

R^8 represents hydrogen,

R^9 and R^{10} together represent a group selected from:



wherein * indicates the point of attachment of said group to the rest of the molecule at R^9 ,

and # indicates the point of attachment of said group to the rest of the molecule at R^{10} ;

R^{11} represents a group selected from :

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phenyl, and heteroaryl ,

wherein phenyl and heteroaryl groups are optionally substituted with one, two, three or four groups, which are independently of each other selected from :

5 C₁-C₄-alkyl, C₁-C₂-alkoxy, C₁-C₃-hydroxyalkyl, C₃-C₄-cycloalkyl, C₁-C₂-haloalkoxy, halogen, cyano, and hydroxy,

R¹³ represents a group selected from :

C₁-C₃-alkyl, and C₃-C₄-cycloalkyl,

R¹⁴ and R¹⁵ are independently of each other selected from :

10 hydrogen, C₁-C₄-alkyl, C₃-C₆-cycloalkyl, (C₃-C₆-cycloalkyl)-(C₁-C₃-alkyl)-, C₂-C₃-hydroxyalkyl, (C₁-C₂-alkoxy)-(C₂-C₃-alkyl)-, (C₁-C₂-haloalkoxy)-(C₂-C₃-alkyl)-, and C₁-C₃-haloalkyl,

or,

15 R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰, and O, and in which one additional ring atom is optionally replaced by C(=O),

said 4- to 7-membered heterocycloalkyl group being optionally substituted with one, two , three or four groups, which are independently of each other selected from :

20 C₁-alkyl, C₁-haloalkyl, C₁-alkoxy , C₁-haloalkoxy, C₃-C₄-cycloalkyl, C₃-C₄-cycloalkoxy, -N(CH₃)₂, NH₂, N(CH₃)H, hydroxy, a halogen atom , and cyano,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, C₁-C₂-alkyl , C₁-C₂-haloalkyl, and C₃-C₄-cycloalkyl,

R²⁵ represents hydrogen, or C₁-C₃-alkyl,

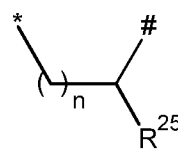
25 R²⁶ represents hydrogen, C₁-C₃-alkyl, C₁-C₃-haloalkyl, (C₁-C₂-alkoxy)-(C₁-C₃-alkyl)- or (C₁-C₂-haloalkoxy)-(C₁-C₃-alkyl)-,

R²⁷ represents hydrogen,

n is 1 or 2,

m is 0, or 1,

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with the proviso that when R^9 and R^{10} together represent a group

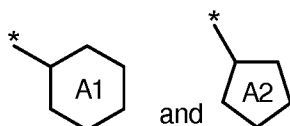
1,

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

5

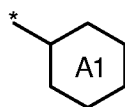
3. The compound of formula (I) according to claim 1 or 2, wherein:

A represents a group selected from:



wherein $*$ indicates the point of attachment of said groups with the rest of the molecule, and wherein said point of attachment is a carbon atom;

10



ring A1 represents a phenyl ring or a 6-membered heteroaryl ring which contains one or two nitrogen atoms;

said phenyl and 6-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

15

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

a) a phenyl ring,

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms, and

20

c) a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, and NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

wherein said rings are fused with ring A1,

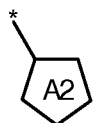
said phenyl, 6-membered heteroaryl and 5-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

25

or,

whereby two substituents R^5 when they are in adjacent positions of the ring A1, can be linked to one another in such a way that they jointly form a ethyleneoxy, or trimethyleneoxy;

5



ring A2 represents:

- a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from NR^{20} , in which one or two ring carbon atoms are optionally further replaced by one or two nitrogen atoms,

10 said 5-membered heteroaryl ring being optionally substituted one, two or three times, independently from each other, with R^5 ,

whereby two substituents R^5 when they are in adjacent positions of the ring A2, can be linked to one another in such a way that together with the atoms to which they are attached they jointly form:

15 a) a phenyl ring, or

b) a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

wherein said rings are fused with ring A2,

said phenyl, and 6-membered heteroaryl rings being optionally substituted one, or two times, independently from each other, with R^5 ;

