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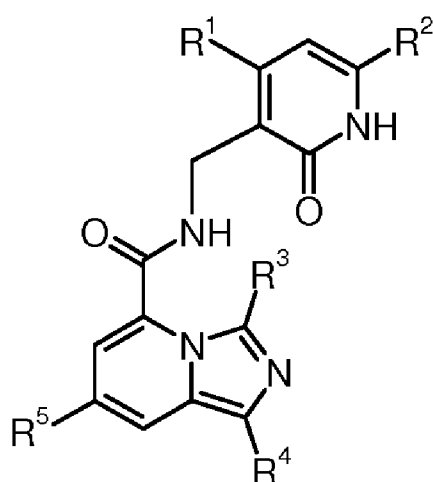
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- (54) **Title:** IMIDAZOPYRIDINE EZH2 INHIBITORS



(I)

(57) **Abstract:** The present invention relates to imidazopyridines of general formula (I), to a method for their preparation, to intermediates for their preparation, to pharmaceutical compositions comprising at least one of those compounds, and to the use thereof.



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Imidazopyridine EZH2 Inhibitors

The present invention relates to imidazopyridines, to a method for their preparation, to intermediates for their preparation, to pharmaceutical compositions, and to the use thereof.

5

Background

Epigenetic changes refer to modifications in gene expression without alterations of the DNA sequence. The DNA within eukaryotic cell nuclei is packaged together with histones and other proteins to form the complex known as chromatin. Gene transcription is regulated by selective, enzyme-catalyzed post-translational modifications of the histone proteins (Jenuwein and Allis, Science, 2001, 10;293(5532):1074-80). The transcription of each gene can change from high-level expression to complete silencing, depending on the influence of the histone modification pattern which regulates the accessibility of promoters and the activity of the transcription machinery (Li *et al.*, Cell, 2007, 23;128(4):707-19). Epigenetic mechanisms are crucial to establish cellular identities during differentiation, and alterations in histone modification marks can result in inappropriate gene expression patterns and subsequent de-regulation of various cellular signaling pathways leading to cancer (Suvà *et al.*, Science, 2013, 29;339(6127):1567-70). In contrast to genetic mutations these alterations in histone modifications are maintained by enzymes that can be targeted with specific inhibitors (Mair *et al.*, Trends Pharmacol Sci., 2014, 35(3):136-45).

The Polycomb Repressive Complex 2 (PRC2) has emerged as a key histone modifying complex frequently de-regulated in cancer (Deb *et al.*, Mol Cancer Res., 2014, 12(5):639-53). PRC2 has a histone methyltransferase function responsible for the mono-, di- and tri-methylation of lysine-27 of histone H3 (H3K27). Methylation of H3K27 is a repressive chromatin mark correlated with silencing of gene expression. PRC2 is composed of the catalytic SET domain-containing histone methyltransferase EZH2 (enhancer of zeste homolog 2) or its functional homologue EZH1 (enhancer of zeste homolog 1) and core accessory proteins EED, SUZ12, and RbAp48. In non-transformed cells the PRC2 complex is a master regulator that controls differentiation by repression of lineage control genes (Bracken and Helin, Nat Rev Cancer., 2009, 9(11):773-84). Overexpression of core proteins of PRC2 has been found in a wide variety of cancers (Simon and Lange, Mutat Res., 2008, 1;647(1-2):21-9). In solid tumors high levels of EZH2 expression have been reported to be especially associated with the development of de-differentiated and highly aggressive tumors with a poor prognosis (Bachmann *et al.*, J Clin Oncol., 2006, 10;24(2):268-73; Kleer *et al.*, Proc Natl Acad Sci U S A, 2003, 100:11606-11.; Crea *et al.*, Crit Rev Oncol Hematol., 2012, 83(2):184-93). EZH2 expression increases with tumor stage in colorectal (Wang *et al.*, World J Gastroenterol., 2010, 21;16(19):2421-7) and lung adenocarcinomas (Lv *et al.*, Oncol Rep.,

2012, 28(1):147-54) and with tumor grade in brain cancer (Crea *et al.*, Mol Cancer., 2010, 30;9:265). EZH2 expression has also been correlated with hormone-independence in both breast (Reijm *et al.*, Breast Cancer Res Treat., 2011, 125(2):387-94) and prostate cancers (Varambally *et al.*, Nature, 2002, 10;419(6907):624-9). In synovial sarcoma high EZH2 expression is associated

5 with low differentiation and was associated with unfavorable clinical outcome (Changchien *et al.* J Transl Med., 2012, 30;10:216). Moreover, activating mutations within the SET domain of EZH2 at tyrosine 641, alanine 677/ 687 have been found in lymphoma and melanoma (Morin *et al.*, Nat Genet., 2010, 42(2):181-5; McCabe *et al.*, Proc Natl Acad Sci U S A., 2012, 21;109(8):2989-94). These mutations change the catalytic preferences of EZH2 and generate a genome-wide increase in

10 tri-methylation of lysine-27 of histone H3 (H3K27me3) (McCabe *et al.*, Proc Natl Acad Sci U S A, 2012, 21;109(8):2989-94). Activating mutations are found especially in germinal center B-cells and induce a sustained silencing of PRC2 target genes, inhibit normal differentiation and promote proliferation and transformation (Béguelin *et al.*, Cancer Cell, 2013, 13;23(5):677-92.18; Harms *et al.*, Human Pathology: Case Reports, 2014, 1,21-28). Beside overexpression or mutations of PRC2

15 core proteins, many additional mutations in proteins influencing H3K27 methylation and PRC2 activity have been found. It has been suggested that these mutations often lead to an increase of H3K27me3 and PRC2 mediated gene silencing and sensitizes those cancers to a therapeutic approach with PRC2 inhibitors (Ezponda and Licht, Clin Cancer Res., 2014, pii: clincanres.2499.2014; Sneeringer *et al.*, Proc Natl Acad Sci U S A., 2010, 107(49):20980-5). For

20 instance mutations in the H3K27me3 demethylase UTX/KDM6A have been found in several cancer cell lines (Van Haaften *et al.*, Nat Genet., 2009, 41(5):521-3) as well as in bladder cancer, multiple myeloma, medulloblastoma, T-cell acute lymphoblastic leukemia, and chronic myelomonocytic leukemia patients (Jankowska *et al.*, Blood, 2011, 6;118(14):3932-41, Jones *et al.*, Nature, 2012, 2;488(7409); Dubuc *et al.*, Acta Neuropathol., 2013, 125(3):373-84; Fuchs, Cardiovasc Hematol Disord Drug Targets., 2013, 1;13(1):16-34; Gui *et al.*, Nat Genet., 2011, 7;43(9):875-8; Van der Meulen *et al.*, Blood., 2014, pii: blood-2014-05-577270). . In subgroup 3 and 4 of medulloblastoma patients PRC2 was proposed as a therapeutic target. since it was demonstrated that different alterations (e.g. somatic copy number aberrations in KDM6A, mutations of the methyltransferase MLL2, increased EZH2 expression, and increased H3K27me3)

25 converged to transcriptional profiles leading to silencing of PRC2-target genes (Dubuc *et al.*, Acta Neuropathol., 2013, 125(3):373-84; Robinson *et al.*, Nature, 2012, 2;488(7409):43-8; Alimova *et al.*, Int J Cancer, 2012, 15;131(8):1800-9). Additionally mutations in the SWI/SNF remodeling complex result in an altered H3K27 methylation regulated expression profile and a tumor dependency on PRC2 for survival (Wilson *et al.*, Cancer Cell. 2010 Oct 19;18(4):316-28.). For

30 example, in malignant rhabdoid or teratoid/rhabdoid tumors (which have frequently an inactivation of the SWI/SNF gene SMARCB1/INI by mutations or deletions) a dependency on PRC2 function has been demonstrated in pre-clinical models (Knutson *et al.*, Proc Natl Acad Sci U S A, 2013, 110(19):7922-7; Alimova *et al.*, Neuro Oncol., 2013,15(2):149-60). On the functional level,

increased PRC2 activity and up-regulation of H3K27 methylation has directly been connected in genome-wide analysis with an altered gene expression program leading to de-differentiation, induction of cell migration and invasion (Yu *et al.*, Cancer Res, 2007, 67:10657-10663 and Ben-Porath *et al.*, Nat Genet., 2008, 40(5):499-507). Gene specific analyses revealed that H3K27

5 methylation caused silencing of key tumor suppressor genes such as p15/16, DAB2IP and CDH1 (Gil and Peters, Nat Rev Mol Cell Biol., 2006,7(9):667-77; Min *et al.* 2010, Nat Med., 2010, 16(3):286-94; Cao *et al.*, Oncogene., 2008, 11;27(58):7274-84.) In addition to histone methylation activity, other non-histone substrates have been described as relevant for the oncogenic function of PRC2, such as the transcription factor STAT3 whose altered methylation leads to de-regulation of

10 the STAT3 signaling pathway (Kim *et al.*, Cancer Cell., 2013, 10;23(6):839-52). PRC2 was validated as an important oncogenic driver, in experiments where overexpression of EZH2 induced neoplastic transformation of benign epithelial cells and this activity was dependent on the catalytic SET domain (Kleer *et al.*, Proc Natl Acad Sci U S A., 2003, 30;100(20):11606-11). Knockdown of EZH2 has been demonstrated to cause re-expression of tumor suppressor genes, as well as

15 inhibition of proliferation, invasion and migration (Crea *et al.* Cancer Metastasis Rev., 2012, 31(3-4):753-61). Furthermore first molecules that directly target EZH2 and compete with the cofactor S-adenosylmethionin (SAM) binding have been described (McCabe *et al.*, Nature 2012, 492:108-12; Knutson *et al.*, Mol Cancer Ther., 2014, 13(4):842-54). These inhibitors show de-repressed expression of PRC2 target genes and decreased tumor cell growth in malignant rhabdoid tumor, synovial sarcoma, MLL-rearranged leukemia, and diffuse large B-cell lymphoma pre-clinical

20 cancer models (Keilhack *et al.*, CTOS 2014 Annual Meeting; Knutson *et al.*, Proc Natl Acad Sci U S A, 2013, 110(19):7922-7; Béguelin *et al.*, Cancer Cell, 2013, 13;23(5):677-92.18; McCabe *et al.*, Nature 2012, 492:108-12). Taken together, de-regulated H3K27 methylation at tumor-suppressive genes is a widespread and important alteration in cancer. In contrast to protein mutations, these

25 changes are reversible and depend on the catalytic activity of PRC2. Therefore PRC2 has emerged as an important therapeutic target with a high need for the development of novel inhibitors.

Several published patent applications disclose various compounds as modulators / inhibitors of EZH2.

30 WO 2013/120104 and WO 2014/151142 (Constellation Pharmaceuticals) disclose carboxamide derivatives as inhibitors of EZH2.

WO 2012/118812 (Epizyme, Inc.) discloses substituted 6,5-fused bicyclic heteroaryl compounds as inhibitors of EZH2. US 2013/0040906 (K. W. Kuntz et. al.) discloses, *inter alia*, compounds and pharmaceutical compositions as inhibitors of EZH2. WO 2014/100665 (Epizyme, Inc.) discloses

35 1,4-pyridone bicyclic heteroaryl compounds as inhibitors of EZH2. WO 2014/144747 (Epizyme Inc.) discloses 6,5-fused bicyclic heteroaryl compounds as inhibitors of the histone methyltransferase activity of EZH2.

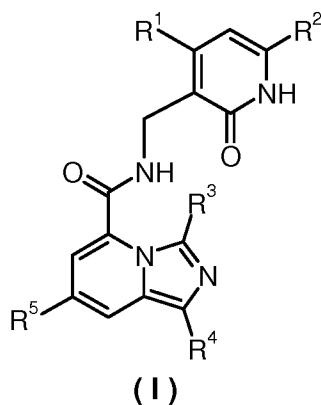
In WO 2011/140324, WO 2011/140325, WO 2012/005805, WO 2012/075080 WO 2013/039988 Indole, Indazole or Azaindole derivatives as inhibitors of EZH2 are disclosed. WO 2013/049770 discloses a method of treating cancer, *inter alia* comprising the administration of an EZH2 inhibitor. WO 2013/067296, WO 2013/067300 and WO 2013/076302 disclose methods of treating

5 T cell mediated immune diseases or T cell mediated hypersensitivity diseases which comprise administering to a human in need thereof an effective amount of a compound which inhibits EZH2 and/or EZH1.

WO 2014/097041 discloses aryl and heteroaryl fused lactams as inhibitors of EZH2.

10 Description

In a first aspect, the present invention relates to compounds of general formula (I)



in which

15 R^1 represents a group selected from C_1 - C_6 -alkyl-, C_2 - C_6 -alkenyl, C_3 - C_7 -cycloalkyl-, (C_3 - C_7 -cycloalkyl)-(L^1)-, 4- to 7-membered monocyclic heterocycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-(L^1)-, C_1 - C_6 -haloalkyl-, C_2 - C_6 -haloalkenyl-, C_1 - C_6 -alkoxy-, C_1 - C_6 -haloalkoxy-, (C_1 - C_3 -alkoxy)-(C_1 - C_3 -alkyl)-, $-NR^6R^7$, and phenyl-(C_1 - C_3 -alkyl)-,

20 wherein any C_3 - C_7 -cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two, or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl-, C_1 - C_3 -alkoxy-, C_1 - C_3 -haloalkoxy-, $-C(=O)-R^8$, $-C(=O)-OR^9$ and $-S(=O)_2-R^8$, and

25 wherein the phenyl group present in said phenyl-(C_1 - C_3 -alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl-, C_1 - C_3 -

alkoxy-, and C₁-C₃-haloalkoxy-;

R² represents a C₁-C₃-alkyl- group;

R³ represents a hydrogen atom or a C₁-C₃-alkyl- group;

5 R⁴ represents a hydrogen atom or a group selected from C₁-C₈-alkyl-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, C₃-C₁₀-cycloalkyl-, 4- to 10-membered heterocycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

10 wherein any C₃-C₁₀-cycloalkyl- or 4- to 10-membered heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

15 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, and C₁-C₃-haloalkoxy-;

R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, C₃-C₁₀-cycloalkyl-, 4- to 10- membered heterocycloalkyl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;

20 R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₃-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

25 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

30 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, including the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group, is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl-, C₁-C₂-

alkoxy-, and C₁-C₂-haloalkoxy-,

or

R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a group selected from C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl-, C₁-C₂-alkoxy-, and C₁-C₂-haloalkoxy-;

R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl-, C₁-C₂-alkoxy-, and C₁-C₂-haloalkoxy-;

R¹⁰ represents a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, wherein said group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, and C₁-C₃-haloalkoxy-;

R¹¹ independently for each occurrence, represents a halogen atom or a group selected from hydroxy-, cyano-, nitro-, C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, C₁-C₆-haloalkyl-, C₁-C₆-haloalkoxy-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, (C₁-C₃-haloalkoxy)-(C₁-C₃-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, C₃-C₇-cycloalkyl-(L³)-, 4- to 7-membered monocyclic heterocycloalkyl-(L³)-, phenyl-(L³)-, 5- to 6-membered monocyclic heteroaryl-(L³)-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -O-C(=O)-R⁸, -N(R⁶)-C(=O)-R⁷, -N(R⁶)-C(=O)-NR⁶R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -SR⁸, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)-R⁸, -S(=O)-NR⁶R⁷, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷, -S(=O)(=NR¹²)-R⁸ and -N=S(=O)(R⁶)-R⁸;

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent

independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₃-C₆-cycloalkyl, cyclopropylmethyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

5 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, and C₁-C₃-haloalkoxy-,

or

10 two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-CH₂-, -CH₂-CH₂-O-, -O-CH₂-O-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-O- and -O-CH₂-CH₂-O-;

R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, phenyl-(C₁-C₃-alkyl)- and -C(=O)-OR⁹;

15 L¹ represents a group selected from -CH₂-, -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C-, -CH₂- and -CH₂CH₂-;

L³ represents, independently for each occurrence, a group selected from -CH₂- and -CH₂CH₂-;

and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

20 In a second embodiment, the present invention relates to compounds of general formula (I)

in which R¹ represents a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl-, (C₃-C₆-cycloalkyl)-(L¹)-, 4- to 6-membered monocyclic heterocycloalkyl-, 4- to 6-membered monocyclic heterocycloalkyl-(L¹)-, C₁-C₄-fluoroalkyl-, C₂-C₄-fluoroalkenyl-, C₁-C₄-alkoxy-, C₁-C₄-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and phenyl-(C₁-C₂-alkyl)- ,

25 wherein any C₃-C₆-cycloalkyl- or 4- to 6-membered monocyclic heterocycloalkyl- group is optionally substituted once with a C₁-C₃-alkyl-, and

30 wherein the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

R² represents a C₁-C₃-alkyl- group;

- R³ represents a hydrogen atom or a methyl- group;
- R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl- and 4- to 7-membered monocyclic heterocycloalkyl-,
- 5 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted once with a C₁-C₃-alkyl-, and
- R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;
- R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;
- 10 R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,
- 15 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹, and
- 20 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,
- or
- 25 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group-;
- R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl-,
- 30 wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

- R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl-,
- wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;
- R¹⁰ represents, independently for each occurrence, a phenyl group which is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;
- R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, (C₁-C₂-fluoroalkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,
- wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and
- wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,
- or
- two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-;
- R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₄-alkyl- and -C(=O)-OR⁹;
- L¹ represents a group selected from -CH₂-O- and -O-;
- L² represents a group selected from -CH=CH-, -C≡C- and -CH₂-;
- and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-

oxides, tautomers, or stereoisomers.

In another embodiment, the present invention relates to compounds of general formula (I)

in which

- 5 R¹ represents a group selected from C₁-C₃-alkyl-, C₃-C₆-cycloalkyl-, (C₃-C₆-cycloalkyl)-(L¹)-, C₁-C₃-fluoroalkyl-, C₂-C₃-fluoroalkenyl-, C₁-C₃-alkoxy-, C₁-C₃-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and benzyl-;
- R² represents a C₁-C₃-alkyl- group;
- R³ represents a hydrogen atom or a methyl- group;
- 10 R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₃-C₆-cycloalkyl- and 4- to 6-membered monocyclic heterocycloalkyl-;
- R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;
- 15 R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;
- R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,
- 20 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C₁-C₃-alkyl-, acetyl- and *tert*-butoxycarbonyl-, and
- wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the
- 25 phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one or two substituents, each substituent selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,
- or
- R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered
- 30 monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;

- R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-;
- R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl- and benzyl-;
- 5 R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, (C₁-C₂-fluoroalkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, -OR⁷, -C(=O)-R⁸,
- 10 R⁸, -C(=O)-OR⁹, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₂-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹, and

15

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

20 or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-.

25 R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₄-alkyl- and -C(=O)-OR⁹;

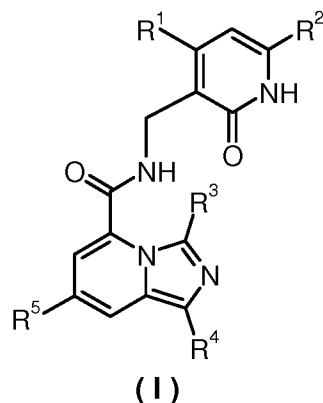
L¹ represents a group selected from -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C- and -CH₂-;

and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

30

In preferred embodiments, the present invention relates to compounds of general formula (I)



in which

- 5 R^1 represents a group selected from C_1 - C_3 -alkyl-, (C_3 - C_6 -cycloalkyl)-(L^1)-, C_1 - C_3 -fluoroalkyl-, C_1 - C_3 -alkoxy-, C_1 - C_3 -fluoroalkoxy-, (C_1 - C_2 -alkoxy)-(C_1 - C_2 -alkyl-) and benzyl-;
- R^2 represents a methylgroup;
- R^3 represents a hydrogen atom or a methyl group;
- R^4 represents a group selected from C_2 - C_5 -alkyl-, C_3 - C_6 -cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-;
- 10 R^5 represents a group selected from phenyl- and 5- to 6-membered monocyclic heteroaryl-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R^{11} ;
- R^6 represents, independently for each occurrence, a hydrogen atom or a C_1 - C_3 -alkyl- group;
- 15 R^7 represents, independently for each occurrence, a hydrogen atom or a group selected from C_1 - C_4 -alkyl-, C_1 - C_4 -fluoroalkyl-, hydroxy-(C_1 - C_4 -alkyl)-, (C_1 - C_2 -alkoxy)-(C_1 - C_2 -alkyl)-, C_3 - C_7 -cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C_1 - C_2 -alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

20 wherein any C_3 - C_7 -cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C_1 - C_3 -alkyl-, acetyl- and *tert*-butoxycarbonyl-, and

25 wherein any phenyl- and 5- to 6-membered monocyclic heteroaryl- group, including the phenyl group present in said phenyl-(C_1 - C_2 -alkyl)- group, is optionally substituted with one or two substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C_1 - C_2 -alkyl-, trifluoromethyl-

and C₁-C₂-alkoxy-,

or

R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-;

R⁹ represents a C₁-C₂-alkyl- group;

R¹¹ represents, independently for each occurrence, a fluoro atom, a chloro atom, a bromo atom, or a group selected from cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, -OR⁷, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

wherein any C₃-C₇-cycloalkyl- and 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one or two substituents, each substituent independently selected from hydroxy-, fluorine, oxo, C₁-C₂-alkyl-, acetyl- and *tert*-butoxycarbonyl-,

or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-;

R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano- and -C(=O)-OR⁹;

L¹ represents a -CH₂-O- group;

and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

In particularly preferred embodiments, the present invention relates to compounds of general formula (I)

in which

R¹ represents a group selected from *n*-propyl-, cyclobutylmethoxy-, 1,1-difluoro-*n*-propyl-,

methoxy-, ethoxy-, *iso*-propoxy-, difluoromethoxy-, 2,2,2-trifluoroethoxy- and benzyl-;

R² represents a methyl- group;

R³ represents a hydrogen atom or a methyl- group;

R⁴ represents a group selected from C₃-C₄-alkyl-, cyclopentyl- and tetrahydropyran-4-yl-;

5 R⁵ represents a group selected from phenyl-, pyridyl-, pyrimidyl- or pyrazolyl-, said group being optionally substituted with one or two substituents, each substituent independently selected from R¹¹;

R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

10 R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-,

wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from oxo and C₁-C₃-alkyl,

or

15 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;

R⁸ represents, independently for each occurrence, a C₁-C₃-alkyl- group;

20 R¹¹ represents, independently for each occurrence, a fluoro atom, a chloro atom, or a group selected from cyano-, C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-, -OR⁷, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NH)-R⁸,

25 wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one or two substituents, each substituent independently selected from oxo and C₁-C₂-alkyl-;

and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

In a further embodiment the present invention relates to compounds of general formula (I) in which

- R¹ represents a group selected from C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-(L¹)-, C₁-C₆-haloalkyl-, C₂-C₆-haloalkenyl-, C₁-C₆-alkoxy-, C₁-C₆-haloalkoxy-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, -NR⁶R⁷, and phenyl-(C₁-C₃-alkyl)-,
- 5 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two, or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and
- 10 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, and C₁-C₃-haloalkoxy-;
- R² represents a C₁-C₃-alkyl- group;
- 15 R³ represents a hydrogen atom or a C₁-C₃-alkyl- group;
- R⁴ represents a hydrogen atom or a group selected from C₁-C₈-alkyl-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, C₃-C₁₀-cycloalkyl-, and phenyl-(C₁-C₃-alkyl)-,
- 20 wherein any C₃-C₁₀-cycloalkyl- or 4- to 10-membered heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and
- 25 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, and C₁-C₃-haloalkoxy-;
- R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, C₃-C₁₀-cycloalkyl-, 4- to 10- membered heterocycloalkyl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;
- 30 R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;
- R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, C₃-

C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₃-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

5 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂R⁸, and

10 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, including the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group, is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl-, C₁-C₂-alkoxy-, and C₁-C₂-haloalkoxy-,

or

15 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a group selected from C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

20 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl-, C₁-C₂-alkoxy-, and C₁-C₂-haloalkoxy-;

R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

25 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl-, C₁-C₂-alkoxy-, and C₁-C₂-haloalkoxy-;

30 R¹⁰ represents a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, wherein said group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, and C₁-C₃-haloalkoxy-;

R¹¹ independently for each occurrence, represents a halogen atom or a group selected from

hydroxy-, cyano-, nitro-, C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, C₁-C₆-haloalkyl-, C₁-C₆-haloalkoxy-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, (C₁-C₃-haloalkoxy)-(C₁-C₃-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, C₃-C₇-cycloalkyl-(L³)-, 4- to 7-membered monocyclic heterocycloalkyl-(L³)-, phenyl-(L³)-, 5- to 6-membered monocyclic heteroaryl-(L³)-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -O-C(=O)-R⁸, -N(R⁶)-C(=O)-R⁷, -N(R⁶)-C(=O)-NR⁶R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -SR⁸, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)-R⁸, -S(=O)-NR⁶R⁷, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷, -S(=O)(=NR¹²)-R⁸ and -N=S(=O)(R⁶)-R⁸;

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₃-C₆-cycloalkyl, cyclopropylmethyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen-, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, and C₁-C₃-haloalkoxy-,

or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-CH₂-, -CH₂-CH₂-O-, -O-CH₂-O-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-O- and -O-CH₂-CH₂-O-;

R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, phenyl-(C₁-C₃-alkyl)- and -C(=O)-OR⁹;

L¹ represents a group selected from -CH₂-, -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C-, -CH₂- and -CH₂CH₂-;

L³ represents, independently for each occurrence, a group selected from -CH₂- and -CH₂CH₂-;

and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

In another embodiment, the present invention relates to compounds of general formula (I)

in which

5 R¹ represents a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl-, 4- to 6-membered monocyclic heterocycloalkyl-, 4- to 6-membered monocyclic heterocycloalkyl-(L¹)-, C₁-C₄-fluoroalkyl-, C₂-C₄-fluoroalkenyl-, C₁-C₄-alkoxy-, C₁-C₄-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and phenyl-(C₁-C₂-alkyl)-,

wherein any C₃-C₆-cycloalkyl- or 4- to 6-membered monocyclic heterocycloalkyl-group is optionally substituted once with a C₁-C₃-alkyl-, and

10 wherein the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

R² represents a C₁-C₃-alkyl- group;

R³ represents a hydrogen atom or a methyl- group;

15 R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted once with a C₁-C₃-alkyl-, and

20 R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;

R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

25 R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹, and

30 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from

fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

5 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group-;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl- ,

10 wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl-,

15 wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

20 R¹⁰ represents, independently for each occurrence, a phenyl group which is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

25 R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, (C₁-C₂-fluoroalkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

30 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is

optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

- 5 two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-;

R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₄-alkyl- and -C(=O)-OR⁹;

- 10 L¹ represents a group selected from -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C- and -CH₂- and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

- 15 In another embodiment, the present invention relates to compounds of general formula (I)

in which

R¹ represents a group selected from C₁-C₃-alkyl-, C₃-C₆-cycloalkyl-, C₁-C₃-fluoroalkyl-, C₂-C₃-fluoroalkenyl-, C₁-C₃-alkoxy-, C₁-C₃-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and benzyl-;

- 20 R² represents a C₁-C₃-alkyl- group;

R³ represents a hydrogen atom or a methyl- group;

R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₃-C₆-cycloalkyl-;

- R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents,
25 each substituent independently selected from R¹¹;

R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

- R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-,
30 phenyl- and 5- to 6-membered monocyclic heteroaryl-,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C₁-C₃-alkyl-, acetyl- and *tert*-butoxycarbonyl-, and

5 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one or two substituents, each substituent selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

10 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-;

15 R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl- and benzyl-;

R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, (C₁-C₂-fluoroalkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

20

25 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₂-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹, and

30 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered

monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-.