20 R^4 represents a hydrogen atom,

R^5 represents, independently of each other, a group selected from :

halogen, C_1 -alkyl, and C_1 -alkoxy,

R^5 represents C_1 -alkyl,

25 wherein C_1 -alkyl is optionally substituted one, or two times with a group independently selected from oxo ($C=O$), and $-N(R^{14})R^{15}$,

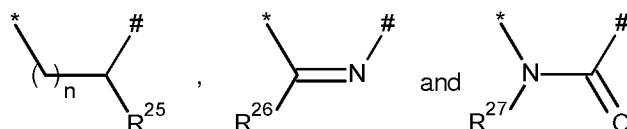
R^6 represents hydrogen;

R^7 represents hydrogen;

R^8 represents hydrogen,

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R⁹ and R¹⁰ together represent a group selected from:



wherein * indicates the point of attachment of said group to the rest of the molecule at R⁹,

5 and # indicates the point of attachment of said group to the rest of the molecule at R¹⁰ ;

R¹¹ represents a group selected from :

phenyl, and pyridinyl ,

10 wherein phenyl and pyridinyl groups are optionally substituted with one, two, or three groups, which are independently of each other selected from :

fluorine, and chlorine,

R¹³ represents a group C₁-C₃-alkyl,

R¹⁴ and R¹⁵ are independently of each other selected from :

15 hydrogen, C₁-C₃-alkyl, C₃-cycloalkyl, (C₁-alkoxy)-(C₂-alkyl)-, (C₁-haloalkoxy)-(C₂-alkyl)-, and C₂-haloalkyl,

or,

R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocycloalkyl group, in which one carbon atom is optionally replaced by a further heteroatom-containing group selected from NR²⁰,

20 said 4- to 6-membered heterocycloalkyl group being optionally substituted with one, or two groups, which are independently of each other selected from :

C₁-alkyl, and a halogen atom, preferably fluorine ,

R²⁰ represents, independently of each other, a group selected from :

hydrogen, and C₁-alkyl,

25 R²⁵ represents hydrogen, or C₁-alkyl,

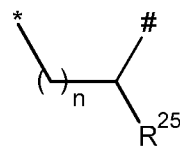
R²⁶ represents hydrogen, C₁-C₂-alkyl, or (C₁-alkoxy)-(C₁-alkyl)-,

R²⁷ represents hydrogen,

n is 1,

220

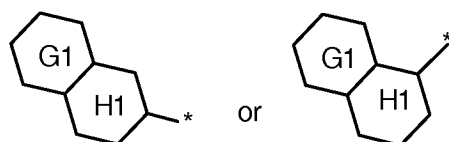
m is 0, or 1,



with the proviso that when R^9 and R^{10} together represent a group 1,

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

4. The compound according to any of of claims 1 to 3, wherein ring A represents:



wherein * indicates the point of attachment of said groups with the rest of the molecule, and in which :

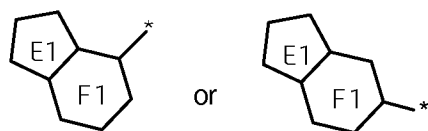
10 ring G1 represents a phenyl or a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

ring H1 represents phenyl or a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

with the proviso that when G1 or H1 is phenyl, then the other is a 6-membered heteroaryl 15 group which contains one or two nitrogen atoms,

said ring G1 and ring H1 being optionally substituted independently with one or two R^5 groups.

5. The compound according to any one of claims 1 to 3, wherein ring A represents:



wherein * indicates the point of attachment of said

20 groups with the rest of the molecule, and in which :

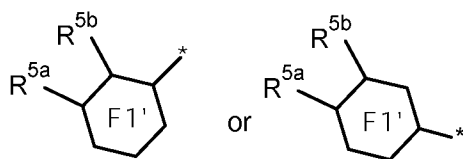
ring F1 represents phenyl or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

ring E1 represents a 5-membered heteroaryl ring which contains one heteroatom-containing group selected from N, NR^{20} , O and S, in which one or two ring carbon atoms are optionally 25 further replaced by one or two nitrogen atoms, or

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said ring E1 and ring F1 being optionally substituted independently with one or two R⁵ groups.