R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₄-alkyl- and -C(=O)-OR⁹;

5 L¹ represents a group selected from -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C- and -CH₂-;

and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

10 In preferred embodiments, the present invention relates to compounds of general formula (I)

in which

R¹ represents a group selected from C₁-C₃-alkyl-, C₁-C₃-fluoroalkyl-, C₁-C₃-alkoxy-, C₁-C₃-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and benzyl-;

R² represents a methyl- group;

15 R³ represents a hydrogen atom or a methyl- group;

R⁴ represents a group selected from C₂-C₅-alkyl-, C₃-C₆-cycloalkyl-;

R⁵ represents a group selected from phenyl- and 5- to 6-membered monocyclic heteroaryl-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;

20 R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

25 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C₁-C₃-alkyl-, acetyl- and *tert*-butoxycarbonyl-, and

30 wherein any phenyl- and 5- to 6-membered monocyclic heteroaryl- group, including the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group, is

optionally substituted with one or two substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

- 5 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-;

- 10 R⁹ represents a C₁-C₂-alkyl- group;

R¹¹ represents, independently for each occurrence, a fluoro atom, a chloro atom, a bromo atom, or a group selected from cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, -OR⁷, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷,
15 -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

wherein any C₃-C₇-cycloalkyl- and 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one or two substituents, each substituent independently selected from hydroxy-, fluorine, oxo, C₁-C₂-alkyl-, acetyl- and *tert*-butoxycarbonyl-,

- 20 or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-;

- 25 R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano- and -C(=O)-OR⁹;

L¹ represents a -CH₂-O- group;

and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.

- 30 In other preferred embodiments, the present invention relates to compounds of general formula (I) in which

- R¹ represents a group selected from *n*-propyl-, 1,1-difluoro-*n*-propyl-, methoxy-, ethoxy-, *iso*-propoxy-, difluoromethoxy-, 2,2,2-trifluoroethoxy- and benzyl-;
- R² represents a methyl- group;
- R³ represents a hydrogen atom or a methyl- group;
- 5 R⁴ represents a group selected from C₃-C₄-alkyl- and cyclopentyl-;
- R⁵ represents a group selected from phenyl-, pyridyl-, pyrimidyl- or pyrazolyl-, said group being optionally substituted with one or two substituents, each substituent independently selected from R¹¹;
- R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;
- 10 R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-,
- wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from oxo and C₁-C₃-alkyl,
- 15 or
- R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;
- R⁸ represents, independently for each occurrence, a C₁-C₃-alkyl- group;
- 20 R¹¹ represents, independently for each occurrence, a fluoro atom, a chloro atom, or a group selected from cyano-, C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-, -OR⁷, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NH)-R⁸,
- wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally
- 25 substituted with one or two substituents, each substituent independently selected from oxo and C₁-C₂-alkyl-;
- and to N-oxides, salts, tautomers, or stereoisomers of said compounds, and to salts of said N-oxides, tautomers, or stereoisomers.
- 30 In certain embodiments, the present invention relates to compounds of general formula (I), in

which R^1 represents a group selected from C_1 - C_6 -alkyl-, C_3 - C_7 -cycloalkyl-, (C_3 - C_7 -cycloalkyl)-(L^1)-, 4- to 7-membered monocyclic heterocycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-(L^1)-, C_1 - C_6 -haloalkyl-, C_2 - C_6 -haloalkenyl-, C_1 - C_6 -alkoxy-, C_1 - C_6 -haloalkoxy-, (C_1 - C_3 -alkoxy)-(C1-C3-alkyl)-, $-NR^6R^7$ and phenyl-(C_1 - C_3 -alkyl)-,

5 wherein any C_3 - C_7 -cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, $-C(=O)-R^8$, $-C(=O)-OR^9$ and $-S(=O)_2-R^8$, and

10 wherein the phenyl group present in said phenyl-(C_1 - C_3 -alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl- and C_1 - C_3 -alkoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R^1 represents a group selected from C_1 - C_4 -alkyl-, C_3 - C_6 -cycloalkyl-, (C_3 - C_6 -cycloalkyl)-(L^1)-, 4- to 6-membered monocyclic heterocycloalkyl-, 4- to 6-membered
15 monocyclic heterocycloalkyl-(L^1)-, C_1 - C_4 -fluoroalkyl-, C_2 - C_4 -fluoroalkenyl-, C_1 - C_4 -alkoxy-, C_1 - C_4 -fluoroalkoxy-, (C_1 - C_2 -alkoxy)-(C1-C2-alkyl-) and phenyl-(C_1 - C_2 -alkyl)-,

wherein any C_3 - C_6 -cycloalkyl- or 4- to 6-membered monocyclic heterocycloalkyl- group is optionally substituted once with a C_1 - C_3 -alkyl-, and

20 wherein the phenyl group present in said phenyl-(C_1 - C_2 -alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently, selected from fluorine, chlorine, bromine, cyano-, C_1 - C_2 -alkyl-, trifluoromethyl- and C_1 - C_2 -alkoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R^1 represents a group selected from C_1 - C_3 -alkyl-, C_3 - C_6 -cycloalkyl-, (C_3 - C_6 -cycloalkyl)-(L^1)-, C_1 - C_3 -fluoroalkyl-, C_2 - C_3 -fluoroalkenyl-, C_1 - C_3 -alkoxy-,
25 C_1 - C_3 -fluoroalkoxy-, (C_1 - C_2 -alkoxy)-(C1-C2-alkyl-) and benzyl-.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R^1 represents a group selected from C_1 - C_3 -alkyl-, (C_3 - C_6 -cycloalkyl)-(L^1)-, C_1 - C_3 -fluoroalkyl-, C_1 - C_3 -alkoxy-, C_1 - C_3 -fluoroalkoxy-, (C_1 - C_2 -alkoxy)-(C1-C2-alkyl-) and benzyl-.

In certain preferred embodiments, the present invention relates to compounds of general formula
30 (I), in which R^1 represents a group selected from C_1 - C_3 -alkyl-, C_1 - C_3 -fluoroalkyl-, C_1 - C_3 -alkoxy-, C_1 - C_3 -fluoroalkoxy-, (C_1 - C_2 -alkoxy)-(C1-C2-alkyl-) and benzyl-.

In particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R^1 represents a group selected from *n*-propyl-, cyclobutylmethoxy-, 1,1-difluoro-*n*-propyl-, methoxy-, ethoxy-, *iso*-propoxy-, difluoromethoxy-, 2,2,2-trifluoroethoxy- and
35 benzyl-.

In particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹ represents a group selected from *n*-propyl-, 1,1-difluoro-*n*-propyl-, methoxy-, ethoxy-, *iso*-propoxy-, difluoromethoxy-, 2,2,2-trifluoroethoxy- and benzyl-.

In other particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹ represents a group selected from *n*-propyl-, 1,1-difluoro-*n*-propyl- and benzyl-.

In other particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹ represents a group selected from cyclobutylmethoxy-, methoxy-, ethoxy-, *iso*-propoxy-, difluoromethoxy- and 2,2,2-trifluoroethoxy-.

10 In other particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹ represents a group selected from methoxy-, ethoxy-, *iso*-propoxy-, difluoromethoxy- and 2,2,2-trifluoroethoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R² represents a C₁-C₃-alkyl- group.

15 In certain such embodiments, the present invention relates to compounds of general formula (I), in which R² represents an *n*-propyl- group.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R² represents a C₁-C₂-alkyl- group, especially a methyl group.

20 In certain embodiments, the present invention relates to compounds of general formula (I), in which R³ represents a hydrogen atom or a C₁-C₃-alkyl- group.

In certain such embodiments, the present invention relates to compounds of general formula (I), in which R³ represents a C₁-C₃-alkyl- group.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R³ represents a hydrogen atom or a C₁-C₂-alkyl- group, especially a methyl group.

25 In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R³ represents a hydrogen atom or a methyl- group.

In particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R³ represents a hydrogen atom.

30 In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a hydrogen atom or a group selected from C₁-C₈-alkyl-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, C₃-C₁₀-cycloalkyl-, 4- to 10-membered heterocycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

wherein any C₃-C₁₀-cycloalkyl- or 4- to 10-membered heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

- 5 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-.

- In certain such embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a hydrogen atom or a group selected from C₁-C₈-alkyl-, (C₁-C₃-alkoxy)-(C₁-
10 C₃-alkyl)-, C₃-C₁₀-cycloalkyl-, 4- to 10-membered heterocycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

wherein any C₃-C₁₀-cycloalkyl- or 4- to 10-membered heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

- 15 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-,

with the proviso that said 4- to 10-membered heterocycloalkyl- group is attached to the rest of the molecule *via* a carbon ring atom.

- 20 In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl- and 4- to 7-membered monocyclic heterocycloalkyl-,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted once with a C₁-C₃-alkyl-.

- 25 In certain such embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl- and 4- to 7-membered monocyclic heterocycloalkyl-,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted once with a C₁-C₃-alkyl-,

- 30 with the proviso that said 4- to 7-membered monocyclic heterocycloalkyl- group is attached to the rest of the molecule *via* a carbon ring atom.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₃-C₆-cycloalkyl- and 4- to 6-membered monocyclic heterocycloalkyl-.

- 35 In certain embodiments, the present invention relates to compounds of general formula (I), in

which R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₃-C₆-cycloalkyl- and 4- to 6-membered monocyclic heterocycloalkyl-,
with the proviso that said 4- to 6-membered monocyclic heterocycloalkyl- group is attached to the rest of the molecule *via* a carbon ring atom.

- 5 In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a group selected from C₂-C₅-alkyl-, C₃-C₆-cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a group selected from C₂-C₅-alkyl- and C₃-C₆-cycloalkyl-.

- 10 In certain such preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a group selected from C₂-C₅-alkyl-, C₃-C₆-cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-,
with the proviso that said 5- to 6-membered monocyclic heterocycloalkyl- group is attached to the rest of the molecule *via* a carbon ring atom.

- 15 In particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a group selected from C₃-C₄-alkyl-, cyclopentyl- and tetrahydropyran-4-yl-.

In particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a group selected from C₃-C₄-alkyl- and cyclopentyl-.

- 20 In certain other particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a group selected from *iso*-propyl-, *iso*-butyl-, *sec*-butyl-, cyclopentyl- and tetrahydropyran-4-yl-.

In certain other particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁴ represents a group selected from *iso*-propyl-, *iso*-butyl-, *sec*-butyl-

- 25 and cyclopentyl-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, C₃-C₁₀-cycloalkyl-, 4- to 10- membered heterocycloalkyl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹.

- 30

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, C₃-C₇-cycloalkyl-, 4- to 7- membered monocyclic heterocycloalkyl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group

being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, -NR⁶R¹⁰, phenyl-(L²)-
5 and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from group R¹¹.

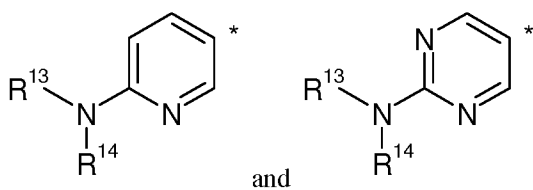
In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each
10 substituent independently selected from R¹¹.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a group selected from phenyl- and 5- to 6-membered monocyclic heteroaryl-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹.

15 In certain particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a group selected from phenyl-, pyridyl-, pyrimidyl- or pyrazolyl-, said group being optionally substituted with one or two substituents, each substituent independently selected from R¹¹.

In certain other particularly preferred embodiments, the present invention relates to compounds of
20 general formula (I), in which R⁵ represents a phenyl- group which is optionally substituted with one or two substituents, each substituent independently selected from R¹¹.

In certain other particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a group selected from



25 the pyridyl- or pyrimidyl- ring of which being optionally additionally substituted with one fluoro atom,

in which "*" represents the point of attachment to the rest of the molecule,

and in which R¹³ represents a hydrogen atom or a methyl- group, and R¹⁴ represents a group selected from C₁-C₃-alkyl- and hydroxy-(C₁-C₄-alkyl)-, or

30 in which R¹³ and R¹⁴, together with the nitrogen atom they are attached to, represent a 4- to 7-

membered monocyclic heterocycloalkyl- group which is optionally substituted with one or two substituents, each substituent independently selected from oxo and C₁-C₂-alkyl-.

In certain other particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁵ represents a pyrazolyl- group which is optionally substituted with one or two substituents, each substituent independently selected from C₁-C₃-alkyl- group.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group.

In certain such embodiments, the present invention relates to compounds of general formula (I), in which R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₂-alkyl- group.

10 In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁶, independently for each occurrence, represents a hydrogen atom or a methyl- group.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁶ represents a hydrogen atom.

15 In certain other preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁶ represents a methyl- group.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₃-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

25 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂R⁸, and

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

30 or

R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a group selected from C₁-C₃-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹.

In certain other embodiments, the present invention relates to compounds of general formula (I), in

which R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

- 5 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹, and wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or
10 three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group.

- 15 In certain other embodiments, the present invention relates to compounds of general formula (I), in which R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,
20 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹, and wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or
25 three substituents, each substituent independently , selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain other embodiments, the present invention relates to compounds of general formula (I), in which R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl-
30 group.

- In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl-
35 and 5- to 6-membered monocyclic heteroaryl-,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is

optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C₁-C₃-alkyl-, acetyl- and *tert*-butoxycarbonyl-, and wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one or two substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C₁-C₃-alkyl-, acetyl- and *tert*-butoxycarbonyl-, and wherein said phenyl- and 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one or two substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-,

wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from oxo and C₁-C₃-alkyl-,

or

R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group.

In certain particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-,

wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from oxo and C₁-C₃-alkyl-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁸ represents, independently for each occurrence, a group selected from C₁-C₆-alkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

10 In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl-,

wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, 15 bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-,

wherein the phenyl group present in said benzyl- group is optionally substituted with one, 20 two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-.

25 In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁸ represents, independently for each occurrence, a C₁-C₃-alkyl- group.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

30 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from

C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl-,

wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

- 5 In certain embodiments, the present invention relates to compounds of general formula (I), in which R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl- and benzyl-.

In certain such embodiments, the present invention relates to compounds of general formula (I), in which R⁹ represents, independently for each occurrence, a C₁-C₄-alkyl- group.

- 10 In other such embodiments, the present invention relates to compounds of general formula (I), in which R⁹ represents a benzyl- group.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R⁹ represents, independently for each occurrence, a C₁-C₂-alkyl- group.

- 15 In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹⁰ represents, independently for each occurrence, a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, wherein said groups are optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-.

- 20 In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹⁰ represents, independently for each occurrence, a phenyl group which is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-.

- 25 In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹⁰ represents, independently for each occurrence, a 5- to 6-membered monocyclic heteroaryl- group which is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-.

- 30 In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹⁰ represents, independently for each occurrence, a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, wherein said groups are optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in

which R¹⁰ represents, independently for each occurrence, a phenyl group which is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹⁰ represents, independently for each occurrence, a 5- to 6-membered monocyclic heteroaryl- group which is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, nitro-, C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, C₁-C₆-haloalkyl-, C₁-C₆-haloalkoxy-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, (C₁-C₃-haloalkoxy)-(C₁-C₃-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, C₃-C₇-cycloalkyl-(L³)-, 4- to 7-membered monocyclic heterocycloalkyl-(L³)-, phenyl-(L³)-, 5- to 6-membered monocyclic heteroaryl-(L³)-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -O-C(=O)-R⁸, -N(R⁶)-C(=O)-R⁷, -N(R⁶)-C(=O)-NR⁶R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -SR⁸, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)-R⁸, -S(=O)-NR⁶R⁷, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷, -S(=O)(=NR¹²)-R⁸ and -N=S(=O)(R⁶)-R⁸;

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₃-C₆-cycloalkyl-, cyclopropylmethyl-, C₁-C₃-alkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-,

or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-CH₂-, -CH₂-CH₂-O-, -O-CH₂-O-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-O- and -O-CH₂-CH₂-O-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, (C₁-C₂-fluoroalkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸

R^8 , $-S(=O)_2-NR^6R^7$ and $-S(=O)(=NR^{12})-R^8$;

wherein any C_3 - C_7 -cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, $-C(=O)-R^8$, $-C(=O)-OR^9$ and $-S(=O)_2-R^8$, and

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently, selected from fluorine, chlorine, bromine, cyano-, C_1 - C_2 -alkyl-, trifluoromethyl- and C_1 - C_2 -alkoxy-,

or

two R^{11} groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from $-CH_2-CH_2-O-$, $-O-CH_2-O-$ and $-O-CH_2-CH_2-O-$.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R^{11} represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, C_1 - C_4 -alkyl-, C_1 - C_4 -fluoroalkyl-, C_1 - C_4 -fluoroalkoxy-, hydroxy- $(C_1$ - C_4 -alkyl)-, $(C_1$ - C_2 -alkoxy)- $(C_1$ - C_2 -alkyl)-, $(C_1$ - C_2 -fluoroalkoxy)- $(C_1$ - C_2 -alkyl)-, C_3 - C_7 -cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, $-OR^7$, $-C(=O)-R^8$, $-C(=O)-OR^9$, $-N(R^6)-C(=O)-R^7$, $-NR^6R^7$, $-C(=O)-NR^6R^7$, $-S(=O)-R^8$, $-S(=O)_2-R^8$, $-N(R^6)-S(=O)_2-R^8$, $-S(=O)_2-NR^6R^7$ and $-S(=O)(=NR^{12})-R^8$,

wherein any C_3 - C_7 -cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C_1 - C_2 -alkyl-, $-C(=O)-R^8$ and $-C(=O)-OR^9$, and

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently selected

from fluorine, chlorine, bromine, cyano-, C_1 - C_2 -alkyl-, trifluoromethyl- and C_1 - C_2 -alkoxy-,

or

two R^{11} groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from $-CH_2-CH_2-O-$, $-O-CH_2-O-$ and $-O-CH_2-CH_2-O-$.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R^{11} represents, independently for each occurrence, a fluoro atom, a chloro atom, a bromo atom, or a group selected from cyano-, C_1 - C_4 -alkyl-, C_1 - C_4 -fluoroalkyl-, C_1 - C_4 -fluoroalkoxy-, hydroxy- $(C_1$ - C_4 -alkyl)-, $(C_1$ - C_2 -alkoxy)- $(C_1$ - C_2 -alkyl)-, C_3 - C_7 -cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, $-OR^7$, $-N(R^6)-C(=O)-R^7$, $-NR^6R^7$, $-C(=O)-NR^6R^7$, $-S(=O)_2-R^8$, $-N(R^6)-S(=O)_2-R^8$, $-S(=O)_2-NR^6R^7$ and $-S(=O)(=NR^{12})-R^8$,

wherein any C_3 - C_7 -cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one or two substituents, each substituent independently selected

from fluorine, hydroxy-, oxo, C₁-C₂-alkyl-, acetyl- and *tert*-butoxycarbonyl-,

or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-,
 5 -O-CH₂-O- and -O-CH₂-CH₂-O-;

In particularly preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹¹ represents, independently for each occurrence, a fluoro atom, a chloro atom, or a group selected from cyano-, C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-, -OR⁷, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -
 10 S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NH)-R⁸,

wherein said 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one or two substituents, each substituent independently selected from oxo and C₁-C₂-alkyl-.

In certain embodiments, the present invention relates to compounds of general formula (I), in
 15 which R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, phenyl-(C₁-C₃-alkyl)- and -C(=O)-OR⁹.

In certain embodiments, the present invention relates to compounds of general formula (I), in which R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₄-alkyl- and -C(=O)-OR⁹.

20 In preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano- and -C(=O)-OR⁹.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹² represents, independently for each occurrence, a hydrogen atom or a cyano-
 25 group.

In other preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹² represents, independently for each occurrence, a hydrogen atom or a group -C(=O)-OR⁹.

In certain preferred embodiments, the present invention relates to compounds of general formula
 30 (I), in which R¹² represents a cyano- group.

In other preferred embodiments, the present invention relates to compounds of general formula (I), in which R¹² represents a group -C(=O)-OR⁹.

In particularly preferred embodiments, the present invention relates to compounds of general

formula (I), in which R¹² represents a hydrogen atom.

In certain embodiments, the present invention relates to compounds of general formula (I), in which L¹ represents a group selected from -CH₂-, -CH₂-O- and -O-.

In certain such embodiments, the present invention relates to compounds of general formula (I), in
5 which L¹ represents a group selected from -CH₂-O- and -O-.

In other such embodiments, the present invention relates to compounds of general formula (I), in which L¹ represents a group selected from -CH₂- and -O-.

In yet other such embodiments, the present invention relates to compounds of general formula (I), in which L¹ represents a group selected from -CH₂- and -CH₂-O-.

10 In certain embodiments, the present invention relates to compounds of general formula (I), in which L¹ represents a group -CH₂-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which L¹ represents a group -O-.

In certain preferred embodiments, the present invention relates to compounds of general formula
15 (I), in which L¹ represents a group -CH₂-O-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which L² represents a group selected from -CH=CH-, -C≡C-, -CH₂- and -CH₂CH₂-.

In certain such embodiments, the present invention relates to compounds of general formula (I), in which L² represents a group selected from -CH=CH-, -C≡C- and -CH₂-.

20 In certain such embodiments, the present invention relates to compounds of general formula (I), in which L² represents a group selected from -CH=CH- and -C≡C-.

In other embodiments, the present invention relates to compounds of general formula (I), in which L² represents a group selected from -C≡C- and -CH₂-.

In yet other embodiments, the present invention relates to compounds of general formula (I), in
25 which L² represents a group selected from -CH=CH- and -CH₂-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which L² represents a group -CH=CH-.

In certain embodiments, the present invention relates to compounds of general formula (I), in which L² represents a group -CH₂-.

30 In certain embodiments, the present invention relates to compounds of general formula (I), in

which L^2 represents a group $-C\equiv C-$.

In certain embodiments, the present invention relates to compounds of general formula (I), in which L^3 represents, independently for each occurrence, a group selected from $-CH_2-$ and $-CH_2CH_2-$.

- 5 In certain such embodiments, the present invention relates to compounds of general formula (I), in which L^3 represents a group $-CH_2-$.

In certain preferred embodiments, the present invention relates to compounds of general formula (I), in which R^1 represents a group selected from C_1-C_3 -alkyl-, $(C_3-C_6$ -cycloalkyl)-(L^1)-, C_1-C_3 -fluoroalkyl-, C_1-C_3 -alkoxy-, C_1-C_3 -fluoroalkoxy-, $(C_1-C_2$ -alkoxy)-(C_1-C_2 -alkyl-) and benzyl-,

- 10 R^2 represents a methyl- group, R^3 represents a hydrogen atom, and R^4 represents a group selected from C_2-C_5 -alkyl-, C_3-C_6 -cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-.

In other preferred embodiments, the present invention relates to compounds of general formula (I), in which R^2 represents a methyl- group, R^3 represents a hydrogen atom, R^4 represents a group selected from C_2-C_5 -alkyl-, C_3-C_6 -cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-,
15 and R^5 represents a group selected from phenyl- and 5- to 6-membered monocyclic heteroaryl-, said phenyl- and 5- to 6-membered monocyclic heteroaryl- group being optionally substituted with one, two or three substituents, each substituent independently selected from R^{11} .

- In other preferred embodiments, the present invention relates to compounds of general formula (I), in which R^2 represents a methyl- group, R^3 represents a hydrogen atom, and R^4 represents a group
20 selected from C_2-C_5 -alkyl-, C_3-C_6 -cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-.

- In other preferred embodiments, the present invention relates to compounds of general formula (I), in which R^2 represents a methyl- group, R^3 represents a hydrogen atom, and R^4 represents a group selected from C_2-C_5 -alkyl-, C_3-C_6 -cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-, with the proviso that said 5- to 6-membered monocyclic heterocycloalkyl- group is attached to the
25 rest of the molecule *via* a carbon ring atom.

It is to be understood that the present invention relates to any further sub-combination of the various embodiments of the present invention of compounds of general formula (I), *supra*.

In particularly preferred embodiments, the present invention covers compounds of general formula (I) which are disclosed in the Example section of this text, *infra*.

30

Definitions

The terms "halogen atom", "halogen", "halo" or "Hal" mean a fluorine, chlorine, bromine or iodine atom.

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

The term "C₁-C₈-alkyl-" means a linear or branched, saturated hydrocarbon group having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, *e.g.*, a methyl-, ethyl-, propyl-, *iso*-propyl-, *n*-butyl-, *iso*-butyl-, *sec*-butyl-, *tert*-butyl-, *n*-pentyl-, *iso*-pentyl-, 2-methylbutyl-, 1-methylbutyl-, 1-ethylpropyl-, 1,2-dimethylpropyl-, *neo*-pentyl-, 1,1-dimethylpropyl-, *n*-hexyl-, 4-methylpentyl-, 3-methylpentyl-, 2-methylpentyl-, 1-methylpentyl-, 2-ethylbutyl-, 1-ethylbutyl-, 3,3-dimethylbutyl-, 2,2-dimethylbutyl-, 1,1-dimethylbutyl-, 2,3-dimethylbutyl-, 1,3-dimethylbutyl-, 1,2-dimethylbutyl-, *n*-heptyl-, 5-methylhexyl-, 4-methylhexyl-, 2-methylhexyl-, 1-methylhexyl-, 2-ethylpentyl-, 1-ethylpentyl-, 3,3-dimethylpentyl-, 2,2-dimethylpentyl-, 1,1-dimethylpentyl-, 2,3-dimethylpentyl-, 1,3-dimethylpentyl-, 1,2-dimethylpentyl-, *n*-octyl-, 6-methylheptyl-, 4-methylheptyl-, 2-methylheptyl-, 1-methylheptyl-, 2-ethylhexyl-, 1-ethylhexyl-, 3,3-dimethylhexyl-, 2,2-dimethylhexyl-, 1,1-dimethylhexyl-, 2,3-dimethylhexyl-, 1,3-dimethylhexyl-, 1,2-dimethylhexyl- group, or an isomer thereof. Preferably, said group has 1, 2, 3, 4, 5 or 6 carbon atoms ("C₁-C₆-alkyl-"), *e.g.*, a methyl-, ethyl-, *n*-propyl-, *iso*-propyl-, *n*-butyl-, *iso*-butyl-, *sec*-butyl-, *tert*-butyl-, *n*-pentyl-, *iso*-pentyl-, 2-methylbutyl-, 1-methylbutyl-, 1-ethylpropyl-, 1,2-dimethylpropyl-, *neo*-pentyl-, 1,1-dimethylpropyl-, *n*-hexyl-, 4-methylpentyl-, 3-methylpentyl-, 2-methylpentyl-, 1-methylpentyl-, 2-ethylbutyl-, 1-ethylbutyl-, 3,3-dimethylbutyl-, 2,2-dimethylbutyl-, 1,1-dimethylbutyl-, 2,3-dimethylbutyl-, 1,3-dimethylbutyl- or 1,2-dimethylbutyl- group, or an isomer thereof. More preferably, said group has 1, 2, 3 or 4 carbon atoms ("C₁-C₄-alkyl-"), *e.g.*, a methyl-, ethyl-, *n*-propyl-, *iso*-propyl-, *n*-butyl-, *iso*-butyl-, *sec*-butyl- or *tert*-butyl- group, 1, 2 or 3 carbon atoms ("C₁-C₃-alkyl-"), *e.g.*, a methyl-, ethyl-, *n*-propyl- or *iso*-propyl- group, or 1 or 2 carbon atoms ("C₁-C₂-alkyl-"), *e.g.*, a methyl-, ethyl- group.

The term "C₂-C₆-alkenyl-" means a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, preferably 2, 3 or 4 carbon atoms ("C₂-C₄-alkenyl-") or 2 or 3 carbon atoms ("C₂-C₃-alkenyl-"), it being understood that in the case in which said alkenyl- group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other. Representative alkenyl- groups include, for example, an ethenyl-, prop-2-enyl-, (*E*)-prop-1-enyl-, (*Z*)-prop-1-enyl-, *iso*-propenyl-, but-3-enyl-, (*E*)-but-2-enyl-, (*Z*)-but-2-enyl-, (*E*)-but-1-enyl-, (*Z*)-but-1-enyl-, 2-methylprop-2-enyl-, 1-methylprop-2-enyl-, 2-methylprop-1-enyl-, (*E*)-1-methylprop-1-enyl-, (*Z*)-1-methylprop-1-enyl-, buta-1,3-dienyl-, pent-4-enyl-, (*E*)-pent-3-enyl-, (*Z*)-pent-3-enyl-, (*E*)-pent-2-enyl-, (*Z*)-pent-2-enyl-, (*E*)-pent-1-enyl-, (*Z*)-pent-1-enyl-, 3-methylbut-3-enyl-,

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

The term “C₂-C₆-alkynyl-” means a linear or branched, monovalent hydrocarbon group which contains one or more triple bonds, and which contains 2, 3, 4, 5 or 6 carbon atoms, preferably 2, 3 or 4 carbon atoms (“C₂-C₄-alkynyl-”) or 2 or 3 carbon atoms (“C₂-C₃-alkynyl-”). Representative C₂-C₆-alkynyl- groups include, for example, ethynyl-, prop-1-ynyl-, prop-2-ynyl-, but-1-ynyl-,
 30 but-2-ynyl-, but-3-ynyl-, pent-1-ynyl-, pent-2-ynyl-, pent-3-ynyl-, pent-4-ynyl-, hex-1-ynyl-,
 hex-2-ynyl-, hex-3-ynyl-, hex-4-ynyl-, hex-5-ynyl-, 1-methylprop-2-ynyl-, 2-methylbut-3-ynyl-,
 1-methylbut-3-ynyl-, 1-methylbut-2-ynyl-, 3-methylbut-1-ynyl-, 1-ethylprop-2-ynyl-,
 3-methylpent-4-ynyl-, 2-methylpent-4-ynyl-, 1-methylpent-4-ynyl-, 2-methylpent-3-ynyl-,
 1-methylpent-3-ynyl-, 4-methylpent-2-ynyl-, 1-methylpent-2-ynyl-, 4-methylpent-1-ynyl-,
 35 3-methylpent-1-ynyl-, 2-ethylbut-3-ynyl-, 1-ethylbut-3-ynyl-, 1-ethylbut-2-ynyl-,
 1-propylprop-2-ynyl-, 1-isopropylprop-2-ynyl-, 2,2-dimethylbut-3-ynyl-, 1,1-dimethylbut-3-ynyl-,
 1,1-dimethylbut-2-ynyl- and 3,3-dimethylbut-1-ynyl- group. Particularly, said alkynyl- group is

ethynyl-, prop-1-ynyl- or prop-2-ynyl-.

The term “C₁-C₆-haloalkyl-” means a linear or branched, saturated hydrocarbon group in which one or more of the hydrogen atoms of a “C₁-C₆-alkyl-” as defined *supra* are each replaced, identically or differently, by a halogen atom. Preferably, each said halogen atom is fluorine, resulting in a group referred herein as “C₁-C₆-fluoroalkyl-”. Exemplary C₁-C₆-fluoroalkyl- groups include, for example, -CF₃, -CHF₂, -CH₂F, -CH₂CH₂F, -CH₂CHF₂, -CF₂CF₃, -CH₂CF₃, -CH₂CH₂CF₃ and -CH(CH₂F)₂.

The term “C₂-C₆-haloalkenyl-” means a linear or branched hydrocarbon group in which one or more of the hydrogen atoms of a “C₂-C₆-alkenyl-” as defined *supra* are each replaced, identically or differently, by a halogen atom. Preferably, said halogen atom is fluorine, resulting in a group referred herein as “C₂-C₆-fluoroalkenyl-”. Representative C₂-C₆-fluoroalkenyl- groups include, for example, -CH=CF₂, -CF=CH₂, -CF=CF₂, -C(CH₃)=CF₂, -CH=C(F)-CH₃, -CH₂-CF=CF₂ and -CF₂-CH=CH₂.

The term “hydroxy-(C₁-C₆-alkyl)-” means a linear or branched, saturated, hydrocarbon group in which one or more hydrogen atoms of a “C₁-C₆-alkyl-” as defined *supra* are each 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-, or 1-hydroxy-2-methyl-propyl- group.

The term “C₁-C₆-alkoxy-” means a linear or branched, saturated, monovalent group of formula (C₁-C₆-alkyl)-O-, in which the term “C₁-C₆-alkyl” is as defined *supra*, *e.g.*, a methoxy-, ethoxy-, *n*-propoxy-, *iso*-propoxy-, *n*-butoxy-, *iso*-butoxy-, *tert*-butoxy-, *sec*-butoxy-, pentyloxy-, *iso*-pentyloxy- or *n*-hexyloxy- group, or an isomer thereof.

The term “C₁-C₆-haloalkoxy-” means a linear or branched, saturated, monovalent C₁-C₆-alkoxy-group, as defined *supra*, in which one or more of the hydrogen atoms are each replaced, identically or differently, by a halogen atom. Preferably, said halogen atom in “C₁-C₆-haloalkoxy-” is fluorine, resulting in a group referred herein as “C₁-C₆-fluoroalkoxy-”. Representative C₁-C₆-fluoroalkoxy-groups include, for example, -OCF₃, -OCHF₂, -OCH₂F, -OCF₂CF₃ and -OCH₂CF₃.

The term “C₃-C₁₀-cycloalkyl-” means a saturated mono- or bicyclic hydrocarbon ring which contains 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms (“C₃-C₁₀-cycloalkyl-”). Said C₃-C₁₀-cycloalkyl- group may be, for example, a monocyclic hydrocarbon ring, *e.g.*, a cyclopropyl-, cyclobutyl-, cyclopentyl-, cyclohexyl- or cycloheptyl- group, or a bicyclic hydrocarbon ring, such as decalinyl-. Preferably, said hydrocarbon ring is monocyclic and contains 3, 4, 5, 6 or 7 carbon atoms (“C₃-C₇-cycloalkyl-”), *e.g.*, a cyclopropyl-, cyclobutyl-, cyclopentyl-, cyclohexyl- or cycloheptyl- group, or 3, 4, 5 or 6 carbon atoms (“C₃-C₆-cycloalkyl-”), *e.g.*, a cyclopropyl-, cyclobutyl-, cyclopentyl- or cyclohexyl- group. A cycloalkyl group may be optionally substituted as defined at the respective part wherein such term is used.

The term "4- to 10-membered heterocycloalkyl-" means a saturated mono- or bicyclic hydrocarbon ring which contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and which contains 1, 2, 3 or 4 heteroatoms which may be identical or different, said heteroatoms preferably selected from oxygen, nitrogen or sulfur, and wherein carbon atoms and heteroatoms add up to 4, 5, 6, 7, 8, 9 or 10 ring atoms in total, it being possible for said heterocycloalkyl- group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. "Heterospirocycloalkyl-", "heterobicycloalkyl-" and "bridged heterocycloalkyl-", as defined *infra*, are also included within the scope of this definition.

Preferably, said "4- to 10-membered heterocycloalkyl-" is monocyclic and contains 3, 4, 5 or 6 carbon atoms, and one or two of the above-mentioned heteroatoms, adding up to 4, 5, 6 or 7 ring atoms in total (a "4- to 7-membered monocyclic heterocycloalkyl-"), or contains 3, 4 or 5 carbon atoms, and one or two of the above-mentioned heteroatoms, adding up to 4, 5 or 6 ring atoms in total (a "4- to 6-membered monocyclic heterocycloalkyl-"), or contains 3, 4 or 5 carbon atoms, and one or two of the above-mentioned heteroatoms, adding up to 5 or 6 ring atoms in total (a "5- to 6-membered monocyclic heterocycloalkyl-"); it being possible for said heterocycloalkyl- group to be attached to the rest of the molecule via any one of the carbon atoms or the nitrogen atoms, if present.

Exemplarily, without being limited thereto, said "4- to 7-membered monocyclic heterocycloalkyl-", can be a 4-membered ring, a "4-membered heterocycloalkyl-", such as azetidiny- or oxetany-; or a 5-membered ring, a "5-membered heterocycloalkyl-", such as tetrahydrofurany-, dioxoliny-, pyrrolidiny-, imidazolidiny-, pyrazolidiny- or pyrroliny-; or a 6-membered ring, a "6-membered heterocycloalkyl-", such as tetrahydropyrany-, piperidiny-, morpholiny-, dithianyl-, thiomorpholiny- or piperaziny-; or a 7-membered ring, a "7-membered heterocycloalkyl-", such as azepany-, diazepany- or oxazepany-, for example. Preferred are the heterocycloalkyl moieties as disclosed in the example section, N-morpholiny-, N-piperaziny- and N-Methyl-piperaziny-.

The term "heterobicycloalkyl-" is to be understood as meaning a saturated, monovalent bicyclic hydrocarbon radical in which the two rings share two immediately adjacent ring atoms, and wherein said bicyclic hydrocarbon radical contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms and which contains 1, 2, 3 or 4 heteroatoms which may be identical or different, said heteroatoms preferably selected from oxygen, nitrogen or sulfur; it being possible for said heterobicycloalkyl- group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Exemplary heterobicycloalkyl- groups include, for example, azabicyclo[3.3.0]octyl-, azabicyclo[4.3.0]nonyl-, diazabicyclo[4.3.0]nonyl-, oxazabicyclo[4.3.0]nonyl-, thiazabicyclo[4.3.0]nonyl-, and azabicyclo[4.4.0]decyl-.

The term "bridged heterocycloalkyl-" is to be understood as meaning a saturated, monovalent

bicyclic hydrocarbon radical in which the two rings share two common ring atoms which are not immediately adjacent, and wherein said bicyclic hydrocarbon radical contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and which contains 1, 2, 3 or 4 heteroatoms which may be identical or different, said heteroatoms preferably selected from oxygen, nitrogen and sulfur; it being possible for said bridged heterocycloalkyl- group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Exemplary bridged heterocycloalkyl- groups include, for example, azabicyclo[2.2.1]heptyl-, oxazabicyclo[2.2.1]heptyl-, thiazabicyclo[2.2.1]heptyl-, diazabicyclo[2.2.1]heptyl-, azabicyclo[2.2.2]octyl-, diazabicyclo[2.2.2]octyl-, oxazabicyclo[2.2.2]octyl-, thiazabicyclo[2.2.2]octyl-, azabicyclo[3.2.1]octyl-, diazabicyclo[3.2.1]octyl-, oxazabicyclo[3.2.1]octyl-, thiazabicyclo[3.2.1]octyl-, azabicyclo[3.3.1]nonyl-, diazabicyclo[3.3.1]nonyl-, oxazabicyclo[3.3.1]nonyl-, thiazabicyclo[3.3.1]nonyl-, azabicyclo[4.2.1]nonyl-, diazabicyclo[4.2.1]nonyl-, oxazabicyclo[4.2.1]nonyl-, thiazabicyclo[4.2.1]nonyl-, azabicyclo[3.3.2]decyl-, diazabicyclo[3.3.2]decyl-, oxazabicyclo[3.3.2]decyl-, thiazabicyclo[3.3.2]decyl-, or azabicyclo[4.2.2]decyl-.

The term "heterospirocycloalkyl-" is to be understood as meaning a saturated, bicyclic hydrocarbon radical in which the two rings share one common ring carbon atom, and wherein said bicyclic hydrocarbon radical contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and which contains 1, 2, 3 or 4 heteroatoms which may be identical or different, said heteroatoms preferably selected from oxygen, nitrogen or sulfur; it being possible for said heterospirocycloalkyl- group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Exemplary heterospirocycloalkyl- groups include, for example, azaspiro[2.3]hexyl-, azaspiro[3.3]heptyl-, oxaazaspiro[3.3]heptyl-, thiaazaspiro[3.3]heptyl-, oxaspiro[3.3]heptyl-, oxazaspiro[5.3]nonyl-, oxazaspiro[4.3]octyl-, oxazaspiro[5.5]undecyl-, diazaspiro[3.3]heptyl-, thiazaspiro[3.3]heptyl-, thiazaspiro[4.3]octyl-, and azaspiro[5.5]decyl-.

The term "heteroaryl-" means a monocyclic, bicyclic or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a "5- to 14-membered heteroaryl-" group), preferably 5, 6, 9 or 10 ring atoms, and which contains 1, 2, 3 or 4 heteroatoms which may be identical or different, said heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. Said heteroaryl- group can be a 5-membered heteroaryl- group, such as, for example, thienyl-, furanyl-, pyrrolyl-, oxazolyl-, thiazolyl-, imidazolyl-, pyrazolyl-, isoxazolyl-, isothiazolyl-, oxadiazolyl-, triazolyl-, thiadiazolyl- or tetrazolyl-; or a 6-membered heteroaryl- group, such as, for example, pyridyl-, pyridazinyl-, pyrimidyl-, pyrazinyl- or triazinyl-; or a benzo-fused 5-membered heteroaryl- group, such as, for example, benzofuranyl-, benzothienyl-, benzoxazolyl-, benzisoxazolyl-, benzimidazolyl-, benzothiazolyl-, benzotriazolyl-, indazolyl-, indolyl- or isoindolyl-; or a benzo-fused 6-membered heteroaryl- group, such as, for example, quinolinyl-, quinazolinyl-, isoquinolinyl-, cinnolinyl-, phthalazinyl- or quinoxalinyl-; or another bicyclic group,

such as, for example, indoliziny-, purinyl- or pteridinyl-; or a tricyclic heteroaryl- group, such as, for example, carbazolyl-, acridinyl- or phenazinyl-.

Preferably, “heteroaryl-” is a monocyclic aromatic ring system having 5 or 6 ring atoms and which contains at least one heteroatom, if more than one, they may be identical or different, said
5 heteroatom being selected from the group consisting of oxygen, nitrogen and sulfur (“5- to 6-membered monocyclic heteroaryl-”), such as, for example, thienyl-, furanyl-, pyrrolyl-, oxazolyl-, thiazolyl-, imidazolyl-, pyrazolyl-, isoxazolyl-, isothiazolyl-, oxadiazolyl-, triazolyl-, thiadiazolyl-, tetrazolyl-, pyridyl-, pyridazinyl-, pyrimidyl-, pyrazinyl- or triazinyl-.

In general, and unless otherwise mentioned, said heteroaryl- groups include all the possible
10 isomeric forms thereof, *e.g.*, the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridyl- includes pyridin-2-yl-, pyridin-3-yl- and pyridin-4-yl-; the term thienyl- includes thien-2-yl- and thien-3-yl-. Furthermore, said heteroaryl- groups can be attached to the rest of the molecule via any one of the carbon atoms, or, if applicable, a nitrogen atom, *e.g.*, pyrrol-1-yl-, pyrazol-1-yl- or imidazol-1-yl-.

As used herein, the term “leaving group” refers to an atom or a group of atoms that is displaced in a
15 chemical reaction as stable species taking with it the bonding electrons, *e.g.*, typically forming an anion. Preferably, a leaving group is selected from the group comprising: halo, in particular chloro, bromo or iodo, (methylsulfonyl)oxy-, [(4-methylphenyl)sulfonyl]oxy-, [(trifluoromethyl)sulfonyl]oxy-, [(nonafluorobutyl)sulfonyl]oxy-, [(4-bromophenyl)sulfonyl]oxy-,
20 [(4-nitrophenyl)sulfonyl]oxy-, [(2-nitrophenyl)sulfonyl]oxy-, [(4-isopropylphenyl)sulfonyl]oxy-, [(2,4,6-triisopropylphenyl)sulfonyl]oxy-, [(2,4,6-trimethylphenyl)sulfonyl]oxy-, [(4-*tert*-butylphenyl)sulfonyl]oxy-, (phenylsulfonyl)oxy- and [(4-methoxyphenyl)sulfonyl]oxy-.

The term “C₁-C₆”, as used throughout this text, *e.g.*, in the context of the definition of “C₁-C₆-alkyl-”, “C₁-C₆-haloalkyl-”, “C₁-C₆-alkoxy-” or “C₁-C₆-haloalkoxy-” is to be understood as
25 meaning an alkyl group having a whole number of carbon atoms from 1 to 6, *i.e.*, 1, 2, 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term “C₁-C₆” is to be interpreted as disclosing any sub-range comprised therein, *e.g.* C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; preferably C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more preferably C₁-C₄; in the case of “C₁-C₆-haloalkyl-” or “C₁-C₆-haloalkoxy-” even more preferably C₁-C₂.

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

Further, as used herein, the term “C₃-C₇”, as used throughout this text, *e.g.*, in the context of the

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definition of "C₃-C₇-cycloalkyl-", is to be understood as meaning a cycloalkyl- group having a whole number of carbon atoms of 3 to 7, *i.e.*, 3, 4, 5, 6 or 7 carbon atoms. It is to be understood further that said term "C₃-C₇" is to be interpreted as disclosing any sub-range comprised therein, *e.g.*, C₃-C₆, C₄-C₅, C₃-C₅, C₃-C₄, C₄-C₆, C₅-C₇; preferably C₃-C₆.

- 5 Should a residue be composed of several parts which were defined only separately in the section above it is to be understood that the respective parts of said residue are defined as shown above and connected by the bond as shown at any carbon atom of each respective part of the residue, *e.g.* (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)- is not defined itself but both of its parts, "(C₁-C₃-alkoxy)" and "(C₁-C₃-alkyl)" shall have the definition as shown above, with the understanding that the alkoxy group
10 replaces a hydrogen atom of the alkyl group..

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

- The present invention includes all possible stereoisomers of the compounds of the present
15 invention as single stereoisomers, or as any mixture of said stereoisomers, in any ratio. Isolation of a single stereoisomer, *e.g.*, a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable method, such as chromatography, especially chiral chromatography, for example.

- The compounds of this invention may contain one or more asymmetric centres, depending upon the
20 location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration. 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 (atropisomerism).

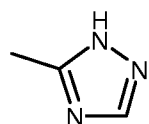
- Substituents on sp³ carbons in a ring may also be disposed in either cis or trans dispositions relative
25 to each other. It is intended that all such configurations are included within the scope of the present invention.

- 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,
30 diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral
35 chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation,

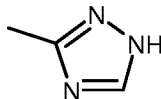
optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically
5 active starting materials, enantioselective catalytic reactions, and other suitable methods.

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

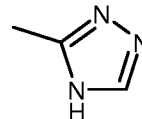
Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for
10 example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, *viz.*:



1H-tautomer



2H-tautomer



4H-tautomer.

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

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 incorporated into
20 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), ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁷O, ¹⁸O, ³²P, ³³P, ³³S, ³⁴S, ³⁵S, ³⁶S, ¹⁸F, ³⁶Cl, ⁸²Br, ¹²³I, ¹²⁴I, ¹²⁹I and ¹³¹I, respectively. Accordingly, recitation of "hydrogen" or "H" should be understood to encompass ¹H (protium), ²H (deuterium), and ³H (tritium) unless otherwise specified. Certain isotopic variations of a compound
25 of the invention, for example, those in which one or more radioactive isotopes such as ³H or ¹⁴C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, *i.e.*, ¹⁴C, 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
30 requirements and hence may be preferred in some circumstances. Isotopic variations of a 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.

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
5 includes all such possible N-oxides.

The present invention also concerns other forms related to the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the
10 compounds of the present invention form a crystal that contains molecules of polar solvents, in particular water, methanol or ethanol, for example, as structural element of the crystal lattice of the compounds. The molecules of polar solvents, in particular water, may be present in a stoichiometric or non-stoichiometric ratio with the molecules of the compound. In the case of stoichiometric solvates, *e.g.*, a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.*
15 solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Furthermore, derivatives of the compounds of formula (I) and the salts thereof which are converted into a compound of formula (I) or a salt thereof in a biological system (bioprecursors or pro-drugs) are covered by the invention. Said biological system may be, for example, a mammalian organism,
20 particularly a human subject. The bioprecursor is, for example, converted into the compound of formula (I) or a salt thereof by metabolic processes.

Further, the compounds of the present invention can exist in free form, *e.g.*, as a free base or 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
25 pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

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

Salts which are preferred for the purposes of administration are physiologically acceptable salts of
30 the compounds according to the invention. However, salts which are not suitable for pharmaceutical applications per se, but which, for example, can be used for the isolation or purification of the compounds according to the invention, are also part of the present invention.

Physiologically acceptable salts of the compounds according to the invention encompass acid addition salts of mineral acids, carboxylic acids and sulfonic acids, for example salts of hydrochloric acid, hydrobromic acid, hydroiodic, sulfuric acid, bisulfuric acid, phosphoric acid, nitric acid or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-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.

Physiologically acceptable salts of the compounds according to the invention also comprise salts of conventional bases, such as, by way of example and by preference, alkali metal salts (for example lithium, sodium and potassium salts), alkaline earth metal salts (for example calcium, strontium and magnesium salts), other salts (such as, e.g., aluminium salts) and ammonium salts derived from ammonia or organic amines with 1 to 16 C atoms, such as, by way of example and by preference, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, ethylenediamine, *N*-methylpiperidine, *N*-methylglucamine, dimethylglucamine, ethylglucamine, 1,6-hexadiazine, glucosamine, sarcosine, serinol, tris(hydroxymethyl)aminomethane, aminopropanediol, Sovak base, and 1-amino-2,3,4-butanetriol.