6. The compound according to any one of claims 1 to 3, wherein ring A represents:



wherein * indicates the point of attachment of said

5 groups with the rest of the molecule, and in which :

ring F1' represents phenyl or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

R^{5a} and R^{5b} are linked to one another in such a way that they jointly form a ethyleneoxy, or a trimethyleneoxy group,

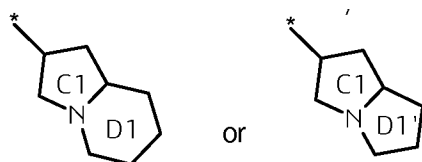
10 said ring F1' being optionally substituted one time with a group selected from :

fluorine, chlorine, bromine, hydroxy, C₁-C₄-alkyl, C₃-cycloalkyl, C₁-alkoxy, -NH₂, and -C(O)OR¹³,

wherein C₁-C₄-alkyl is optionally substituted one or two times with a group independently selected from fluorine, oxo (C=O), and -NH(C₁-alkyl).

15

7. The compound according to any one of claims 1 to 3, wherein ring A represents:



wherein * indicates the point of attachment of said groups

with the rest of the molecule, and in which :

20 ring C1 represents a 5-membered heteroaryl ring in which one or two ring carbon atoms are optionally further replaced by a heteroatom selected from N, NR²⁰, O and S,

ring D1 is a 6-membered heteroaryl ring which contains one or two nitrogen atoms,

ring D1' is a 5-membered heteroaryl ring in which one ring carbon atom is optionally further replaced by a heteroatom selected from N, NR²⁰, O and S,

25 said rings D1 and D1' being optionally substituted independently with one or two R⁵ groups.

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8. The compound according to any one of claims 1 to 3, wherein ring A represents a group selected from:

phenyl, pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl,

said groups being optionally substituted independently with one or two R^5 groups.

5

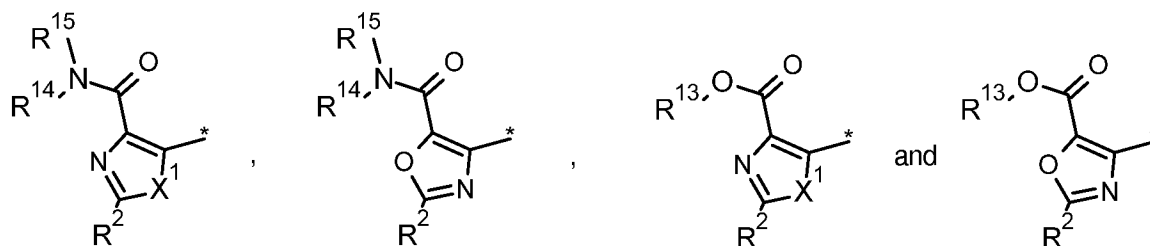
9. The compound according to any one of claims 1 to 3, wherein ring A represents a group selected from:

imidazolyl, pyrazolyl, 1,3-thiazolyl, and 1,2-oxazolyl,

said groups being optionally substituted independently with one or two R^5 groups.

10

10. The compound according to any one of claims 1 to 3, wherein ring A represents a group selected from:



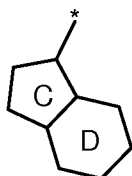
15 X¹ represents NR³ or O,

R² represents a group selected from :

hydrogen, C₁-C₃-alkyl, and C₃-C₄-cycloalkyl,

R³ represents a hydrogen atom.

20 11. The compound according to any one of claims 1 to 3, wherein ring A represents a group:



represents a bicyclic aromatic ring system, wherein ring C represents a 5-membered heteroaryl group which contains one heteroatom-containing group selected from N, NH, and N(C₁-C₃-alkyl), in which one or two carbon atoms are optionally further replaced by one or two N atoms,

said ring C being optionally substituted with one or two R^{5'} groups, and

ring D represents a phenyl group or a 6-membered heteroaryl group which contains one, or two nitrogen heteroatoms, said ring D being optionally substituted with one, two or three R¹² groups;

- 5 R¹² represents, independently of each other, halogen, hydroxy, C₁-C₄-alkyl, C₃-C₄-cycloalkyl, C₁-C₃-alkoxy, C₁-C₃-haloalkoxy, -N(R¹⁴)R¹⁵,

wherein C₁-C₄-alkyl is optionally substituted one, two or three times with a group independently selected from halogen, hydroxy, oxo (C=O), C₁-C₃-alkoxy, C₃-C₆-cycloalkyl, -N(R¹⁴)R¹⁵, OR¹³.