Additionally, the compounds according to the invention may form salts with a quaternary ammonium ion obtainable, e.g., by quaternisation of a basic nitrogen-containing group with agents such as lower alkylhalides such as methyl-, ethyl-, propyl-, and butylchlorides, -bromides and -iodides; dialkylsulfates such as dimethyl-, diethyl-, dibutyl- and diamylsulfates, long chain halides such as decyl-, lauryl-, myristyl- and stearylchlorides, -bromides and -iodides, aralkylhalides such as benzyl- and phenethylbromides and others. Examples of suitable quaternary ammonium ions are tetramethylammonium, tetraethylammonium, tetra(*n*-propyl)ammonium, tetra(*n*-butyl)ammonium, or *N*-benzyl-*N,N,N*-trimethylammonium.

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.

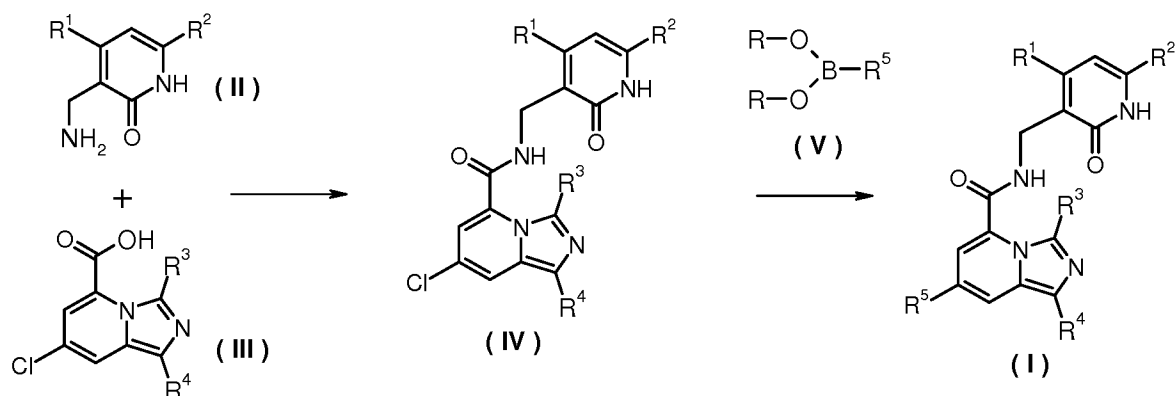
Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

General synthesis of compounds of general formula (I)

The following paragraphs outline a variety of synthetic approaches suitable to prepare compounds of the general formula (I), and intermediates useful for their synthesis.

In addition to the routes described below, also other routes may be used to synthesise the target compounds, in accordance with common general knowledge of a person skilled in the art of organic synthesis. The order of transformations exemplified in the following schemes is therefore not intended to be limiting, and suitable synthesis steps from various schemes can be combined to form additional synthesis sequences. In addition, interconversion of any of the substituents, such as R^1 , R^2 , R^3 , R^4 or R^5 , can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protective groups, cleavage of protective groups, reduction or oxidation of functional groups, halogenation, metallation, metal catalysed coupling reactions, exemplified by but not limited to Suzuki, Sonogashira and Ullmann coupling, ester saponifications, amide coupling reactions, and/or substitution or other reactions known to a person skilled in the art. These transformations include those which introduce a functionality allowing for further interconversion of substituents. Appropriate protective groups and their introduction and cleavage are well-known to a person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 4th edition, Wiley 2006).

Specific examples of said interconversions are described in the subsequent paragraphs and in the experimental section, *infra*, e.g. for the elaboration of a sulfoximino group from a sulfoxide (see the protocols for Intermediates 149A and 151A).



Scheme 1a: Preparation of compounds of general formula (I) from 3-aminomethyl pyridone derivatives of formula (II) and chloroimidazopyridine carboxylic acids of formula (III).

Compounds of general formula (I) can be readily prepared from chloroimidazopyridine derivatives of formula (IV), in which R^1 , R^2 , R^3 and R^4 are as defined for the compounds of general formula

(I), and boronic acid derivatives $R^5-B(OR)_2$ of formula (V), in which R^5 is as defined for the compound of general formula (I), by means of a palladium catalysed Suzuki coupling reaction well known to the person skilled in the art, according to Scheme 1a. Said boronic acid derivatives of formula (V) may preferably be boronic acids ($R = -H$), or, also preferably, a cyclic ester, in which
5 R-R together represent a $-C_2-C_6$ -alkylene- group, more preferably a cyclic ester derived from pinacol in which the $-B(OR)_2$ forms a -4,4,5,5-tetramethyl-1,3,2-dioxaborolane ($R-R = -C(CH_3)_2-C(CH_3)_2-$), or, alternatively, acyclic esters of said boronic acids, in which R represents a C_1-C_3 -alkyl- group, *e.g.* an isopropyl ester ($R = -CH(CH_3)_2$). Boronic acids and their esters are commercially available and well-known to the person skilled in the art; see *e.g.* D.G. Hall, Boronic
10 Acids, **2005** WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, ISBN 3-527-30991-8 and references cited therein; see also the protocols of Intermediates 150A and 152A for boronic acid esters featuring a sulfoximino group and which are not commercially available.

The Suzuki coupling reaction is catalyzed by palladium catalysts, such as tetrakis(triphenylphosphine)palladium(0) $[Pd(PPh_3)_4]$, tris(dibenzylideneacetone)di-palladium(0)
15 $[Pd_2(dba)_3]$, dichlorobis(triphenylphosphine)-palladium(II) $[Pd(PPh_3)_2Cl_2]$, palladium(II) acetate and triphenylphosphine, by $[1,1'$ -bis(diphenylphosphino)ferrocene]palladium dichloride, or by palladacycle precatalysts known to the person skilled in the art, for example (2'-aminobiphenyl-2-yl)(chloro)dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)palladium (CAS 1375325-68-0, 2nd generation RuPhos precatalyst). Preferred is the use of tetrakis(triphenylphosphine)palladium(0)
20 $[Pd(PPh_3)_4]$, or (2'-aminobiphenyl-2-yl)(chloro)dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)palladium.

The reaction is carried out in solvents selected from water, toluene, 1,2-dimethoxyethane, 1,4-dioxane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one,
25 tetrahydrofuran, and an aliphatic alcohol of the formula C_1-C_3 -alkyl-OH, or a mixture containing two or more of said solvents, preferably a mixture of two solvents selected from ethanol, toluene and 1,2-dimethoxyethane, optionally containing up to 20 v/v % of water, more preferred a mixture of toluene and ethanol, optionally containing up to 10 v/v % of water, or a mixture of toluene and 1,2-dimethoxyethane, optionally containing up to 10 v/v % of water.

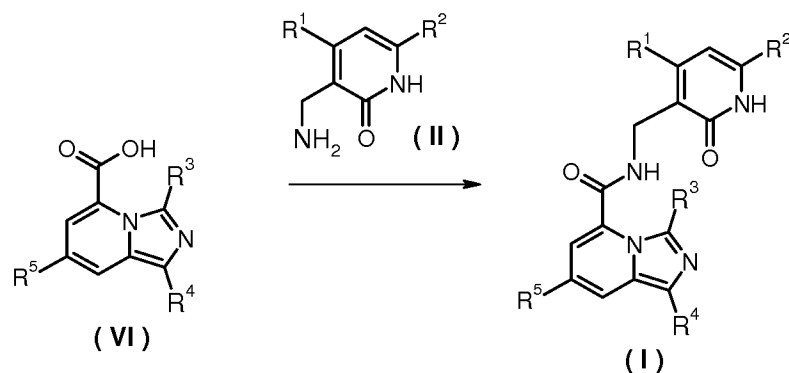
30 The reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate or potassium phosphate, in solid form or in aqueous solution in a concentration ranging from 0.5 N to 3 N, preferably sodium carbonate or potassium carbonate, in solid form or in aqueous solution in a concentration ranging from 1.0 N to 2.5 N, more preferably sodium carbonate in aqueous solution in a concentration ranging from 1.5 N to 2.5 N.

35 The reaction is carried out in a temperature range between 60°C and 180°C, preferably 80°C and 150°C, more preferably 100°C and 140 °C, over a time between 15 minutes and 24 hours,

preferably between 30 minutes and 4 hours, preferably under an atmosphere of argon, in a microwave oven or in an oil bath.

Said chloroimidazopyridine derivatives of formula (IV) can, in turn, be assembled from 3-aminomethyl pyridone derivatives of formula (II), in which R¹ and R² are as defined for the compounds of general formula (I), and chloroimidazopyridine carboxylic acid derivatives of formula (III), in which R³ and R⁴ are as defined for the compounds of general formula (I), by means of carboxamide (or peptide) coupling reaction well known to the person skilled in the art, according to Scheme 1a. Said coupling reaction can be performed by reaction of compounds of the formulae (II) and (III) in the presence of a suitable coupling reagent, such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate), T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide), or EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in combination with HOBT (1-hydroxy-1H-benzotriazole hydrate), in the presence of a base such as an aliphatic or aromatic tertiary amine, preferably a tertiary aliphatic amine of the formula N(C₁-C₄-alkyl)₃, in an appropriate solvent, *e.g.* N,N-dimethylformamide.

The preparation of amides from 3-aminomethyl pyridone derivatives of formula (II), in which R¹ and R² are as defined for the compounds of general formula (I), and chloroimidazopyridine carboxylic acid derivatives of formula (III), in which R³ and R⁴ are as defined for the compounds of general formula (I), can furthermore be accomplished, as well known to the person skilled in the art, by converting carboxylic acids of the formula (III) into the corresponding acyl halides, *e.g.* by reacting with a halogenating agent such as thionyl chloride, oxalyl chloride, or phosphoroxy chloride, and subsequent aminolysis using said 3-aminomethyl pyridone derivatives of formula (II).

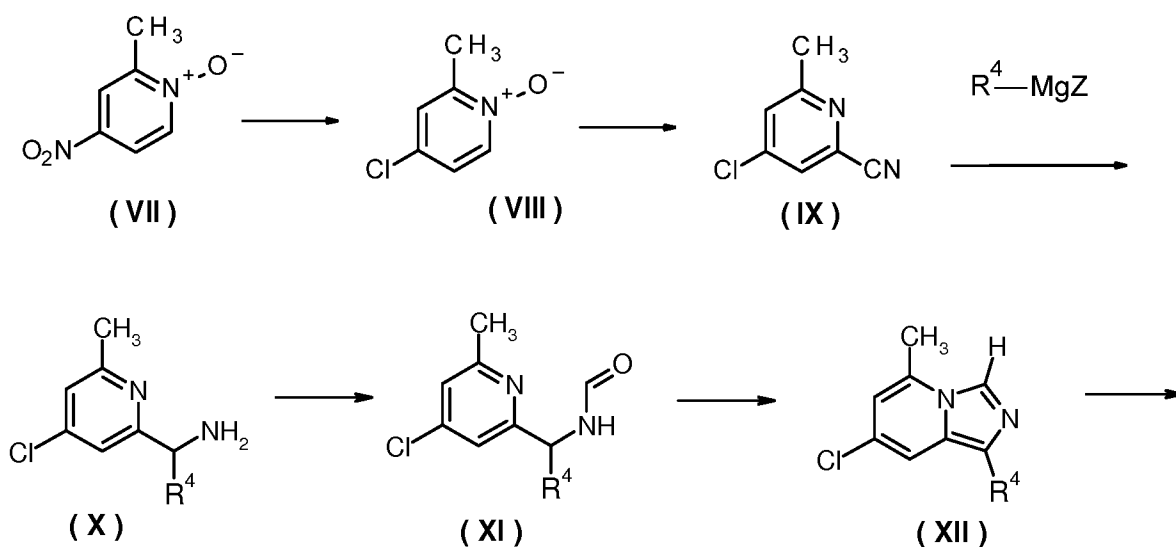


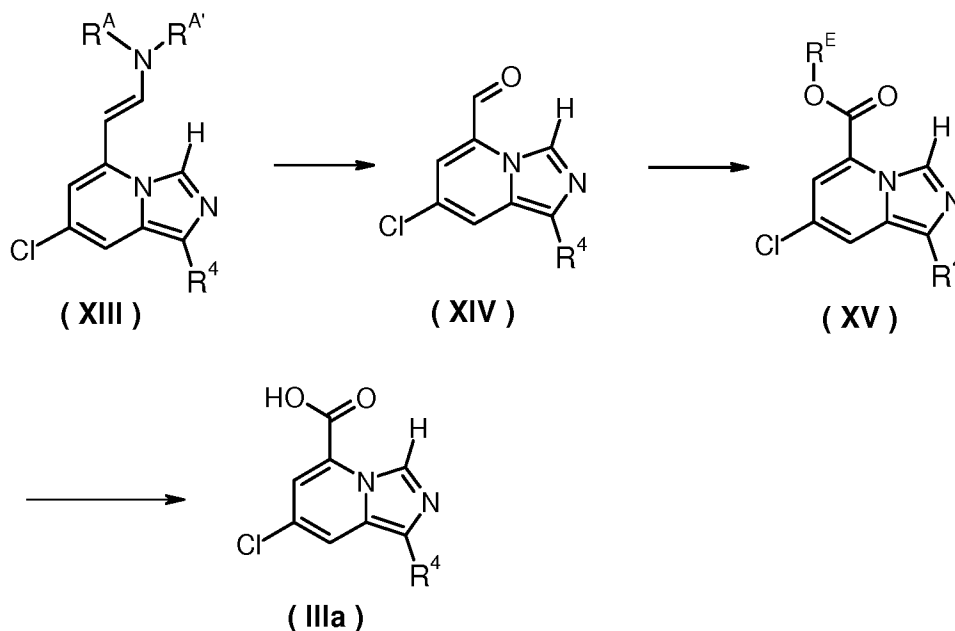
Scheme 1b: Preparation of compounds of general formula (I) from 3-aminomethyl pyridone derivatives of formula (II) and imidazopyridine carboxylic acids of formula (VI).

Vice versa, compounds of general formula (I) can also be assembled from 3-aminomethyl pyridone derivatives of formula (II), in which R^1 and R^2 are as defined for the compounds of general formula (I), and imidazopyridine carboxylic acid derivatives of formula (VI), in which R^3 , R^4 and R^5 are as defined for the compounds of general formula (I), by means of carboxamide (or peptide) coupling reaction well known to the person skilled in the art, according to Scheme 1b. Said coupling reaction can be performed by reaction of compounds of the formulae (II) and (VI) in the presence of a suitable coupling reagent, such as HATU (O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate), TBTU (O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate), PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate), T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide), or EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in combination with HOBT (1-hydroxy-1H-benzotriazole hydrate), in the presence of a base such as an aliphatic or aromatic tertiary amine, preferably a tertiary aliphatic amine of the formula $N(C_1-C_4\text{-alkyl})_3$, in an appropriate solvent.

Preferred herein is the performance of said carboxamide coupling reaction using O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) as a coupling agent, in the presence of *N,N*-diisopropylethylamine as a base, and in *N,N*-dimethylformamide as a solvent, within a temperature range from 0°C to 50°C.

3-Aminomethyl pyridone derivatives and imidazopyridine carboxylic acids of formulae (II), (III) and (VI) can be prepared using synthetic methods described in more detail as according to Schemes 2a, 2b, 2c, 3a, 3b, 3c, 3d, 3e, 4a and 4b, shown below.

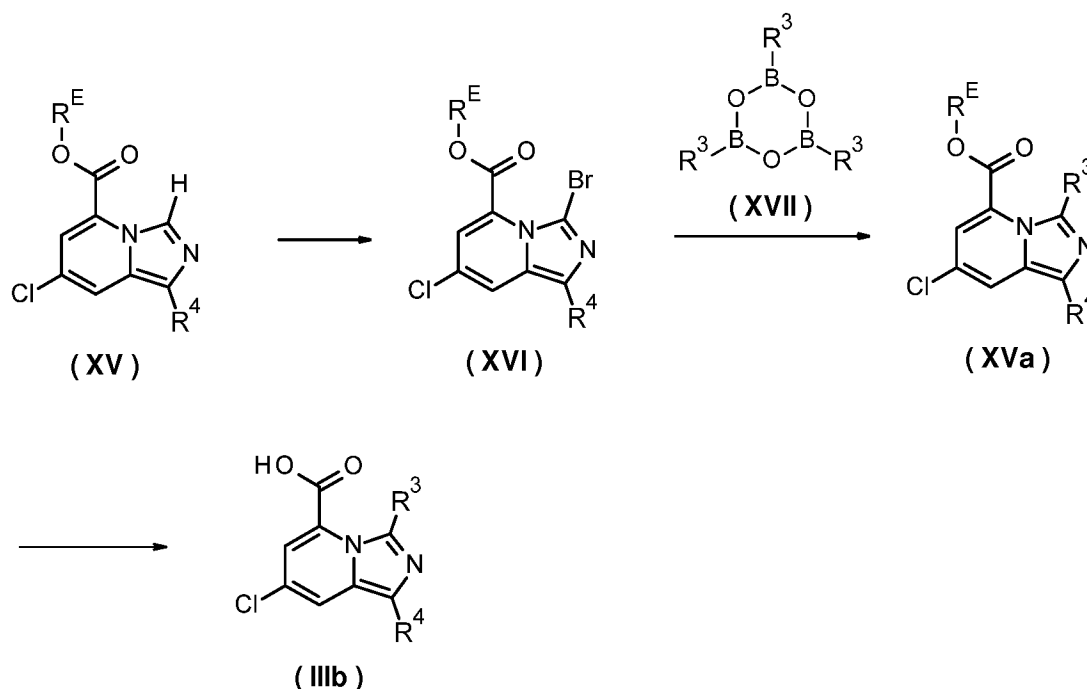




Scheme 2a: Preparation of chloroimidazopyridine carboxylic acids of formula **(IIIa)** from 2-methyl-4-nitropyridine 1-oxide **(VII)**.

- 5 Scheme 2a displays a synthesis route which can be used for the preparation of chloroimidazopyridine carboxylic acids of formula **(IIIa)**, in which R^3 represents a hydrogen atom and in which R^4 is as defined for the compounds of general formula **(I)** and which constitutes a sub-compartment of formula **(III)**, from 2-methyl-4-nitropyridine 1-oxide **(VII)**, which can be converted into 4-chloro-2-methylpyridine 1-oxide **(VIII)** by reaction with sodium chloride in the
- 10 presence of concentrated aqueous hydrochloric acid and a quaternary ammonium halide, such as benzyltrimethyl ammonium chloride, followed by rearrangement of thus formed **(VIII)** in the presence of trimethylsilyl cyanide and a base such as a tertiary aliphatic amine $N(C_1-C_3\text{-alkyl})_3$, preferably triethylamine, in an aliphatic nitrile of the formula $(C_1-C_3\text{-alkyl})\text{-CN}$, preferably propionitrile, to give 4-chloro-6-methylpyridine-2-carbonitrile **(IX)**. Said intermediate **(IX)** can be
- 15 subsequently reacted with Grignard reagents of formula $R^4\text{MgZ}$, in which Z represents chloro, bromo or iodo, and in which R^4 is as defined for the compounds of general formula **(I)**, in an ether such as tetrahydrofuran as a solvent, followed by reduction with a suitable agent such as sodium borohydride, in order to convert the intermediate imines to amines of formula **(X)**. Amines of formula **(X)** can be further elaborated into formamides of formula **(XI)** by means of reaction with
- 20 formic acid or a C_1-C_3 -alkyl ester thereof, such as ethyl formate. Heating of formamides **(XI)** in the presence of phosphorus oxychloride (POCl_3) in a suitable solvent such as toluene can be used to obtain chloroimidazopyridine derivatives of formula **(XII)** featuring a methyl group at C-7, which can be subsequently converted into enamines of formula **(XIII)** by reacting with *N,N*-dimethylformamide dimethylacetal ($\text{CH}_3\text{O-C(H)-N(CH}_3)_2$) in the presence of a secondary amine
- 25 $R^A R^{A'}\text{NH}$, preferably pyrrolidine (in which R^A and $R^{A'}$ together represent a group $-(\text{CH}_2)_4-$).

- Oxidative cleavage of said enamines of formula (XIII) using an oxidant such as sodium periodate can be used to obtain aldehydes of formula (XIV), which can be further elaborated into carboxylic esters of formula (XV), in which R^E represents a C₁-C₃-alkyl- group, preferably a methyl- group, by reacting with sodium cyanide in the presence of manganese dioxide in a mixture of
- 5 tetrahydrofuran and methanol as a solvent, followed by saponification of carboxylic esters of formula (XV) using an alkali hydroxide such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, in an aqueous aliphatic alcohol of the formula (C₁-C₃-alkyl)-OH, optionally additionally containing a cyclic ether such as tetrahydrofuran, as a solvent, as well known to the person skilled in the art, to give rise to the desired chloroimidazopyridine carboxylic acids of formula (IIIa).
- 10 Alternatively, the conversion of aldehydes of formula (XIV) into to the desired chloroimidazopyridine carboxylic acids of formula (IIIa) can be accomplished in one step by reaction with aqueous hydrogen peroxide in formic acid.

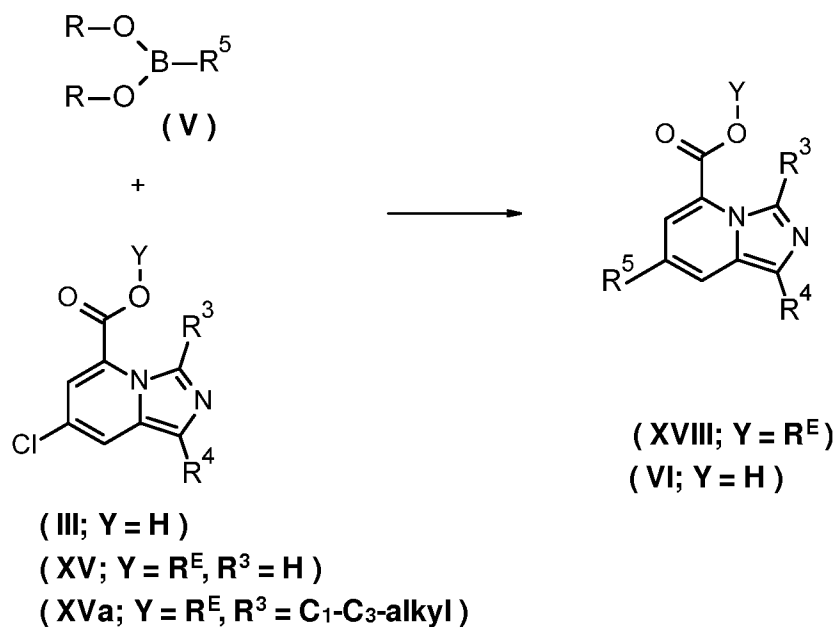


- Scheme 2b:** Preparation of chloroimidazopyridine carboxylic acids of formula (IIIb) from carboxylic esters of formula (XV).
- 15

- Scheme 2b illustrates the preparation of chloroimidazopyridine carboxylic acids of formula (IIIb), in which R³ represents a C₁-C₃-alkyl- group, and in which R⁴ is as defined for the compounds of general formula (I) and which constitutes a further sub-set of formula (III), from carboxylic esters of formula (XV), in which R^E represents a C₁-C₃-alkyl- group, preferably a methyl- group, and in
- 20 which R⁴ is as defined for the compounds of general formula (I). Said carboxylic esters of formula (XV) can also be prepared from carboxylic acids of formula (IIIa; see Scheme 2a) by an esterification reaction well known to the person skilled in the art, *e.g.* using an alkylating agent of the formula (C₁-C₃-alkyl)-LG, in which LG represents a leaving group as defined herein, preferably

bromo, iodo or (methylsulfonyl)oxy-, in the presence of a base, such as sodium carbonate, potassium carbonate or cesium carbonate, in a solvent such as *N,N*-dimethylformamide.

Said carboxylic esters of formula (XV) can be brominated using a suitable brominating agent, preferably *N*-bromo succinimide, in *N,N*-dimethylformamide as a solvent, to give 2-bromo
 5 imidazopyridine derivatives of formula (XVI), which can be subsequently reacted in a palladium catalysed coupling reaction with a boroxine reagent (see *e.g.* EP 1792904) of formula (XVII), in which R³ represents a C₁-C₃-alkyl- group, preferably in the presence of tetrakis (triphenylphosphinato)palladium(0) as a catalyst, sodium carbonate as a base, and aqueous 1,4-dioxane as a solvent, to give chloroimidazopyridine carboxylic esters of formula (XVa), in which
 10 R³ a C₁-C₃-alkyl- group, followed by saponification using an alkali hydroxide such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, in an aqueous aliphatic alcohol of the formula (C₁-C₃-alkyl)-OH, optionally additionally containing a cyclic ether such as tetrahydrofuran, as a solvent, as well known to the person skilled in the art, to give rise to the desired chloroimidazopyridine carboxylic acids of formula (IIIb), in which R³ represents a C₁-C₃-alkyl- group, or, depending on the work-up, their salts, *e.g.* lithium, sodium or potassium salts.
 15 Boroxine reagents of the formula (XVII) are well known to the person skilled in the art and commercially available in certain cases.

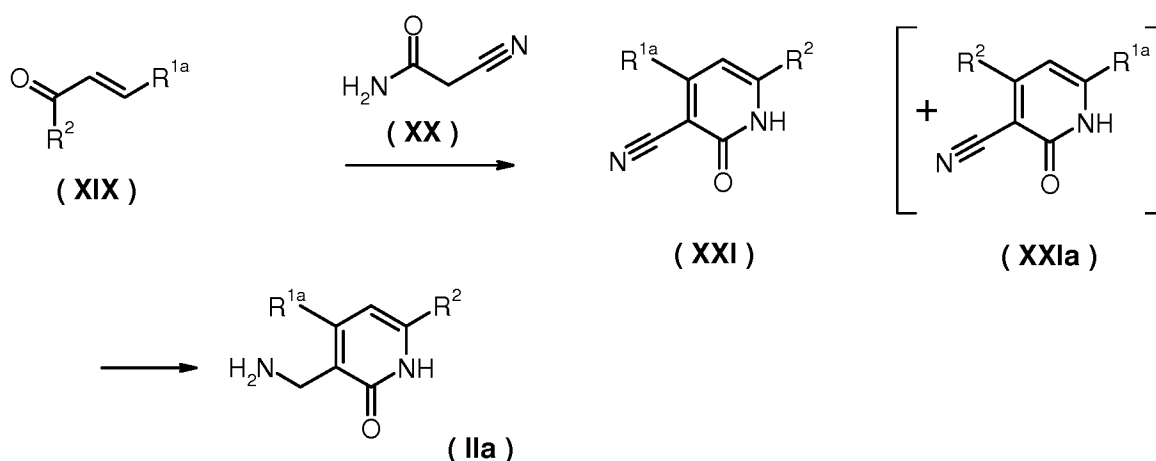


20 **Scheme 2c:** Preparation of imidazopyridine carboxylic acids of formula (VI) from chloroimidazopyridine carboxylic acids and their esters of formulae (III), (XV) and (XVa).

Imidazopyridine carboxylic acid derivatives of formula (VI) are available from chloroimidazopyridine carboxylic acids of formula (III), or the corresponding carboxylic esters,

(XV) or (XVa), in which R^E represents a C₁-C₃-alkyl- group, and boronic acid derivatives R⁵-B(OR)₂ of formula (V), in which R⁵ is as defined for the compound of general formula (I), and in which R represents a hydrogen atom or a C₁-C₃-alkyl- group, or R-R together represent a -C₂-C₆-alkylene- group, by means of a palladium catalysed Suzuki coupling reaction well known to the person skilled in the art, according to Scheme 2c, in an analogous fashion as described for the conversion of chloroimidazopyridine derivates of formula (IV) into compounds of general formula (I) in context of Scheme 1a, *supra*. If carboxylic esters of formulae (XV) or (XVa) are employed, carboxylic esters of formula (XVIII) are formed initially which can be cleaved by methods known to the person skilled in the art, in a similar fashion as discussed *supra* for the conversion of chloroimidazopyridine carboxylic esters (XV) into chloroimidazopyridine carboxylic acids (Scheme 2a).

Schemes 3a, 3b, 3c, 3d and 3e display synthesis routes suitable for the preparation of 3-aminomethyl pyridone intermediates of formulae (IIa), (IIb), (IIc), all of them constituting sub-compartments of the formula (II) shown *supra*.



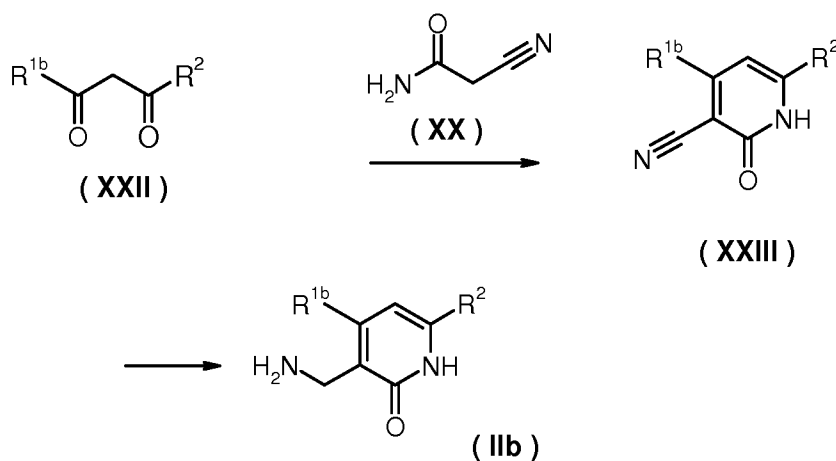
Scheme 3a: Preparation of 3-aminomethyl pyridone intermediates of formula (IIa) from α,β -unsaturated ketones of formula (XIX).

Scheme 3a illustrates the synthesis of 3-aminomethyl pyridone intermediates of formula (IIa), in which R^{1a} represents a group selected from the groups representing R¹ as defined for the compounds of general formula (I) which is linked to the pyridone ring *via* a carbon atom, *e.g.* C₁-C₃-alkyl-, C₁-C₃-haloalkyl- or benzyl- group, and in which R² represents a C₁-C₃-alkyl- group, and their salts, *e.g.* hydrochloride, hydrobromide or trifluoroacetate salts, preferably hydrochloride salts, from α,β -unsaturated ketones of formula (XIX), which can be reacted with 2-cyanoacetamide (XX; see also *e.g.* WO 2011/140325), in the presence of a suitable base, such as an aliphatic amine, preferably piperidine, in an aliphatic alcohol of the formula (C₁-C₃-alkyl)-OH, preferably ethanol,

or, alternatively, in the presence of an alkoxide of an alkali metal, preferably potassium *tert*-butoxide, as a base, and in dimethyl sulfoxide as a solvent, to give 2-oxo-1,2-dihydropyridine-3-carbonitriles of formula (XXI). Said 2-oxo-1,2-dihydropyridine-3-carbonitriles of formula (XXI) can subsequently be reduced to 3-aminomethyl pyridone derivatives of formula (IIa) by methods known to the person skilled in the art, such as by reaction with hydrogen gas in the presence of palladium(II)hydroxide (Pd(OH)₂) in methanol containing aqueous hydrochloric acid, or by reaction with hydrogen gas in the presence of Raney Nickel in *N,N*-dimethylformamide as a solvent. Depending on the substituents R^{1a} and R², concomitant formation of regioisomers of formula (XXIa) may occur. Said regioisomers can be separated either immediately after their formation, or at a later stage, by methods well known to the person skilled in the art, exemplified by but not limited to the introduction of a *tert*-butoxycarbonyl group onto the aminomethyl group present in compounds of the formula (IIa) and their regioisomers, followed by isomer separation by means of column chromatography or preparative HPLC, and removal of the *tert*-butoxycarbonyl group as illustrated in the experimental section (see *e.g.* protocols of intermediates 145A and 147A).

The resulting 3-aminomethyl pyridone intermediates of formula (IIa) can be isolated as free bases, or, depending on the reaction conditions in the final step, and/or the work-up procedure, as salts, *e.g.* hydrochloride, hydrobromide or trifluoroacetate salts. Preferably, the intermediates of formula (IIa) are isolated as hydrochloride salts.

The α,β -unsaturated ketones of formula (XIX) used as starting material are well known to the person skilled in the art and commercially available in certain cases, see also Scheme 4a for less common starting materials of formula (XIX).

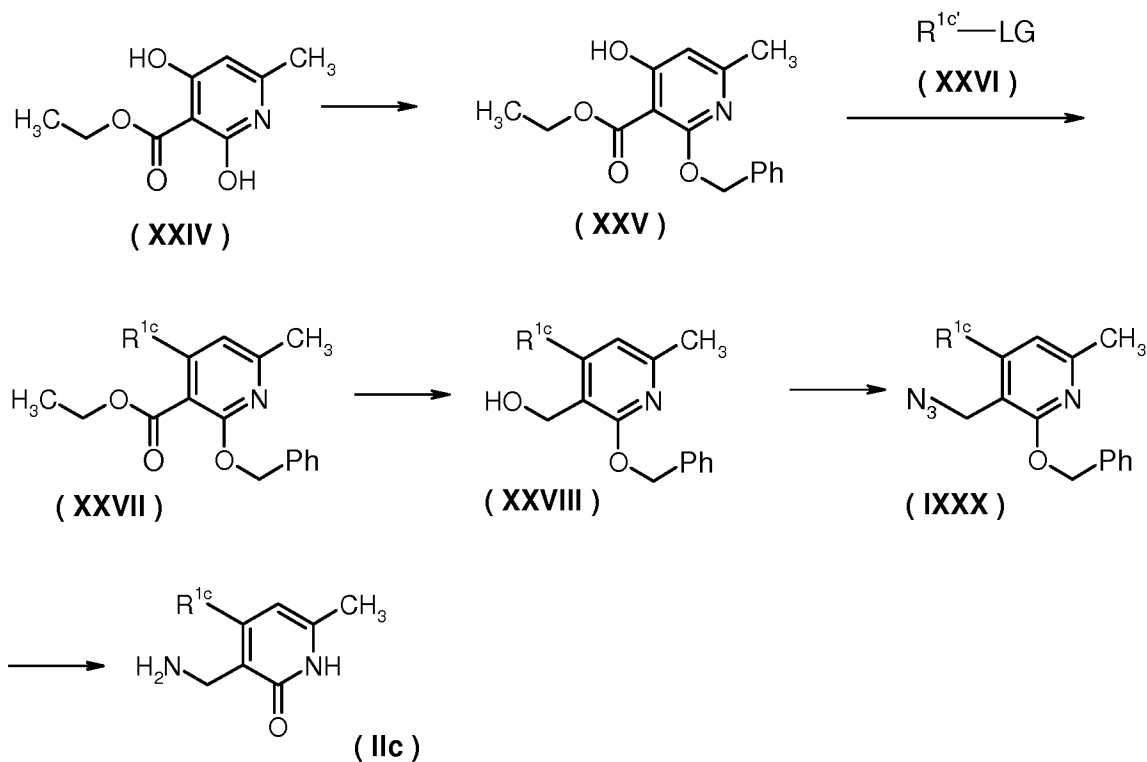


Scheme 3b: Preparation of 3-aminomethyl pyridone intermediates of formula (IIb) from β -diketones of formula (XXII).

Scheme 3b illustrates the synthesis of 3-aminomethyl pyridone intermediates of formula (IIb), in which R^{1b} represents a group selected from the groups representing R^1 as defined for the compounds of general formula (I) which is linked to the pyridone ring *via* a carbon atom, *e.g.* a (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)- or C₁-C₃-haloalkyl- group, and in which R^2 represents a C₁-C₃-alkyl-group, and their salts, *e.g.* hydrochloride, hydrobromide or trifluoroacetate salts, preferably hydrochloride salts, from β -diketones of formula (XXII), which can be reacted with 2-cyanoacetamide (XX), in the presence of a suitable base, such as an aliphatic amine, preferably piperidine, in an aliphatic alcohol of the formula (C₁-C₃-alkyl)-OH, preferably ethanol, to give 2-oxo-1,2-dihydropyridine-3-carbonitriles of formula (XXIII), which can be further converted into 3-aminomethyl pyridone intermediates of formula (IIb) in a similar fashion as described in Scheme 3a, *supra*.

The resulting 3-aminomethyl pyridone intermediates of formula (IIb) can be isolated as free bases, or, depending on the reaction conditions in the final step, and/or the work-up procedure, as salts, *e.g.* hydrochloride, hydrobromide or trifluoroacetate salts. Preferably, the intermediates of formula (IIb) are isolated as hydrochloride salts.

The β -diketones of formula (XXII) used as starting material are well known to the person skilled in the art and commercially available in certain cases, see also Scheme 4b for less common starting material of formula (XXII).

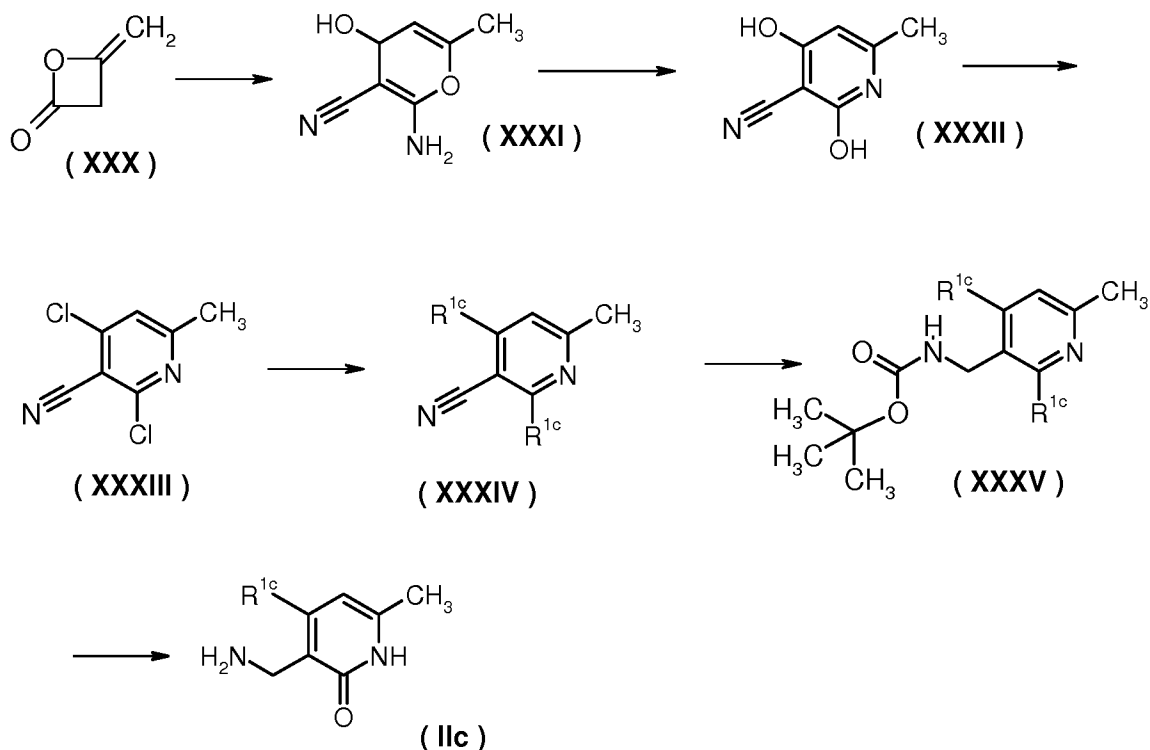


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Scheme 3c: Preparation of 3-aminomethyl pyridone intermediates of formula (IIc) from ethyl 2,4-

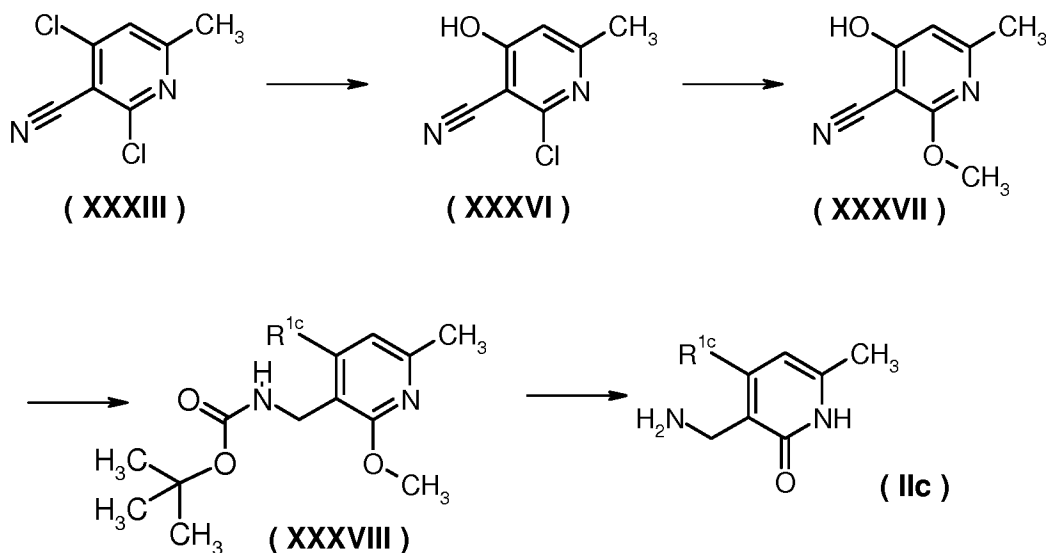
dihydroxynicotinate (**XXIV**).

Various routes are suitable for the preparation of 3-aminopyridone intermediates of formula (**IIc**), in which R^{1c} represents a group selected from the groups representing R¹ as defined for the compounds of general formula (**I**) which is linked to the pyridone ring *via* an oxygen atom, *e.g.* a C₁-C₃-alkoxy- or C₁-C₃-haloalkoxy- group, or a (C₃-C₇-cycloalkyl)-(L¹)- group in which L¹ represents -CH₂O- or -O-, and in which R² represents a methyl- group, as outlined in Schemes 3c, 3d and 3e. Scheme 3c illustrates the preparation of said 3-aminopyridone intermediates of formula (**IIc**) starting from ethyl 2,4-dihydroxynicotinate (CAS-No. 10350-10-4; **XXIV**) which can be selectively benzylated at 2-OH using benzyl bromide and silver carbonate in tetrahydrofuran to give monobenzyl ether (**XXV**), which, in turn, can be reacted with a compound of formula (**XXVI**), in which R^{1c} represents *e.g.* a C₁-C₃-alkyl-, C₃-C₇-cycloalkyl-, C₃-C₇-cycloalkylmethyl- or C₁-C₃-haloalkyl- group, and in which LG represents a leaving group as defined herein, preferably bromo, iodo or [(trifluoromethyl)sulfonyl]oxy-, to give intermediates of formula (**XXVII**). Reduction of the carboxylic ester present in compounds of formula (**XXVII**) by methods known to the person skilled in the art, *e.g.* using lithium aluminium hydride in tetrahydrofuran or sodium bis(2-methoxyethoxy)aluminium dihydride in toluene, can be used to obtain the corresponding hydroxymethyl pyridine derivatives of formula (**XXVIII**), which can be readily converted into the corresponding azides of formula (**IXXX**) *via* intermediate mesylates by reacting compounds of formula (**XXVIII**) with methanesulfonyl chloride in the presence of a base such as triethylamine or *N,N*-diisopropylethylamine, in dichloromethane as a solvent, followed by work-up and subsequent reaction with sodium azide in *N,N*-dimethylformamide. Reduction of the azide group with concomitant cleavage of the benzyl ether present in azides of formula (**IXXX**) can be achieved using methods well known to the person skilled in the art, such as reaction with hydrogen gas in the presence of palladium on carbon in an aliphatic alcohol of the formula (C₁-C₃-alkyl)-OH, preferably methanol, or in the presence of palladium(II) hydroxide, in a mixture comprising an aliphatic alcohol of the formula (C₁-C₃-alkyl)-OH, preferably ethanol, and an aliphatic carboxylic acid of the formula (C₁-C₂-alkyl)-OH, preferably acetic acid, under elevated hydrogen pressure if needed, and optionally followed by treatment with an acid, to yield 3-aminomethyl pyridone intermediates of formula (**IIc**) either as free base or as salt, preferably as hydrochloride salt.



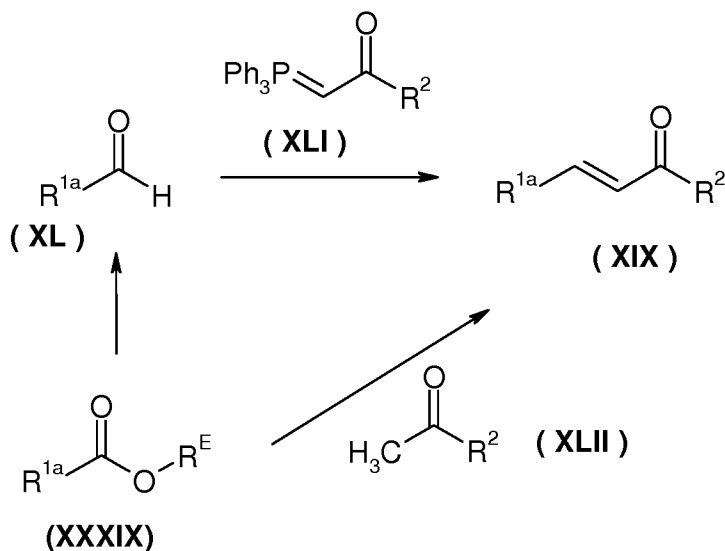
Scheme 3d: Preparation of 3-aminomethyl pyridone intermediates of formula (IIc) from 4-methyleneoxetan-2-one (XXX).

- 5 Scheme 3d illustrates an alternative preparation of said 3-aminomethylpyridone intermediates of formula (IIc) starting from commercially available 4-methyleneoxetan-2-one (XXX), which can be reacted with malonodinitrile in the presence of sodium hydride to give 2-amino-6-methyl-4-oxo-4H-pyran-3-carbonitrile (XXXI) which can be further converted into 2,4-dihydroxy-6-methylnicotinonitrile (XXXII) by heating in aqueous hydrochloric acid. (XXXII) can be
- 10 chlorinated using *e.g.* phosphorus oxychloride (POCl₃) in *N,N*-dimethylformamide to give 2,4-dichloro-6-methylnicotinonitrile (XXXIII), which can be reacted with a suitable alkoxide, *e.g.* with sodium methoxide in methanol, to yield intermediates of formula (XXXIV), followed by reduction of the cyano group by methods known to the person skilled in the art, *e.g.* with hydrogen gas in the presence of Raney Nickel, triethylamine as a base and di-*tert*-butyl dicarbonate (Boc₂O) in a
- 15 mixture of tetrahydrofuran and methanol as a solvent, to give carbamate intermediates of formula (XXXV). Reacting of carbamate intermediates (XXXV) with aqueous hydrochloric acid can be used to obtain 3-aminomethyl pyridone intermediates of formula (IIc), preferably as hydrochloride salt.



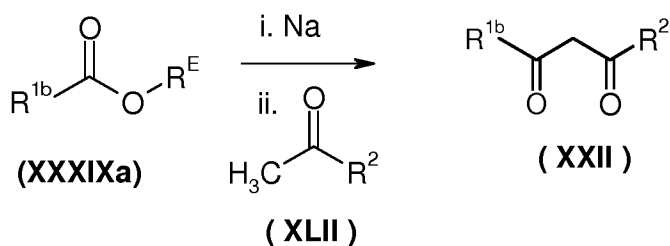
Scheme 3e: Preparation of 3-aminomethyl pyridone intermediates of formula (IIc) from 2,4-dichloro-6-methylnicotinonitrile (XXXIII).

- As a further alternative, Scheme 3e outlines the synthesis of 3-aminomethylpyridone intermediates of formula (IIc) starting from 2,4-dichloro-6-methylnicotinonitrile (XXXIII). Selective hydrolysis of 4-Cl can be achieved under suitable conditions, *e.g.* using potassium acetate in *N,N*-dimethylformamide at a temperature of 80°C to give hydroxypyridine (XXXVI), which can be converted into monomethyl ether (XXXVII), allowing for the elaboration of R^{1c}, either by standard alkylation reactions analogous to the conversion of (XXV) into (XXVII) in Scheme 3c, or, if mandated by the nature or the respective R^{1c}, by specific methodology such as the use of ethyl 2-chloro-2,2-difluoroacetate and sodium hydride in *N,N*-dimethylformamide for the elaboration of R^{1c} = F₂HC-O- (see also protocol of Intermediate 135A). The further conversion into 3-aminomethylpyridone intermediates of formula (IIc) can be accomplished *via* carbamate (XXXVIII) using the methods outlined in Scheme 3d for the conversion of intermediates of formula (XXXIV) into 3-aminomethyl pyridone intermediates of formula (IIc), which are preferably isolated as hydrochloride salt.



Scheme 4a: Preparation of α,β-unsaturated ketones of formula (XIX) from carboxylic esters of formula (XXXIX).

Scheme 4a describes a synthetic approach to starting materials of formula (XIX) which are not commercially available, by methods which however are well known to the person skilled in the art. Carboxylic esters of formula (XXXIX), in which R^{1a} represents *e.g.* a C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl- or benzyl- group, and in which R^E represents a C_1 - C_3 -alkyl- group, can be readily converted into the corresponding aldehydes (XL) using well-known standard reduction and oxidation protocols (*e.g.* reduction with sodium borohydride, lithium borohydride or lithium aluminium hydride, followed by oxidation with Dess-Martin's reagent or tetrapropyl perruthenate / *N*-methylmorpholine *N*-oxide). Said aldehydes can be subjected to a Wittig olefination using phosphoranes of formula (XLI), in which R^2 represents a C_1 - C_3 -alkyl- group, to give α,β-unsaturated ketones of formula (XIX). Alternatively, carboxylic esters of formula (XXXIX) can be directly converted into α,β-unsaturated ketones of formula (XIX) by reaction with methyl ketones of formula (XLII), in which R^2 represents a C_1 - C_3 -alkyl- group, in the presence of an alkali amide, *e.g.* sodium amide.



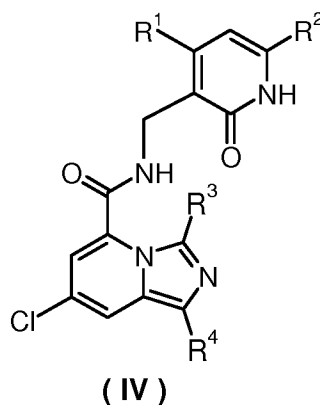
Scheme 4b: Preparation of β-diketones of formula (XXII) from carboxylic esters of formula (XXXIXa).

Scheme 4b describes the synthesis of starting materials of formula (XXII) which are not

commercially available. They can be readily prepared by reacting commercially available carboxylic esters of formula (XXXIXa) in which R^{1b} represents *e.g.* a (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)- or C₁-C₃-haloalkyl- group, and in which R^E represents a C₁-C₃-alkyl- group, with sodium metal in toluene, followed by a methyl ketone of formula (XLII).

- 5 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.

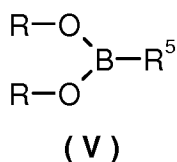
In a preferred embodiment, the present invention relates to a method of preparing compounds of general formula (I), *supra*, in which method an intermediate compound of formula (IV)



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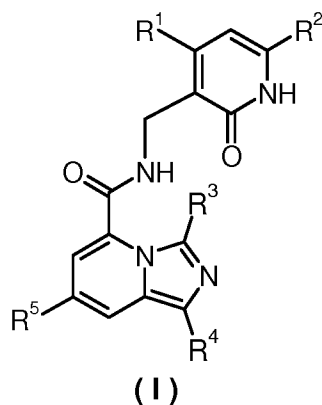
in which R^1 , R^2 , R^3 , and R^4 are as defined for the compounds of general formula (I), *supra*;

is allowed to react with a compound of formula (V) :



- 15 in which R^5 is as defined for the compounds of general formula (I), *supra*, and in which R represents a hydrogen atom or a C₁-C₃-alkyl- group, or R-R together represent a -C₂-C₆-alkylene-group,

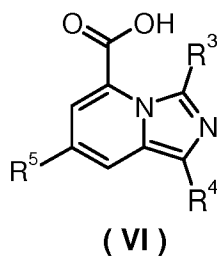
thus providing a compound of general formula (I) :



in which R^1 , R^2 , R^3 , R^4 , and R^5 are as defined for the compounds of general formula (I), *supra*.