10

12. The compound according to any one of claims 1 to 3, which is selected from the group consisting of :

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-6-methoxy-1,5-naphthyridine-4-carboxamide,

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-2-carboxamide,

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide,

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1,5-naphthyridine-4-carboxamide,

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-methylpyridine-2-carboxamide,

N-[(trans)-1-ethyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-methylpyridine-2-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-6-methoxy-1,5-naphthyridine-4-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-a]pyridine-5-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-imidazole-2-carboxamide,

5-bromo-N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-2,3-dihydro-1-benzofuran-7-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-2-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoline-8-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-ethyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-(methoxymethyl)-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrimidine-4-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-pyrrolo[2,3-b]pyridine-6-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-5-methylpyridine-2-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-pyrrolo[3,2-b]pyridine-3-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]quinoxaline-5-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-1H-indazole-6-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-b]pyridazine-3-carboxamide,

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-methyl-1H-imidazole-4,5-dicarboxamide,

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-ethyl-1H-imidazole-4,5-dicarboxamide,

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(propan-2-yl)-1H-imidazole-4,5-dicarboxamide,

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(2-methoxyethyl)-1H-imidazole-4,5-dicarboxamide,

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-cyclopropyl-1H-imidazole-4,5-dicarboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-imidazole-5-carboxamide,

N-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-4-[(3-fluoroazetidin-1-yl)carbonyl]-1H-imidazole-5-carboxamide,

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-(2,2,2-trifluoroethyl)-1H-imidazole-4,5-dicarboxamide,

N⁵-[(trans)-3-(2-chloro-4-fluorophenyl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]-N⁴-[2-(trifluoromethoxy)ethyl]-1H-imidazole-4,5-dicarboxamide,

N-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-1-methyl-4-oxo-3-phenyl-2,3-diazaspiro[4.5]dec-1-en-8-yl]imidazo[1,2-b]pyridazine-3-carboxamide,

N-[(trans)-3-(3-chloropyridin-4-yl)-1-methyl-4-oxo-2,3-diazaspiro[4.5]dec-1-en-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(cis)-3-(2-chlorophenyl)-2,4-dioxo-1,3-diazaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-3-(2-chlorophenyl)-2,4-dioxo-1,3-diazaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(cis)-2-(2-chloro-4-fluorobenzyl)-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(3RS,trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-[(trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (enantiomer 1), and

N-[(trans)-2-(2-chloro-4-fluorobenzyl)-3-methyl-1-oxo-2-azaspiro[4.5]dec-8-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (enantiomer 2),

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

13. A compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 12, for use in the treatment or prophylaxis of a disease.

14. A pharmaceutical composition comprising a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 12, and a pharmaceutically acceptable diluent or carrier.

15. A pharmaceutical combination comprising :

- one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 12, and
- 5 - one or more second active ingredients selected from chemotherapeutic anti-cancer agents.

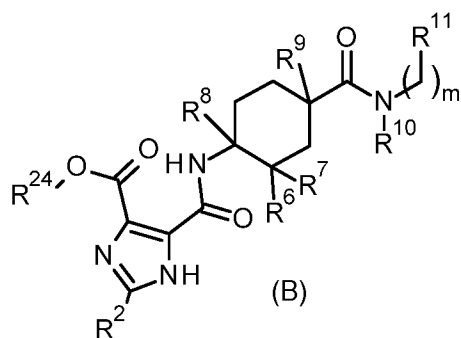
16. Use of a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or
10 a mixture of same, according to any one of claims 1 to 12, for the prophylaxis or treatment of a disease.

17. Use of a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or
15 a mixture of same, according to any one of claims 1 to 12, for the preparation of a medicament for the prophylaxis or treatment of a disease.