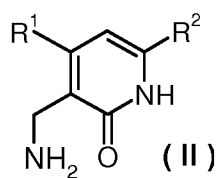
In another preferred embodiment, the present invention relates to a method of preparing compounds of general formula (I), *supra*;

- 5 in which method an intermediate compound of formula (VI):



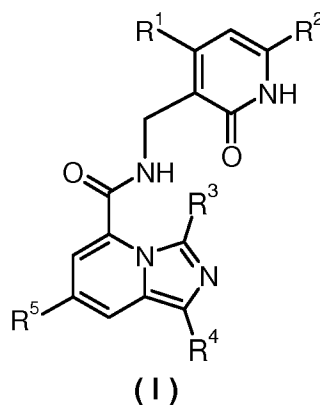
in which R^3 , R^4 , and R^5 are as defined for the compounds of general formula (I), *supra*;

is allowed to react with a compound of formula (II):



- 10 in which R^1 and R^2 are as defined for the compounds of general formula (I), *supra*;

thus providing a compound of general formula (I):

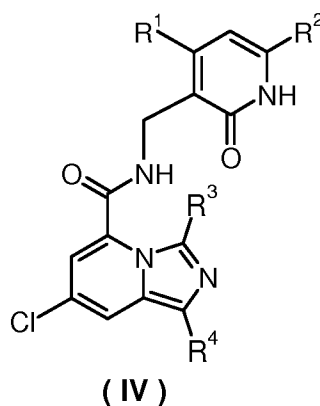


in which R^1 , R^2 , R^3 , R^4 , and R^5 are as defined for the compounds of general formula (I), *supra*.

In accordance with a further aspect, the present invention relates to intermediate compounds which are useful for the preparation of compounds of the present invention of general formula (I),

5 particularly in the method described herein.

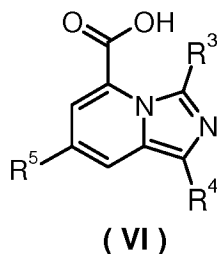
In particular, the present invention relates to intermediate compounds of formula (IV):



10 in which R^1 , R^2 , R^3 , and R^4 are as defined for the compounds of general formula (I), *supra*; as well as to the use and a method of using intermediate compound (IV) for the preparation of compounds of general formula (I).

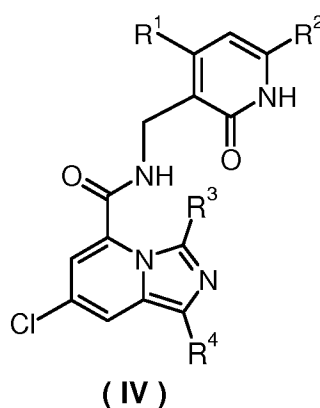
In another preferred embodiment, the present invention relates to intermediate compounds which are useful in the preparation of compounds of the present invention of general formula (I), particularly in the method described herein.

In particular, the present invention further covers compounds of formula (VI):



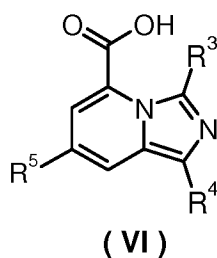
in which R³, R⁴, and R⁵ are as defined for the compounds of general formula (I), *supra*; as well as to the use and the method of using intermediate compound (VI) for the preparation of compounds of general formula (I).

- 5 In accordance with yet another aspect, the present invention relates to the use and a method of using of the intermediate compounds of formula (IV):



in which R¹, R², R³, and R⁴ are as defined for the compounds of general formula (I), *supra*; for the preparation of a compound of general formula (I) as defined *supra*.

- 10 In another preferred embodiment, the present invention covers the use and a method of using of the intermediate compounds of formula (IV):



in which R³, R⁴, and R⁵ are as defined for the compounds of general formula (I), *supra*; for the preparation of a compound of general formula (I) as defined *supra*.

Utility

As discussed in the introduction it has been shown for various tumor types that tumor progression and survival seems to be dependent on PRC2 activation. And thus there is strong evidence that inhibition of EZH2 methylation activity as being a part of the PRC2 complex modulates
5 gene expression and inhibits cell proliferation. PRC2 is widely considered a valuable target for tumor therapy. Consequently compounds inhibiting EZH2 would be useful for the treatment of hyperproliferative disorders, especially in the case of neoplastic disorders, more especially cancer.

The compounds according to general formula (I) have valuable pharmaceutical properties which make them commercially utilizable. In particular the compounds of the formula (I) inhibit PRC2,
10 especially EZH2, its mechanism being explained in the Background section, and exhibit cellular activity. They are expected to be commercially applicable in the treatment of diseases (e.g., characterized in activation of PRC2).

Thus one aspect of the present invention is the use of the compounds of formula (I) for the treatment of diseases.

15 Another aspect of the present invention is a compound of formula (I) for use in the treatment of a disease/diseases.

The compounds of general formula (I) are suitable for prophylaxis and/or treatment of hyperproliferative disorders, for example psoriasis, keloids and other hyperplasias which affect the skin, benign prostate hyperplasias (BPH), solid tumors and haematological tumors.

20 Thus another aspect of the invention is the use of the compounds of formula (I) for prophylaxis and/or treatment of hyperproliferative diseases, especially for treatment of hyperproliferative diseases.

As used herein, "prophylaxis" includes a use of the compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control
25 sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample, when administered to prior to the onset of the disorder or condition.

A further aspect of the invention is the compound of formula (I) for use in the treatment of hyperproliferative diseases.

30 A further aspect is the method of prophylaxis and/or treatment of hyperproliferative diseases comprising administering an effective amount of one or more compound(s) of formula (I), especially a method of treatment of a hyperproliferative disease.

The compounds of formula (I) are also suitable for prophylaxis and/or treatment of benign hyperproliferative diseases, for example endometriosis, leiomyoma and benign prostate hyperplasia.

Thus a further aspect is that the hyperproliferative disease is a benign hyperproliferative disease.

- 5 Another aspect of the present invention is a compound of formula (I) for use in the treatment of cancer . They are particular useful in treating metastatic or malignant tumors.

Thus another aspect of the invention is a method of treatment of cancer comprising administering an effective amount of at least one compound of formula (I) .

- 10 A further aspect of the invention is a method of treatment of metastatic or malignant tumors comprising administering an effective amount of a compound of formula (I).

Another aspect of the invention is the use of a compound of formula (I) for the treatment of solid tumors.

A further aspect of the invention is the compound of formula (I) for use in the treatment of solid tumors.

- 15 A further aspect of the invention is a method of treatment of solid tumors comprising administering an effective amount of a compound of formula (I).

- In accordance with the invention solid tumors that can be treated as, for example, tumors of the breast, the respiratory tract, the brain, the bones, the central and peripheral nervous system, the colon, the rectum, the anus, the reproductive organs (e.g., cervix, ovary, prostate), the
20 gastrointestinal tract, the urogenital tract, the endocrine glands (e.g., thyroid and adrenal cortex), the thyroid gland, the parathyroid gland, the esophagus, the endometrium, the eye, the germ cells, the head and the neck, the kidney, the liver, the larynx and hypopharynx, the lung, the mesothelioma, the pancreas, the prostate, the rectum, the kidney, the small intestine, the skin, the soft tissue, the stomach, the testis, ureter, vagina and vulva and the connective tissue and
25 metastases of these tumors. Malignant neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor.

Still another aspect of the invention is a method of treatment of the tumors mentioned above comprising administering an effective amount of a compound of formula (I).

- 30 Another aspect of the invention is the use of a compound of formula (I) for the treatment of hematological tumors.

A further aspect of the invention is the compound of formula (I) for use in the treatment of hematological tumors.

A further aspect of the invention is a method of treatment of hematological tumors comprising administering an effective amount of a compound of formula (I).

Hematological tumors can be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well as AIDS related malignancies.

Still another aspect of the invention is a method of treatment of the hematological tumors mentioned above comprising administering an effective amount of a compound of formula (I).

10 A further aspect of the invention is a method of administering to a subject having a cancer expressing a mutant EZH2 (e.g., tyrosine 641, alanine 677 and/or alanine 687 mutant EZH2) a therapeutically effective amount of the compound of formula (I), wherein the compound inhibits histone methyltransferase activity of PRC2, thereby treating the cancer.

15 In still another aspect, this invention relates to a method of administering to a subject having a cancer expressing a loss of function mutation in the H3K27 demethylase KDM6A/UTX (e.g., medulloblastoma, bladder cancer, T-cell acute lymphoblastic leukemia) a therapeutically effective amount of the compound of formula (I), wherein the compound inhibits histone methyltransferase activity of PRC2, thereby treating the cancer.

20 Another aspect of the invention is the use of a compound of formula (I) for the treatment of a subject having a cancer with aberrant H3K27 methylation. Examples of aberrant H3K27 methylation may include a genome-wide increase and/or a gene-specific altered distribution of H3K27 mono-, di- or trimethylation within the cancer cell chromatin.

25 Another aspect of the invention is the use of a compound of formula (I) for the treatment of a subject having a cancer with a mutation in a gene of the SWI/SNF chromatin remodeling complex proteins. SWI/SNF complex has been described to antagonizing PRC2 complex activities. Examples of mutations of SWI/SNF chromatin remodeling complex genes are SMARCB1/INI mutations (e.g., found in malignant rhabdoid tumors or atypical teratoid/rhabdoid tumors), ARID1A mutations (e.g., found in endometrial, ovarian, or uterine cancers), SS18-SSX fusion protein caused by the t(X;18)(p11.2;q11.2) translocation in synovial sarcoma, and SMARCA4 30 mutations (e.g., found in lung, bladder, or colorectal cancer).

Breast tumors that can be treated include, for example, mammary carcinoma with positive hormone receptor status, mammary carcinoma with negative hormone receptor status, Her-2-positive mammary carcinoma, hormone receptor- and Her-2-negative mammary carcinoma, BRCA-associated mammary carcinoma and inflammatory mammary carcinoma.

Tumors of the respiratory tract that can be treated include, for example, non-small-cell bronchial carcinoma and small-cell bronchial carcinoma, non-small cell lung cancer, and small cell lung cancer.

5 Brain tumors that can be treated include, for example, glioma, glioblastoma, astrocytoma, meningioma and medulloblastoma.

Tumors of the male reproductive organs that can be treated include, for example, prostate carcinoma, malignant epididymal tumors, malignant testicular tumors and penile carcinoma.

Tumors of the female reproductive organs that can be treated include, for example, endometrial carcinoma, cervical carcinoma, ovarian carcinoma, vaginal carcinoma and vulvar carcinoma.

10 Tumors of the gastrointestinal tract that can be treated include, for example, colorectal carcinoma, anal carcinoma, gastric carcinoma, pancreatic carcinoma, oesophageal carcinoma, gallbladder carcinoma, small-intestinal carcinoma, salivary gland carcinoma, neuroendocrine tumors and gastrointestinal stromal tumors.

15 Tumors of the urogenital tract that can be treated include, for example, urinary bladder carcinoma, renal cell carcinoma, and carcinoma of the renal pelvis and of the urinary tract.

Tumors of the eye that can be treated include, for example, retinoblastoma and intraocular melanoma.

Tumors of the liver that can be treated include, for example, hepatocellular carcinoma and cholangiocellular carcinoma.

20 Tumors of the skin that can be treated include, for example, malignant melanoma, basalioma, spinalioma, Kaposi's sarcoma and Merkel cell carcinoma.

Tumors of the head and neck that can be treated include, for example, laryngeal carcinoma and carcinoma of the pharynx and of the oral cavity.

25 Sarcomas that can be treated include, for example, soft tissue sarcoma, synovial sarcoma, rhabdoid sarcoma and osteosarcoma.

Lymphomas that can be treated include, for example, non-Hodgkin's lymphoma, Hodgkin's lymphoma, cutaneous lymphoma, lymphoma of the central nervous system and AIDS-associated lymphoma.

30 Leukaemias that can be treated include, for example, acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphatic leukaemia, chronic lymphatic leukaemia and hair cell leukaemia.

Advantageously, the compounds of formula (I) can be used for prophylaxis and/or treatment of

Bladder cancer, Brain cancer, Breast cancer, Colorectal cancer, Chronic myelomonocytic leukemia, MLL-rearranged leukemia, Lung adenocarcinomas, Lymphoma, Medulloblastoma, Melanoma, Multiple myeloma, Prostate cancer, Malignant rhabdoid tumors, Synovial sarcoma, Teratoid/rhabdoid tumors, or T-cell acute lymphoblastic leukemia.

5 Thus another aspect of the invention is the use of a compound of formula (I) for the treatment of Bladder cancer, Brain cancer, Breast cancer, Colorectal cancer, Chronic myelomonocytic leukemia, MLL-rearranged leukemia, Lung adenocarcinomas, Lymphoma, Medulloblastoma, Melanoma, Multiple myeloma, Prostate cancer, Malignant rhabdoid tumors, Synovial sarcoma, Teratoid/rhabdoid tumors, or T-cell acute lymphoblastic leukemia.

10 A further aspect of the invention is the compound of formula (I) for use in the treatment of Bladder cancer, Brain cancer, Breast cancer, Colorectal cancer, Chronic myelomonocytic leukemia, MLL-rearranged leukemia, Lung adenocarcinomas, Lymphoma, Medulloblastoma, Melanoma, Multiple myeloma, Prostate cancer, Malignant rhabdoid tumors, Synovial sarcoma, Teratoid/rhabdoid tumors, or T-cell acute lymphoblastic leukemia tumors.

15 A further aspect of the invention is a method of treatment of Bladder cancer, Brain cancer, Breast cancer, Colorectal cancer, Chronic myelomonocytic leukemia, MLL-rearranged leukemia, Lung adenocarcinomas, Lymphoma, Medulloblastoma, Melanoma, Multiple myeloma, Prostate cancer, Malignant rhabdoid tumors, Synovial sarcoma, Teratoid/rhabdoid tumors, T-cell acute lymphoblastic leukemia tumors comprising administering an effective amount of a compound of
20 formula (I).

Particularly advantageously, the compounds of formula (I) can be used for prophylaxis and/or treatment of Breast cancer.

Thus another aspect of the invention is the use of a compound of formula (I) for the treatment of Breast cancer.

25 Another aspect of the invention is the use of the compounds of formula (I) for the production of a medicament for the treatment or prophylaxis of breast cancer.

A further aspect of the invention is the compound of formula (I) for use in the treatment of Breast cancer.

A further aspect of the invention is a method of treatment of Breast cancer comprising
30 administering an effective amount of a compound of formula (I).

Particularly advantageously, the compounds of formula (I) can be used for prophylaxis and/or treatment of mammary carcinoma, particularly for the treatment.

Another aspect of the invention is the use of a compound of formula (I) for the treatment of

mammary carcinoma.

A further aspect of the invention is the compound of formula (I) for use in the treatment of mammary carcinoma.

A further aspect of the invention is a method of treatment of mammary carcinoma comprising
5 administering an effective amount of a compound of formula (I).

The present application further provides the compounds of formula (I) for use as medicaments, especially for prophylaxis and/or treatment of neoplastic disorders.

The invention further provides for the use of the compounds of formula (I) for production of a medicament.

10 A further aspect of the invention is a method of using the compound of formula (I) for the production of a pharmaceutical composition.

The present invention further provides for the use of the inventive compounds for production of a medicament for prophylaxis and/or treatment of neoplastic disorders.

The present application further provides for the use of the inventive compounds for prophylaxis
15 and/or treatment of neoplastic disorders.

The invention further provides for the use of the inventive compounds for treatment of benign hyperplasias, inflammation disorders, autoimmune disorders, sepsis, viral infections, vascular disorders and neurodegenerative disorders.

Pharmaceutical Compositions

20 A further aspect of the invention are pharmaceutical compositions comprising at least a compound of general formula (I) together with one or more excipientspharmaceutically acceptable exipients, especially for the treatment and/or prophylaxis of the diseases mentioned above.

Thus in another aspect the invention relates to a method of treatment according to any one of a method disclosed herein comprising administering a pharmaceutical composition comprising a
25 compound of general formula (I) according to claim 1 together with one or more pharmaceutically acceptable excipients.

Furthermore, the compounds of general formula (I) may be utilized, as such or in compositions, in research and diagnostics, or as analytical reference standards, and the like, which are well known in the art.

30 The compounds according to the invention can act systemically and/or locally.

The administration of the compounds, pharmaceutical compositions or combinations according to

the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, parenteral, pulmonal, nasal, sublingual, lingual, buccal, rectal, dermal, topical, transdermal, conjunctival or otic route, or as an implant or stent.

- 5 For these administration routes, it is possible to administer the compounds according to the invention in suitable application forms.

Suitable for oral administration are administration forms which work as described in the prior art and deliver the compounds according to the invention rapidly and/or in modified form, which comprise the compounds according to the invention in crystalline and/or amorphous and/or
10 dissolved form, such as, for example, tablets (coated or uncoated, for example tablets provided with enteric coatings or coatings whose dissolution is delayed or which are insoluble and which control the release of the compound according to the invention), tablets which rapidly decompose in the oral cavity, or films/wafers, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or
15 solutions.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenously, intraarterially, intracardially, intraspinally or intralumbally) or with inclusion of absorption (for example intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Administration forms suitable for parenteral administration are, inter alia,
20 preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

Examples suitable for the other administration routes are pharmaceutical forms for inhalation (inter alia powder inhalers, nebulizers), nasal drops/solutions/sprays; tablets to be administered lingually, sublingually or buccally, films/wafers or capsules, suppositories, preparations for the eyes or ears,
25 vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, microemulsions, ointments, creams, transdermal therapeutic systems (such as plasters, for example), milk, pastes, foams, dusting powders, implants or stents.

The compounds according to the invention can be converted into the stated administration forms. This can take place in a manner known per se by mixing with inert, nontoxic, pharmaceutically
30 suitable excipients. These excipients include, inter alia,

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

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

example, Kollidon[®]), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),

- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- 5 • penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- 10 • colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore provides medicaments or pharmaceutical composition comprising at least one compound according to the invention, usually together with one or more
15 inert, nontoxic, pharmaceutically suitable excipient, and their use for the purposes mentioned above.

When the compounds of the present invention are administered as pharmaceuticals, to humans or animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (more preferably 0.5% to 90%) of active ingredient in combination with one or
20 more inert, nontoxic, pharmaceutically suitable excipient.

Regardless of the route of administration selected, the compounds of the invention of general formula (I) and/or the pharmaceutical composition of the present invention are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

25 Actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions of the invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient without being toxic to the patient, depending on his/her actual weight.

The pharmaceutical composition can be administered in a single dose per day or in multiple
30 subdoses, for example, 2 to 4 doses per day. A single dose unit of the pharmaceutical composition can contain, e.g., from 0.01 mg to 4000 mg, preferably 0.1 mg to 2000 mg, more preferably 0.5 to 1500 mg, most preferably 1 to 500 mg, of the active compound.

The compounds of the present invention can be used alone or, if required, in combination with one or more further pharmacologically active substances, provided that this combination does not lead to undesirable and unacceptable side effects.

5 The present invention therefore further provides medicaments and compositions comprising an inventive compound and one or more further active ingredients, especially for prophylaxis and/or treatment of the aforementioned disorders.

For example, the compounds of formula (I) can be combined with known antihyperproliferative, cytostatic or cytotoxic chemical and biological substances for treatment of cancer. The combination of the compounds of formula (I) with other substances commonly used for cancer treatment, or else
10 with radiotherapy, is particularly appropriate.

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
15 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
20 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
25 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 term “(chemotherapeutic) anti-cancer agents”, includes but is not limited to

- (i) alkylating/carbamylating agents such as Cyclophosphamid (Endoxan®), Ifosfamid (Holoxan®),
30 Thiotepe (Thiotepe Lederle®), Melphalan (Alkeran®), or chloroethylnitrosourea (BCNU);
- (ii) platinum derivatives like cisplatin (Platinex® BMS), oxaliplatin (Eloxatin®), satraplatin or carboplatin (Cabroplat® BMS);
- (iii) antimitotic agents / tubulin inhibitors such as vinca alkaloids (vincristine, vinblastine, vinorelbine), taxanes such as Paclitaxel (Taxol®), Docetaxel (Taxotere®) and analogs as

- well as new formulations and conjugates thereof (like the nanoparticle formulation Abraxane® with paclitaxel bound to albumin), epothilones such as Epothilone B (Patupilone®), Azaepothilone (Ixabepilone®) or Sagopilone;
- (iv) topoisomerase inhibitors such as anthracyclines (exemplified by Doxorubicin / Adriblastin®),
- 5 epipodophyllotoxins (exemplified by Etoposide / Etopophos®) and camptothecin and camptothecin analogs (exemplified by Irinotecan / Camptosar® or Topotecan / Hycamtin®);
- (v) pyrimidine antagonists such as 5-fluorouracil (5-FU), Capecitabine (Xeloda®),
- Arabinosylcytosine / Cytarabin (Alexan®) or Gemcitabine (Gemzar®);
- 10 (vi) purine antagonists such as 6-mercaptopurine (Puri-Nethol®), 6-thioguanine or fludarabine (Fludara®) and
- (vii) folic acid antagonists such as methotrexate (Famitrexat®) or premetrexed (Alimta®).

The term “target specific anti-cancer agent”, includes but is not limited to

- (i) kinase inhibitors such as e.g. Imatinib (Glivec®), ZD-1839 / Gefitinib (Iressa®), Bay43-9006
- 15 (Sorafenib, Nexavar®), SU11248 / Sunitinib (Sutent®), OSI-774 / Erlotinib (Tarceva®), Dasatinib (Sprycel®), Lapatinib (Tykerb®), or, see also below, Vatalanib, Vandetanib (Zactima®) or Pazopanib;
- (ii) proteasome inhibitors such as PS-341 / Bortezomib (Velcade®);
- (iii) histone deacetylase inhibitors like SAHA (Zolinza®), PXD101, MS275, MGCD0103,
- 20 Depsipeptide / FK228, NVP-LBH589, Valproic acid (VPA), CRA / PCI 24781, ITF2357, SB939 and butyrates
- (iv) heat shock protein 90 inhibitors like 17-allylaminogeldanamycin (17-AAG) or 17-dimethylaminogeldanamycin (17-DMAG);
- (v) vascular targeting agents (VTAs) like combretastin A4 phosphate or AVE8062 / AC7700 and
- 25 anti-angiogenic drugs like the VEGF antibodies, such as Bevacizumab (Avastin®), or KDR tyrosine kinase inhibitors such as PTK787 (Vatalanib®) or Vandetanib (Zactima®) or Pazopanib;
- (vi) monoclonal antibodies such as Trastuzumab (Herceptin®), Rituximab (MabThera / Rituxan®), Alemtuzumab (Campath®), Tositumomab (Bexxar®), C225/ Cetuximab
- 30 (Erbix®), Avastin (see above) or Panitumumab (Vectibix®) as well as mutants and conjugates of monoclonal antibodies, e.g., Gemtuzumab ozogamicin (Mylotarg®) or Ibritumomab tiuxetan (Zevalin®), and antibody fragments;
- (vii) oligonucleotide based therapeutics like G-3139 / Oblimersen (Genasense®) or the DNMT1 inhibitor MG98;
- 35 (viii) Toll-like receptor / TLR 9 agonists like Promune®, TLR 7 agonists like Imiquimod (Aldara®) or Isatoribine and analogues thereof, or TLR 7/8 agonists like Resiquimod as

well as immunostimulatory RNA as TLR 7/8 agonists;

(ix) protease inhibitors; (x) hormonal therapeutics such as anti-estrogens (e.g. Tamoxifen or Raloxifen), anti-androgens (e.g. Flutamide or Casodex), LHRH analogs (e.g. Leuprolide, Goserelin or Triptorelin) and aromatase inhibitors (e.g. Femara, Arimedes or Aromasin).

- 5 Other “target specific anti-cancer agents” include bleomycin, retinoids such as all-trans retinoic acid (ATRA), DNA methyltransferase inhibitors such as 5-Aza-2'-deoxycytidine (Decitabine, Dacogen®) and 5-azacytidine (Vidaza®), alanosine, cytokines such as interleukin-2, interferons such as interferon $\alpha 2$ or interferon- γ , bcl2 antagonists (e.g. ABT-737 or analogs), death receptor agonists, such as TRAIL, DR4/5 agonistic antibodies, FasL and TNF-R agonists (e.g. TRAIL
10 receptor agonists like mapatumumab or lexatumumab).

Specific examples of anti-cancer agents include, but are not limited to 131I-chTNT, abarelix, abiraterone, aclarubicin, afatinib, aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, anecstim, anethole dithiolethione, angiotensin II, antithrombin III,
15 aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, Brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolinate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab,
20 chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftotox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine, doxorubicin,
25 doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric
30 acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon
35 beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, lasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuporelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin,

lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methyl aminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone,

5 mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetate, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, obinutuzumab, octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilofitin, oxaliplatin, oxycodone, oxymetholone,

10 p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglucan, polyestradiol phosphate, polyvinylpyrrolidone +

15 sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib, regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin, romiplostim, romurtide, roniciclib, samarium (153Sm) lexidronam,

20 sargramostim, satumomab, secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa,

25 tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic

30 acid, zorubicin..