18. Use according to claim 13, 16 or 17, wherein said disease is a disease of uncontrolled cell growth, proliferation and/or survival, an inappropriate cellular immune response, or an
20 inappropriate cellular inflammatory response, particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is a haematological tumour, a solid tumour and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax
25 including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

19. A compound, or a salt thereof, selected from:

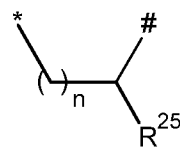
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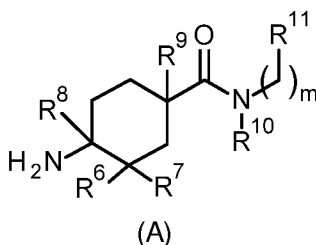
in which R^{24} is phenyl or R^{13} ,

5 m , R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are as defined for the compound of general formula (I) in any one of claims 1 to 3 or 10, and

R^2 is as defined in claim 10,



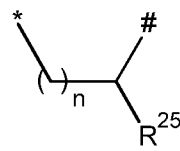
with the proviso that when R^9 and R^{10} together represent a group
or 2, and n and R^{25} are as defined in any one of claims 1 to 3;



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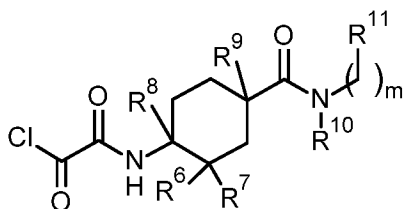
in which,

m , R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are as defined for the compound of general formula (I) in any one of claims 1 to 12, and



15 with the proviso that when R^9 and R^{10} together represent a group or 2, and n and R^{25} are as defined in any one of claims 1 to 12;

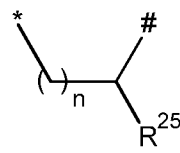
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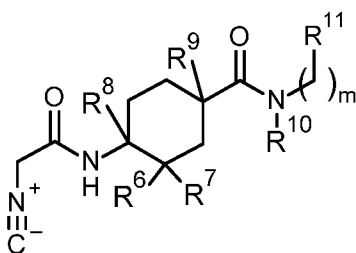
in which,

m, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are as defined for the compound of general formula (I) in any one of claims 1 to 3, and



with the proviso that when R⁹ and R¹⁰ together represent a group
 5 or 2, and n and R²⁵ are as defined in any one of claims 1 to 3;

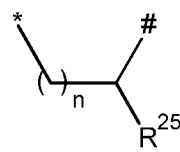
and,



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in which,

10 m, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are as defined for the compound of general formula (I) in any one of claims 1 to 3, and



with the proviso that when R⁹ and R¹⁰ together represent a group
 or 2, and n and R²⁵ are as defined in any one of claims 1 to 3.

15 20. Use of a compound according to claim 19, for the preparation of a compound of general formula (I) according to any one of claims 1 to 12.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/077428

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/12 C07D231/54 C07D401/04 C07D401/12 C07D405/12
 C07D487/04 C07D209/54 A61K31/403 A61K31/416 A61K31/4184
 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 2006/063791 A1 (LI AN-HU [US] ET AL) 23 March 2006 (2006-03-23) page 15, paragraph 198 - page 16, paragraph 199; compounds 3, 17 page 24; claim 1 page 29; claims 19, 21-23 -----	1-11, 13-20 12
X	ANANDA KUMAR, C. S.; BENAKA PRASAD, S. B. BENAKA; VINAYA, K.; CHANDRAPPA, S.; THIMMEGOWDA, N. R.; RANGANATHA, S. R.: "Synthesis and antiproliferative activity of substituted diazасpirohydantoins: a structure-activity relationship study", INVESTIGATIONAL NEW DRUGS, vol. 27, no. 2, 2009, pages 131-139, XP009501798, -----	1-11, 13-20
A	page 133; table 1; compounds 7e, 7f page 135; table 2 page 136; figures 1-4 -----	12



Further documents are listed in the continuation of Box C.



See patent family annex.

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

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

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

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

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Date of the actual completion of the international search

24 November 2017

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/077428

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