In another aspect, the compounds of formula (I) can be combined with antibodies, for example aflibercept, alemtuzumab, bevacizumab, brentuximab, catumaxomab, cetuximab, denosumab, edrecolomab, gemtuzumab, ibritumomab, ipilimumab, ofatumumab, panitumumab, pertuzumab, rituximab, tositumumab or trastuzumab, and also with recombinant proteins.

35 More particularly, the compounds of formula (I) can be used in combination with treatments directed against angiogenesis, for example axitinib, bevacizumab, cediranib, copanlisib, lenalidomide, pomalidomide, regorafenib, sorafenib, sunitinib, or thalidomide.

Combinations with antihormones and steroidal metabolic enzyme inhibitors may also be suitable.

Generally, the following aims can be pursued with the combination of the inventive compounds with other cytostatically or cytotoxically active agents:

- improved efficacy in slowing the growth of a tumour, in reducing its size or even in completely eliminating it, compared with treatment with an individual active ingredient;
- the possibility of using the chemotherapeutics used in a lower dosage than in the case of monotherapy;
- the possibility of a more tolerable therapy with fewer side effects compared with individual administration;
- the possibility of treatment of a broader spectrum of neoplastic disorders;
- the attainment of a higher rate of response to the therapy;
- a longer survival time of the patient compared with present standard therapy.

In addition, the compounds of the invention can also be used in conjunction with radiotherapy and/or surgical intervention.

Experimental Section

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 crystallisation. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash chromatography, using for example pre-packed silica gel cartridges, *e.g.* Biotage®SNAP cartridges containing stationary phases such as silica gel (KP-Sil cartridges), NH-functionalised media (KP-NH cartridges) or reversed phase C18 spherical silica (KP-C18-HS cartridges), in combination with a suitable chromatographic system such as an Isolera system (Biotage) and eluents such as, for example, gradients of hexane/ethyl acetate or DCM/methanol. If not stated otherwise, silica gel has been used herein as stationary phase in flash chromatography. 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 ionisation mass spectrometer in combination with a suitable pre-packed reverse phase column and eluants such as, for example, gradients of water and acetonitrile which may contain additives such

as trifluoroacetic acid, formic acid or aqueous ammonia.

Optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, 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 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.

The IUPAC names of the examples and intermediates were generated using the program 'ACD/Name batch version 12.01' from ACD LABS, and were adapted if needed.

General Methods – UPLC and HPLC conditions**UPLC Conditions 1.1 - “short-basic”**

- 5 **Column:** XBridge BEH C18 2.5 µm, 2.1 mm x 50 mm
 Eluent: A: 10 mM aqueous ammonium hydrogen carbonate (pH10); B: acetonitrile
 Gradient: 0 – 1.0 min 2-98% B, 1.0 – 1.2 min 98% B

UPLC Conditions 1.2 - “short-basic”

- 10 **Column:** XBridge C18 2.5 µm, 2.1 mm x 20 mm IS
 Eluent: A: 10 mM aqueous ammonium hydrogen carbonate (pH10); B: acetonitrile
 Gradient: 0 – 2.0 min 0-95% B, 2.0 – 2.6 min 95% B

15 **LCMS Conditions 2.1:**

Instrument: Waters Acquity LCT

Column: Phenomenex Kinetex C18 2.6 µm, 50 mm x 2.1 mm

Eluents: A: 0.05% aqueous formic acid; B: acetonitrile + 0.05% formic acid

- 20 **Gradient:** 0 – 0.2 min 98% A, 0.2 – 1.7 min: 98-10% A, 1.7 – 1.9 min 10% A, 1.9 – 2.0 min: 10-98% A, 2.0 - 2.5 min 98% A; flow: 1,3 ml/min; temperature: 60°C; UV detection: 200-400 nm.

LCMS Conditions 2.2:

- 25 **Instrument:** Waters Acquity Platform Agilent

Column: Waters BEHC 18 1,7 µm, 50 mm x 2,1 mm

Eluents: A: 0.05% aqueous formic acid; B: acetonitrile + 0.05% formic acid

Gradient: 0 – 0.2 min 98% A, 0.2 – 1.7 min: 98-10% A, 1.7 – 1.9 min 10% A, 1.9 – 2.0 min: 10-98% A, 2.0 - 2.5 min 98% A; flow: 1,3 ml/min; temperature: 60°C; UV detection: 200-400 nm.

30

LCMS Conditions 2.3:

Instrument: Waters Acquity Platform SQD

Column: Waters BEHC 18 1,7µm, 50 mm x 2,1 mm

- 35 **Eluents:** A: 0.05% aqueous formic acid; B: acetonitrile + 0.05% formic acid

Gradient:

 0 – 0.2 min 98% A, 0.2 – 1.7 min: 98-10% A, 1.7 – 1.9 min 10% A, 1.9 – 2.0 min: 10- 98% A, 2.0 - 2.5 min 98% A; flow: 1,3 ml/min; temperature: 60 °C; UV detection: 200-400 nm.

LCMS Conditions 2.4:

Instrument: UPLC Acquity (Waters) with PDA Detector und Waters ZQ mass spectrometer

5 **Column:** Acquity BEH C18 1.7 µm 2.1 mm x 50 mm

Eluents: A: 0.1 % aqueous formic acid; 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; UV detection: 210-400 nm

10 **LCMS Conditions 2.5**

Instrument: Waters Acquity UPLC-MS SQD

Column: Acquity UPLC BEH C18 1.7 µm 50 mm x 2.1 mm

Eluents: A: 0.1 % aqueous formic acid; B: acetonitrile

Gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min

15 **Temperature:** 60 °C; UV detection: 210-400 nm

LCMS Conditions 2.6

Instrument: Waters Acquity UPLC-MS SQD

Column: Acquity UPLC BEH C18 1.7 µm 50 mm x 2.1 mm

20 **Eluents:** A: water + 0.2% aqueous ammonia (32%); B: acetonitrile

Gradient: 0 - 1.6 min 1-99% B, 1.6 - 2.0 min 99% B; flow: 0.8 ml/min

Temperatur: 60 °C; UV detection: 210-400 nm.

Preparative HPLC conditions 1 (acidic)

25

Instrument: Waters Autopurificationsystem SQD

Column: Waters XBrigde C18 5µm 100x30mm

Eluents: A: 0.1% aqueous formic acid; B: acetonitrile

Gradient: 0,00 – 0.50 min 5% B (25ml/min), 0.51 – 5.50 min 10-100% B (70 ml/min), 5.51 – 6.50

30 min 100% B (70 ml/min); temperature: Rt; UV detection: 210-400 nm

Preparative HPLC conditions 2 (basic)

Instrument: Waters Autopurificationsystem SQD

35 **Column:** Waters XBrigde C18 5µm 100x30mm

Eluents: A: water + 0.2% aqueous ammonia (32%); B: acetonitrile

Gradient: 0.00 – 0.50 min 5% B (25mL/min), 0.51 – 5.50 min 10-100% B (70 mL/min), 5.51 –

6.50 min 100% B (70 mL/min); temperature: Rt; UV detection: 210-400 nm

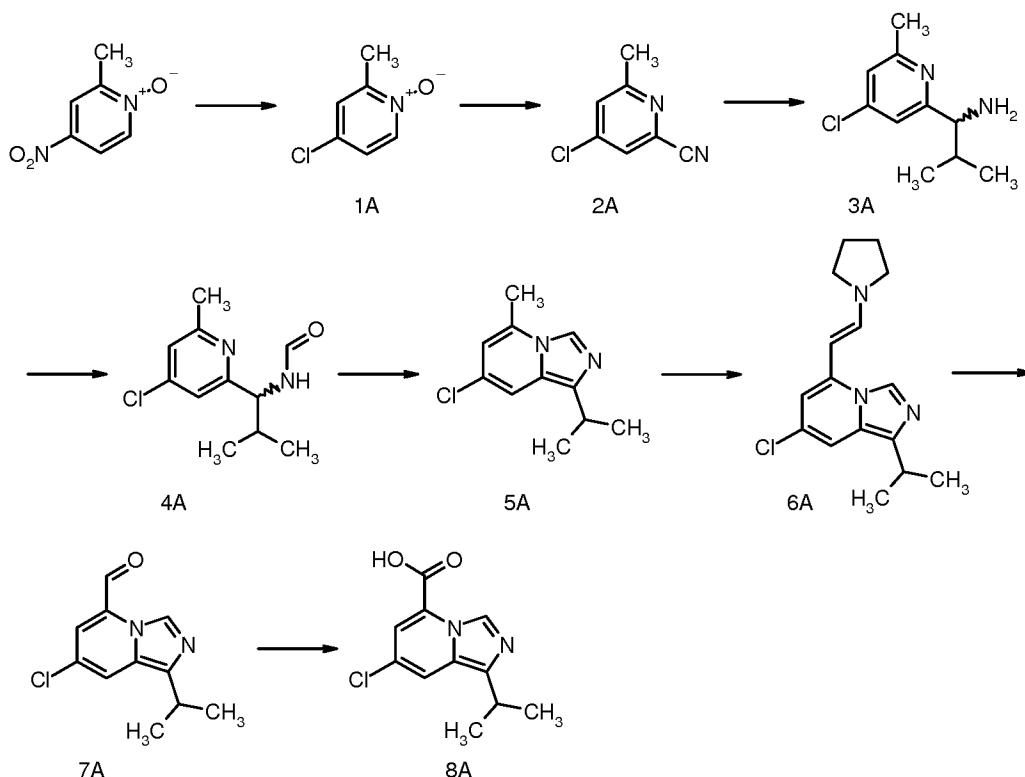
The following table provides a list of abbreviations used in the experimental part.

5

Abbreviation	Meaning
anh	anhydrous
bp.	boiling point
br.	broad signal (in NMR data)
brine	saturated aqueous sodium chloride
d	day(s)
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
ESI	electrospray ionisation
Fmoc	[(9H-fluoren-9-ylmethoxy)carbonyl]
h	hour(s)
HPLC, LC	high performance liquid chromatography
IMS	industrial methylated spirit (denaturated alcohol; denaturated ethanol)
m/z	mass-to-charge ratio (in mass spectrum)
min	minute(s)
MS	mass spectroscopy
neg	negative
NMR	nuclear magnetic resonance
pos	positive
ppm	Chemical shift δ in parts per million
R _t	retention time
SFC	Supercritical Fluid Chromatography
THF	tetrahydrofuran
TLC	thin layer chromatography

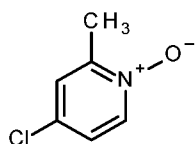
Synthesis of Intermediates – Part 1 - Imidazopyridine cores

10 Synthesis of 7-Chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylic acid 8A (Scheme A)



Scheme A

5 Intermediate 1A - 4-Chloro-2-methylpyridine 1-oxide

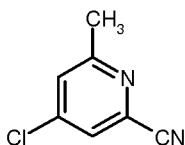


A mixture of 2-methyl-4-nitropyridine 1-oxide (CAS 696-08-2, 168.0 g, 1.09 mol), sodium chloride (191 g, 3.27 mol), conc. aqueous hydrochloric acid (400 ml) and benzyltributylammonium chloride (3.4 g, 11.0 mmol) in acetonitrile (1.7 l) was stirred at reflux for 72 h. The reaction mixture was cooled to -10 °C and basified by the addition of aqueous sodium hydroxide (220 g in 300 ml) whilst maintaining a temperature of < 10 °C. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 750 ml). The dichloromethane layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was crystallized from 2-propanol, the crystals were filtered off to give unreacted starting material. The mother liquors were concentrated and the residue was purified by flash chromatography (silicagel, 0-15% methanol in ethyl acetate) to give intermediate **1A** (128.6 g).

^1H NMR (400 MHz, CDCl_3) δ [ppm] = 8.16 (d, 1H), 7.25 (d, 1H), 7.12 (dd, 1H), 2.48 (s, 3H).

Intermediate 2A - 4-Chloro-6-methylpyridine-2-carbonitrile

5

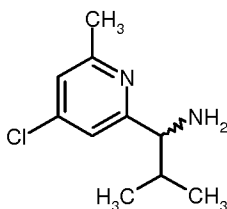


To a solution of intermediate **1A** (128.0 g, 889 mmol) and triethylamine (260 ml) in propionitrile (1.5 l) was added trimethylsilyl cyanide (334 ml, 2.67 mol). The mixture was stirred at reflux for 10 26 h then left to stand at room temperature for 18 h. The reaction was quenched by the addition of 30% aqueous potassium carbonate solution and the layers were separated. The organic layer was washed with 10% aqueous potassium carbonate solution, brine, dried over magnesium sulfate, filtered and concentrated. The resulting dark solid was recrystallized from hot isopropanol (150 ml) and water (300 ml) to give intermediate **2A** (114.3 g, 84%).

15

^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.51 (d, 1H), 7.39 (d, 1H), 2.59 (s, 3H).

Intermediate 3A – *rac*-1-(4-Chloro-6-methylpyridin-2-yl)-2-methylpropan-1-amine



20

To a solution of intermediate **2A** (114 g, 745 mmol) in tetrahydrofuran (1.5 l) was added isopropyl magnesium chloride (2M, 0.48 l, 968 mmol) dropwise, at -78 °C. After the addition was complete the mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was then cooled to 0 °C and methanol (0.5 l) was added over a period of 10 min. The mixture was then 25 warmed to room temperature and sodium borohydride (16.9 g, 447 mmol) was added portionwise over a period of 30 min. The mixture was then stirred at room temperature for 18 h and the reaction was then stopped by the addition of ice. The mixture was concentrated; then, dichloromethane was

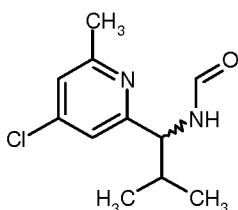
added followed by celite. The mixture was filtered, washed with dichloromethane and the layers separated. The organic layer was dried and concentrated. The residue was purified by flash chromatography (0-15% methanol in ethyl acetate) to give intermediate **3A** (78.5 g, 53%) as a black oil.

5

^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.07 (d, 1H), 7.00 (d, 1H), 3.64 (d, 1H), 2.47 (s, 3H), 2.02 (sept, 1H), 1.68 (bs, 2H), 0.91 (d, 3H), 0.82 (d, 3H).

Intermediate 4A – *rac*-N-[1-(4-Chloro-6-methylpyridin-2-yl)-2-methylpropyl]formamide

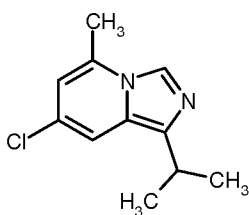
10



A mixture of intermediate **3A** (78.5 g, 394 mmol) and ethyl formate (200 ml) was heated at reflux for 2 h then cooled to room temperature. The mixture was concentrated and subjected to repeated
15 azeotropic distillation with toluene to give intermediate **4A** (87.0 g, 97%) as a dark oil.

^1H NMR (300 MHz, CDCl_3) δ [ppm] = 8.27 (s, 1H), 7.05 (s, 1H), 7.00 (s, 1H), 4.88 (m, 1H), 2.50 (s, 3H), 2.11 (sept., 1H), 0.92 (d, 3H), 0.84 (d, 3H).

20 **Intermediate 5A - 7-Chloro-5-methyl-1-(propan-2-yl)imidazo[1,5-a]pyridine**

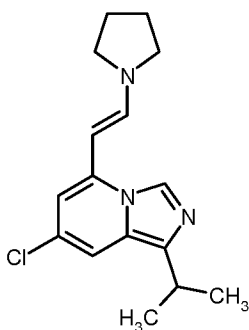


To a solution of intermediate **4A** (87.0 g, 383 mmol) in toluene (800 ml) was added phosphorus
25 oxychloride (POCl_3 ; 43 ml, 460 mmol) portionwise at 100 °C, over a period of 10 min. Once the addition was complete, the mixture was stirred at 100 °C for 1 h and then concentrated. The resultant oil was added carefully to a solution of 10% aqueous sodium carbonate (1 l) and dichloromethane (1 l). The layers were then separated and the aqueous layer was extracted with

dichloromethane (2 x 750 ml). The organic layers were combined, washed with brine, dried over magnesium sulfate and concentrated to give intermediate **5A** (76.0 g, 95%) as a dark solid.

¹H NMR (300 MHz, CDCl₃) δ [ppm] = 7.91 (s, 1H), 7.34 (s, 1H), 6.31 (s, 1H), 3.26 (sept., 1H),
5 2.51 (s, 3H), 1.37 (d, 6H).

Intermediate 6A - 7-Chloro-1-(propan-2-yl)-5-[(E)-2-(pyrrolidin-1-yl)ethenyl]imidazo[1,5-a]pyridine



10

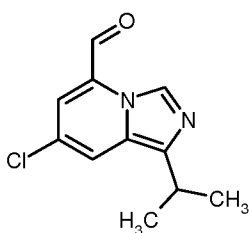
A mixture of intermediate **5A** (76.0 g, 364 mmol), pyrrolidine (91 ml, 1.09 mol) and *N,N*-dimethylformamide dimethyl acetal (96 ml, 727 mmol) was stirred at reflux for 18 h. The mixture was cooled and added to ice-cold water (1.5 kg). The mixture was stirred for 1 h. The resulting solid was filtered, triturated with diethyl ether and dried to give intermediate **6A** (102.8 g, 97%).

15

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 8.00 (s, 1H), 7.32 (d, 1H), 7.06 (d, 1H), 6.24 (d, 1H), 4.91 (s, 1H), 4.87 (m, 4H), 3.33 (m, 4H), 3.20 (sept., 1H), 1.34 (d, 6H).

Intermediate 7A - 7-Chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carbaldehyde

20

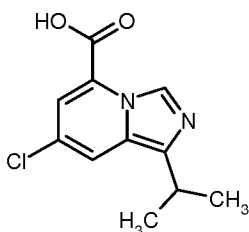


To a solution of intermediate **6A** (83.8 g, 289 mmol) in tetrahydrofuran (1.5 l) and water (300 ml) was added sodium periodate (123.7 g, 578 mmol) portionwise, at 0 °C. After the addition was complete, the mixture was stirred at room temperature for 3 h. The mixture was then filtered
25 through a pad of celite, and the filter cake was then washed thoroughly with ethyl acetate. The

filtrate was concentrated and the residue was poured into saturated aqueous sodium bicarbonate solution (1.0 l), which was subsequently extracted with ethyl acetate (3 x 500 ml). The organic layers were combined, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by flash chromatography (20% ethyl acetate in heptane) to give intermediate **7A** (34.7 g, 54%).

^1H NMR (400 MHz, CDCl_3) δ [ppm] = 9.79 (s, 1H), 9.35 (s, 1H), 7.79 (s, 1H), 7.23 (s, 1H), 3.32 (sept, 1H), 1.39 (d, 6H).

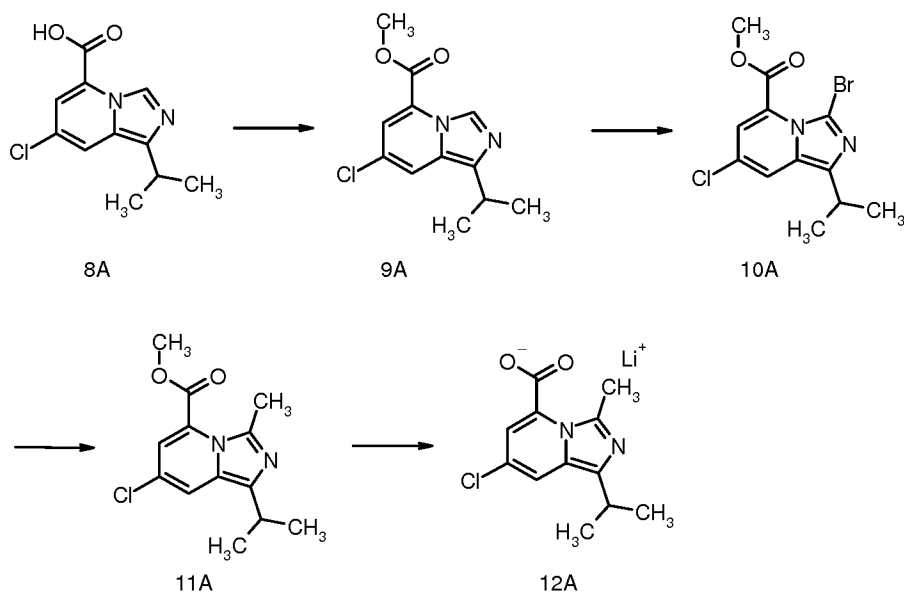
10 Intermediate **8A** - 7-Chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylic acid



To a solution of intermediate **7A** (14.0 g, 62.9 mmol) in formic acid (280 ml) was added 50% aqueous hydrogen peroxide (4.5 ml, 66.0 mmol) dropwise at 5 °C over a period of 15 min. The mixture was then allowed to warm to room temperature and stirred for 18 h – during the day the reaction mixture was cooled occasionally to keep temperature below 22 °C as the reaction was slightly exothermic. The mixture was then cooled to 5 °C and carefully quenched by the addition of brine (300 ml) (an exothermia was observed on small scale when the brine was added in one portion at room temperature which subsequently reduced the yield). The mixture was then extracted with chloroform/2-isopropanol (7:3 mixture, 1 x 500 ml and 2 x 250 ml). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to give a brown solid which was triturated with diethyl ether, filtered, washed and dried to give intermediate **8A** as a brown/green solid (14.5 g, 97%).

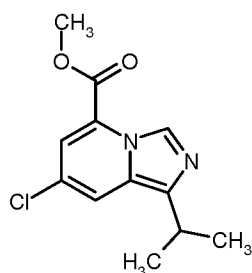
^1H NMR (400 MHz, DMSO-d_6) δ [ppm] = 9.60 (s, 1H), 8.35 (s, 1H), 7.61 (s, 1H), 3.51 (sept, 1H), 1.29 (d, 6H).

Synthesis of lithium 7-chloro-3-methyl-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylate **12A**
(Scheme B)



Scheme B

5 Intermediate 9A - Methyl 7-chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylate

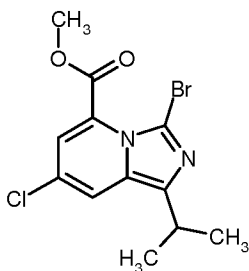


To a solution of intermediate **8A** (1.1 g, 4.61 mmol) in dimethylformamide 23 ml and potassium carbonate (1.9 g, 13.83 mmol) was added iodomethane (0.57 ml, 9.22 mmol) and stirred for 18 h. The reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with brine (40 ml) and the organic layer was collected, dried over sodium sulfate, filtered and concentrated *in vacuo* (azeotrope with toluene) to yield intermediate **9A** as a black crystalline solid, 1.15 g (79% yield, 80% purity).

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.39 (d, 6H), 3.29 (sept, 1H), 4.00 (s, 3H), 7.49 (d, 1H), 7.68 (d, 1H), 9.20 (s, 1H).

UPLC-MS (conditions 1.1): R_t = 0.84 min, 94%. MS (ESIpos): m/z = 253 (M+H)⁺.

Intermediate 10A - Methyl 3-bromo-7-chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylate



5

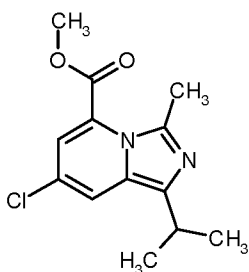
To intermediate **9A** (1.15 g, 4.55 mmol) in DMF (11.5 ml) was added *N*-bromosuccinimide (0.81 g, 4.55 mmol) and the reaction mixture was stirred for 2 h. Brine (10 ml) was added and the product extracted into ethyl acetate (3 x 20 ml). The organic layer was washed with saturated sodium hydrogen carbonate solution (20 ml) and dried over sodium sulfate, filtered and the solvent removed to yield a black oil. Purification by dry flash chromatography was performed (eluent: 1:4 ethyl acetate/heptanes) to yield intermediate **10A** as a yellow oil, 1.15 g (76%).

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.34 (d, 6H), 3.20 (sept, 1H), 4.00 (s, 3H), 6.89 (d, 1H), 7.50 (d, 1H).

15

UPLC-MS (conditions 1.1): R_t = 0.91 min, 91.16%. MS (ESIpos): m/z = 333 (M+H)⁺.

Intermediate 11A - Methyl 7-chloro-3-methyl-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylate



20

To intermediate **10A** (1.15 g, 3.47 mmol) in degassed dioxane (20 ml) was added water (125 μl, 6.94 mmol), sodium carbonate (368 mg, 6.94 mmol), tetrakis(triphenylphosphine)palladium(0) (400 mg, 0.347 mmol) and trimethylboroxine (970 μl, 6.94 mmol). The reaction mixture was heated at 110 °C (oil bath temperature) under argon for 18 h. The reaction mixture was cooled to room temperature then brine solution (20 ml) was added and the crude product was extracted with ethyl acetate (3 x 50 ml). The organic layers were combined, dried over sodium sulfate, filtered and the solvent evaporated *in vacuo* to yield a crude orange oil which was purified by flash

25

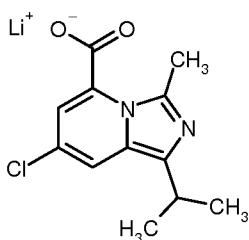
chromatography (eluent: 1:9, 1:4, 1:3 ethyl acetate/heptanes) to yield intermediate **11A** as a yellow oil, 538 mg (58%).

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.35 (d, 6H), 2.52 (s, 3H), 3.22 (sept, 1H), 3.98 (s, 3H),
5 7.02 (d, 1H), 7.52 (d, 1H).

UPLC-MS (conditions 1.2): R_t = 1.96 min, 95%. MS (ESIpos): m/z = 267 (M+H)⁺.

Intermediate 12A - Lithium 7-chloro-3-methyl-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylate

10

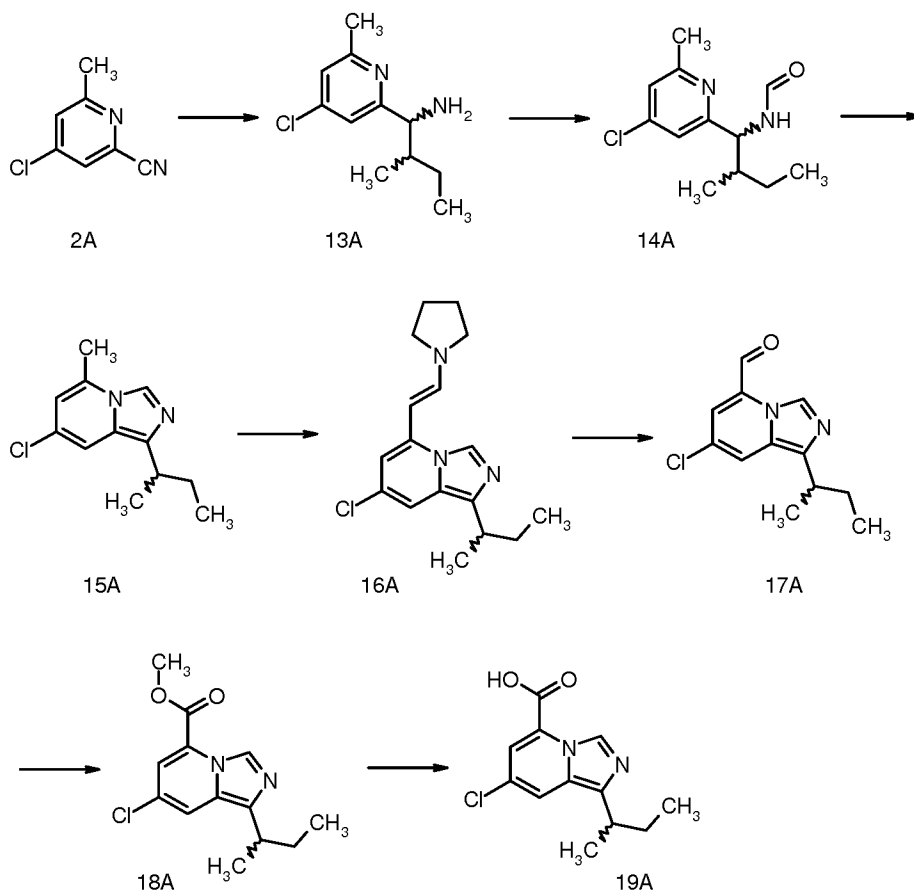


To Intermediate **11A** (538 mg, 2.02 mmol) in tetrahydrofuran (5 ml) was added lithium hydroxide (93 mg, 2.22 mmol) in water (5 ml). The reaction mixture was stirred for 1 hour, then the solvent
15 was evaporated *in vacuo* to give intermediate **12A** as a straw coloured solid, 530 mg (96 %).

¹H NMR (400 MHz, DMSO) δ [ppm] = 1.19 (d, 6H), 2.49 (s, 3H), 3.18 (sept, 1H), 6.10 (d, 1H), 7.36 (d, 1H).

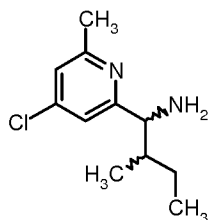
UPLC-MS (conditions 1.2): R_t = 1.41 min, >90%. MS (ESIpos): m/z = 253 (M+H)⁺.

20 **Synthesis of *rac*-1-sec-butyl-7-chloroimidazo[1,5-a]pyridine-5-carboxylic acid – intermediate 19A**
(Scheme C)



Scheme C

Intermediate 13A - 1-(4-chloro-6-methylpyridin-2-yl)-2-methylbutan-1-amine



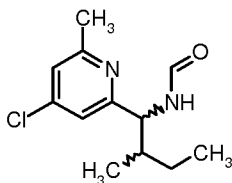
5

4-chloro-6-methylpyridine-2-carbonitrile (CAS 104711-65-1, 45 g, 295 mmol) was dissolved in tetrahydrofuran (700 ml). The mixture was cooled to -60°C and isobutyl magnesium chloride solution (25% w/w in THF, 180 g, 384 mmol) was added dropwise. The mixture was stirred for two hours at room temperature. The mixture was adjusted to 0 °C and methanol (230 ml) was added dropwise. Sodium borohydride (7 g, 177 mmol) was added to the mixture portionwise. The solution was stirred one hour at 0 °C. The solution was poured into an ice/water mixture (1.3 l) and the mixture was stirred overnight at room temperature. Dichloromethane (1.5 l) was added and the resulting emulsion was filtered over Celite. The aqueous layer was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and concentrated to give a black oil (62.2 g). The crude product was purified by column chromatography to give several batches of the

expected product as in a combined yield of 50% as a mixture of diastereomers.

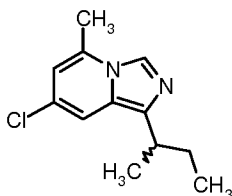
¹H NMR (300 MHz, CDCl₃) δ [ppm] = 7.28 (s, 1H), 7.03 (s, 1H), 3.85 (isomer 1) and 3.73 (isomer 2) (d, 1H), 2.51 (s., 3H), 1.70 – 1.90 (isomer 1) and 1.11 - 1.29 (isomer 2) (m, 2H), 1.52 – 1.67 (isomer 2) and 1.33 – 1.49 (isomer 1) (m, 1 H), 0.80 - 1.01 (m, 3H), 0.74 – 0.88 (m, 3H).

Intermediate 14A – *rac*-N-[1-(4-chloro-6-methylpyridin-2-yl)-2-methylbutyl]formamide



10 1-(4-chloro-6-methylpyridin-2-yl)-2-methylbutan-1-amine (intermediate **13A**) (31.5 g, 148 mmol) was mixed with formic acid (83.7 ml, 2.2 mol) and the solution was heated at 100°C for 1 h. The mixture was allowed to cool to room temperature and concentrated to dryness. The resulting product was co-evaporated twice with toluene. A mixture of dichloromethane (400 ml) and an aqueous saturated sodium bicarbonate solution (400 ml) were added. The mixture was stirred until
15 gas evolution had ceased. The organic layer was collected and the aqueous phase was further extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give the expected product (31.5 g, 88%), which was used in the subsequent step without further purification.

20 **Intermediate 15A – *rac*-1-sec-butyl-7-chloro-5-methylimidazo[1,5-a]pyridine**



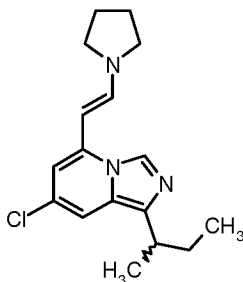
N-[1-(4-chloro-6-methylpyridin-2-yl)-2-methylbutyl]formamide (intermediate **14A**) (31.5 g, 131 mmol) was dissolved in toluene (400 ml). Phosphorus oxychloride (14.6 ml, 157 mmol) was added
25 and the solution was stirred 2 hours at reflux temperature. A TLC analysis (silica gel, heptane/ethyl acetate 1/1) indicated that the reaction was finished. The mixture was allowed to cool to room temperature and concentrated to dryness. A mixture of dichloromethane (400 ml) and an aqueous saturated sodium bicarbonate solution (400 ml) were added. The mixture was stirred until gas evolution had ceased. The organic layer was collected and the aqueous phase was further extracted
30 with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated to give a brown oil (29.5 g). The product was purified by column chromatography

(silica gel, gradient heptane/ethyl acetate) to give the expected product (22.8 g, 78%).

^1H NMR (300 MHz, CDCl_3) δ [ppm] = 7.95 (s, 1H), 7.34 (s, 1H), 6.32 (s, 1H), 2.91 – 3.03 (m, 1H), 2.57 (s, 3H), 1.66 – 1.90 (m, 2 H), 1.37 (d, 3H), 0.82 (t, 3 H).

5

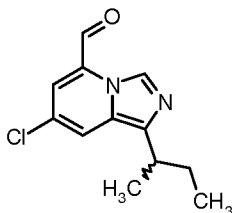
Intermediate 16A - *rac*-1-sec-butyl-7-chloro-5-[(E)-2-(pyrrolidin-1-yl)vinyl]imidazo[1,5-a]pyridine



- 10 1-sec-butyl-7-chloro-5-methylimidazo[1,5-a]pyridine (intermediate **15A**) (10.33 g, 47 mmol) was dissolved in a mixture of dimethylformamide dimethylacetal (12.6 ml, 94 mmol) and pyrrolidine (11.5 ml). The solution was stirred at reflux temperature for 20 hours. The solution was poured into an ice/water mixture and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated to give a
- 15 crude product. The product was triturated in diisopropyl ether at room temperature. The filtrate was concentrated and the resulting solid was triturated in diisopropyl ether at 0 °C. The solid was dried to give the expected product (10.56 g, 74%).

- ^1H NMR (300 MHz, CDCl_3) δ [ppm] = 8.05 (s, 1H), 7.32 (d, 1H), 7.06 (d, 1H), 6.25 (d, 1H), 4.93
- 20 (d, 1H), 3.36 (m, 4H), 2.96 (m, 1H), 2.00 (m, 4 H), 1.70 – 1.90 (m, 2 H), 1.36 (d, 3H), 0.82 (t, 3 H).

Intermediate 17A - *rac*-1-sec-butyl-7-chloroimidazo[1,5-a]pyridine-5-carbaldehyde

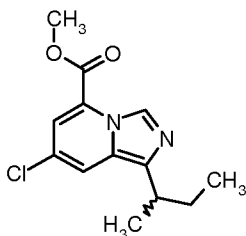


- 25 1-sec-butyl-7-chloro-5-[(E)-2-(pyrrolidin-1-yl)vinyl]imidazo[1,5-a]pyridine (intermediate **16A**) (15.8 g, 52 mmol) was dissolved in a mixture of tetrahydrofuran (166 ml) and water (20.2 ml). Sodium periodate (22 g, 102 mmol) was added at 0 °C and the mixture was stirred at this temperature for 75 minutes. A TLC analysis (silica gel, heptane/ethyl acetate 7/3) indicated that the

reaction was finished. The suspension was filtered and the filter cake was washed thoroughly with ethyl acetate. The organic layer was separated, washed three times with a saturated aqueous sodium bicarbonate solution and once with brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to give a black oil (12.9 g). The product was applied on a silica gel column and the product was eluted with ethyl acetate to give the expected product (9.8 g, 80%).

^1H NMR (300 MHz, CDCl_3) δ [ppm] = 9.80 (s, 1 H), 9.37 (s, 1H), 7.77 (d, 1H), 7.23 (d, 1 H), 3.01 (m, 1H), 1.74 – 1.81 (m, 2 H), 1.38 (d, 3H), 0.82 (t, 3 H).

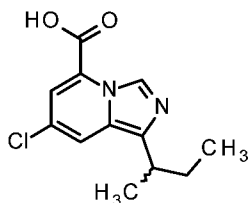
10 **Intermediate 18A - *rac*-methyl 1-sec-butyl-7-chloroimidazo[1,5-a]pyridine-5-carboxylate**



1-sec-Butyl-7-chloroimidazo[1,5-a]pyridine-5-carbaldehyde (9.8 g, 41.4 mmol) (intermediate 17A) was dissolved in tetrahydrofuran (410 ml). Sodium cyanide (2.5 g, 51 mmol), manganese dioxide (28.8 g, 331 mmol) and methanol (8.4 ml) were added. The suspension was heated at reflux temperature for 6 hours. A TLC analysis (silica gel, heptane/ethyl acetate 7/3) indicated that the reaction was finished. The suspension was filtered over Celite and the filter cake was rinsed with hot dichloromethane. The organic phase was washed three times with a saturated aqueous sodium bicarbonate solution and once with brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to give a crude product (12.2 g). The product was purified by column chromatography (silica gel, heptane/ethyl acetate 85/15) to give the expected product (4.97 g, 45%).

^1H NMR (300 MHz, CDCl_3) δ [ppm] = 9.19 (s, 1H), 7.64 (s, 1H), 7.48 (s, 1 H), 4.00 (s, 3 H), 2.97 (m, 1H), 1.72 – 1.82 (m, 2 H), 1.36 (d, 3H), 0.80 (t, 3 H).

Intermediate 19A - *rac*-1-sec-butyl-7-chloroimidazo[1,5-a]pyridine-5-carboxylic acid



30 Methyl 1-sec-butyl-7-chloroimidazo[1,5-a]pyridine-5-carboxylate (intermediate 18A) (6.71 g, 25.1

mmol) was dissolved in diisopropyl ether. The organic layer was extracted three times with an aqueous hydrochloric acid solution (1N). The combined aqueous phases were basified until pH~10 using a sodium hydroxide solution (6 N). The mixture was cooled using an ice/water bath and the precipitated solid was filtered. The solid was re-dissolved into dichloromethane and the product was extracted with water. The aqueous phase was acidified to pH5 and the precipitated solid was filtered giving the expected product (4.75 g, 75%).

^1H NMR (300 MHz, DMSO) δ [ppm] = 9.07 (s, 1H), 8.09 (s, 1H), 7.38 (s, 1 H), 3.10 (m, 1H), 1.60 – 1.70 (m, 2 H), 1.25 (d, 3H), 0.72 (t, 3 H).

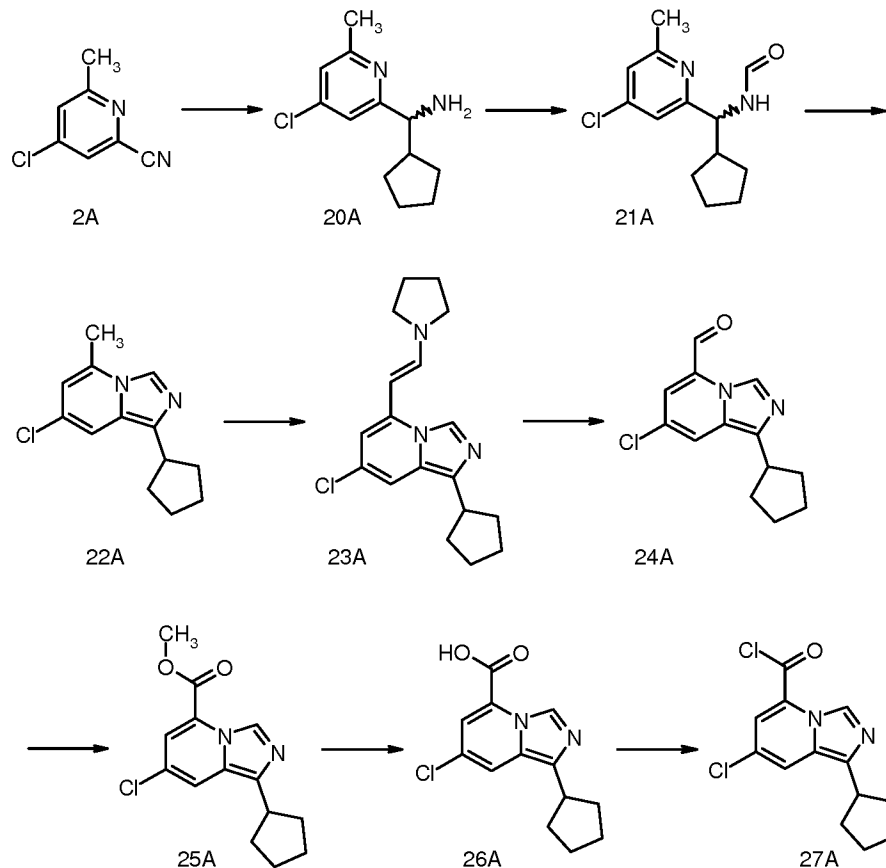
^{13}C NMR (75 MHz, DMSO): 12.42, 21.18, 30.08, 32.84, 120.32, 120.86, 121.50, 125.09, 127.20, 129.06, 138.61, 162.82.

MS (ESIpos): m/z = 253 ($M+H$) $^+$.

15

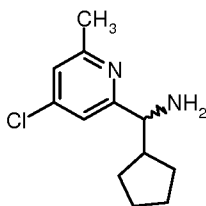
Synthesis of 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carbonyl chloride – intermediate 27A

(Scheme D)



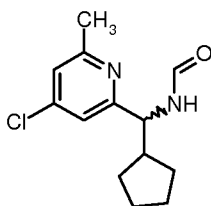
20

Scheme D

Intermediate 20A - *rac*-1-(4-chloro-6-methylpyridin-2-yl)-1-cyclopentylmethanamine

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4-Chloro-6-methylpyridine-2-carbonitrile (CAS 104711-65-1, 43.6 g, 286 mmol) was dissolved in tetrahydrofuran (840 ml). The mixture was cooled to -60°C and cyclopentyl magnesium chloride solution (2M in diethyl ether, 185 mL, 370 mmol) was added dropwise. The mixture was stirred for two hours at room temperature. The mixture was adjusted to 0°C and methanol (284 ml) was added dropwise. Sodium borohydride (6.5 g, 171 mmol) was added to the mixture portionwise. The solution was stirred two hours at 0°C. The solution was poured into an ice/water mixture (1.3 l) and the mixture was stirred overnight at room temperature. Dichloromethane (1.5 l) was added and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and concentrated to give a crude product. The product was mixed with hydrochloric acid solution (400 ml, 2M in ether). The resulting precipitate was filtered and rinsed with tetrahydrofuran. The combined filtrates were concentrated and treated a second time with a hydrochloric acid solution (400 ml, 2M in ether). Diisopropyl ether was added to the resulting suspension and the solid was filtered. The combined solids were re-dissolved into water and the aqueous layer was made basic using a saturated aqueous sodium hydrogen carbonate solution. The product was extracted three times using dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give an impure product that was purified using column chromatography on silica gel eluting with ethyl acetate, giving the expected product (41.8 g, 65%).

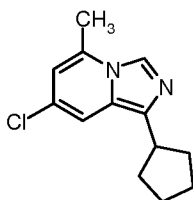
25 Intermediate 21A - *rac*-N-[(4-chloro-6-methylpyridin-2-yl)(cyclopentyl)methyl]formamide

1-(4-Chloro-6-methylpyridin-2-yl)-1-cyclopentylmethanamine (intermediate **20A**) (41.7 g, 185 mmol) was mixed with formic acid (122 ml, 3.23 mol) and the solution was heated at 100°C for 1 h. A TLC analysis (silica gel, dichloromethane/methanol/ammonia 98/2/1%) indicated that the

30

reaction was finished. The mixture was allowed to cool to room temperature and concentrated to dryness. The resulting product was co-evaporated twice with toluene. A mixture of dichloromethane (400 ml) and an aqueous saturated sodium bicarbonate solution (400 ml) were added. The mixture was stirred until gas evolution had ceased. The organic layer was collected and the aqueous phase was further extracted with dichloromethane. The combined organics were dried over magnesium sulfate, filtered and concentrated to give the expected product (44 g, 94%), which was used in the subsequent step without further purification.

Intermediate 22A - 7-chloro-1-cyclopentyl-5-methylimidazo[1,5-a]pyridine

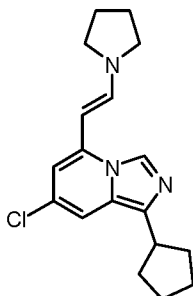


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N-[(4-Chloro-6-methylpyridin-2-yl)(cyclopentyl)methyl]formamide (intermediate 21A) (44 g, 174 mmol) was dissolved in toluene (708 ml). About 200 mL of solvent was evaporated to remove residual water. Phosphorus oxychloride (27.7 ml, 264 mmol) was added and the solution was stirred 1 h at reflux temperature. A TLC analysis (silica gel, heptane/ethyl acetate 1/1) indicated that the reaction was finished. The mixture was allowed to cool to room temperature and concentrated to dryness. A mixture of dichloromethane (500 ml) and an aqueous saturated aqueous sodium bicarbonate solution (500 ml) were added. The mixture was stirred until gas evolution had ceased. The organic layer was collected and the aqueous phase was further extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated to give a brown oil (29.5 g). The product was purified by column chromatography (silica gel, gradient heptane/ethyl acetate) to give the expected product (21.03 g, 51%).

^1H NMR (300 MHz, CDCl_3) δ [ppm] = 7.91 (s, 1H), 7.34 (s, 1H), 6.29 (s, 1H), 3.31 (m., 1H), 2.50 (s, 3H), 2.00 – 2.12 (m, 2 H), 1.80 – 1.95 (m, 4 H), 1.70 – 1.82 (m, 2 H).

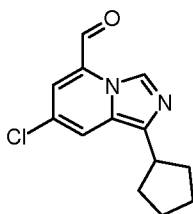
Intermediate 23A - 7-chloro-1-cyclopentyl-5-[(E)-2-(pyrrolidin-1-yl)vinyl]imidazo[1,5-a]pyridine



7-Chloro-1-cyclopentyl-5-methylimidazo[1,5-a]pyridine (intermediate **22A**) (20.94 g, 89 mmol) was dissolved in a mixture of dimethylformamide dimethylacetal (23.6 ml, 178.5 mmol) and pyrrolidine (18.3 ml). The solution was stirred at reflux temperature for 20 h. The solution was poured into an ice/water mixture and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated to give a crude product. The crude product was purified on a column of silica gel eluting with ethyl acetate resulting in a solid product. The product was triturated in diisopropyl ether at 0 °C giving the expected product (17.2 g, 61%).

¹H NMR (300 MHz, CDCl₃) δ [ppm] = 8.02 (s, 1H), 7.31 (d, 1H), 7.07 (s, 1H), 6.24 (s, 1H), 4.91 (d, 1H), 3.34 (m, 4H), 3.30 (m, 1H), 1.80 – 2.10 (m, 10 H), 1.60 – 1.80 (m, 2 H).

Intermediate 24A - 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carbaldehyde

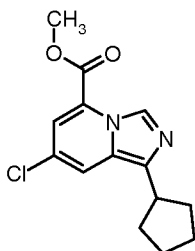


7-Chloro-1-cyclopentyl-5-[(E)-2-(pyrrolidin-1-yl)vinyl]imidazo[1,5-a]pyridine (intermediate **23A**) (17.11 g, 54.2 mmol) was dissolved in a mixture of tetrahydrofuran (172 ml) and water (20 ml). Sodium periodate (23.2 g, 108.5 mmol) was added at 0 °C and the mixture was stirred at this temperature for 1 h. The suspension was filtered over Celite and the filter cake was washed thoroughly with ethyl acetate. The organic layer was separated, washed three times with a saturated aqueous sodium bicarbonate solution and once with brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to give a black oil (18.2 g). The product was applied on a silica gel column and the product was eluted with ethyl acetate to give the expected product (10.6 g, 79%).

¹H NMR (300 MHz, CDCl₃) δ [ppm] = 9.79 (s, 1 H), 9.35 (s, 1H), 7.80 (d, 1H), 7.23 (d, 1 H), 3.37

(m, 1H), 2.00 – 2.15 (m, 2 H), 1.80 – 1.95 (m, 4 H), 1.70 – 1.80 (m, 2 H).

Intermediate 25A - Methyl 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carboxylate

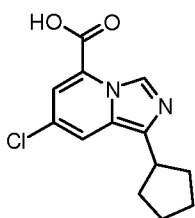


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7-Chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carbaldehyde (intermediate **24A**) (10.6 g, 42.6 mmol) was dissolved in tetrahydrofuran (43 ml). Sodium cyanide (2.5 g, 51 mmol), manganese dioxide (22.4 g, 257 mmol) and methanol (8.6 ml) were added. The suspension was heated at reflux temperature for 7 hours. A TLC analysis (silica gel, heptane/ethyl acetate 7/3) indicated that the reaction was finished. The suspension was filtered over Celite and the filter cake was rinsed with hot dichloromethane. The organic phase was washed two times with a saturated aqueous sodium bicarbonate solution and once with brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to give a crude product (11.4 g). The product was purified by column chromatography (silica gel, heptane/ethyl acetate 85/15) to give the expected product (4.97 g, 42%).

¹H NMR (300 MHz, CDCl₃) δ [ppm] = 9.18 (s, 1H), 7.69 (s, 1H), 7.48 (s, 1 H), 4.01 (s, 3 H), 2.34 (m, 1H), 2.00 – 2.15 (m, 2 H), 1.85 – 2.00 (m, 4 H), 1.65 – 1.85 (m, 2 H).

20 **Intermediate 26A - 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carboxylic acid**



Methyl 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carboxylate (intermediate **25A**) (3.98 g, 14.3 mmol) was dissolved in a mixture of water (12.2 ml) and dioxane (122 ml). Potassium hydroxide (4 g, 71 mmol) was added and the mixture was heated at 50 °C for 30 min. The mixture was concentrated to dryness and the residue was re-dissolved in water (60 ml). The aqueous layer was washed with diisopropyl ether and residual organic solvent was removed by evaporation. The aqueous phase was acidified to pH~5.4 using an aqueous solution of hydrochloric acid (1N). The solid was filtered and dried *in vacuo* over phosphorus pentoxide giving the expected product (3.72

25

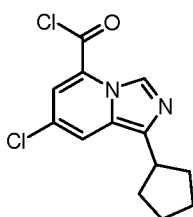
g, 98%).

^1H NMR (300 MHz, DMSO) δ [ppm] = 9.09 (s, 1H), 8.04 (s, 1H), 7.34 (s, 1 H), 3.44 (pent., 1H), 1.90 – 2.10 (m, 2 H), 1.70 – 1.90 (m, 4 H), 1.60 – 1.70 (m, 2 H).

5 ^{13}C NMR (75 MHz, DMSO): 25.70, 33.39, 36.97, 119.75, 120.89, 121.00, 126.17, 126.90, 129.00, 137.72, 162.85.

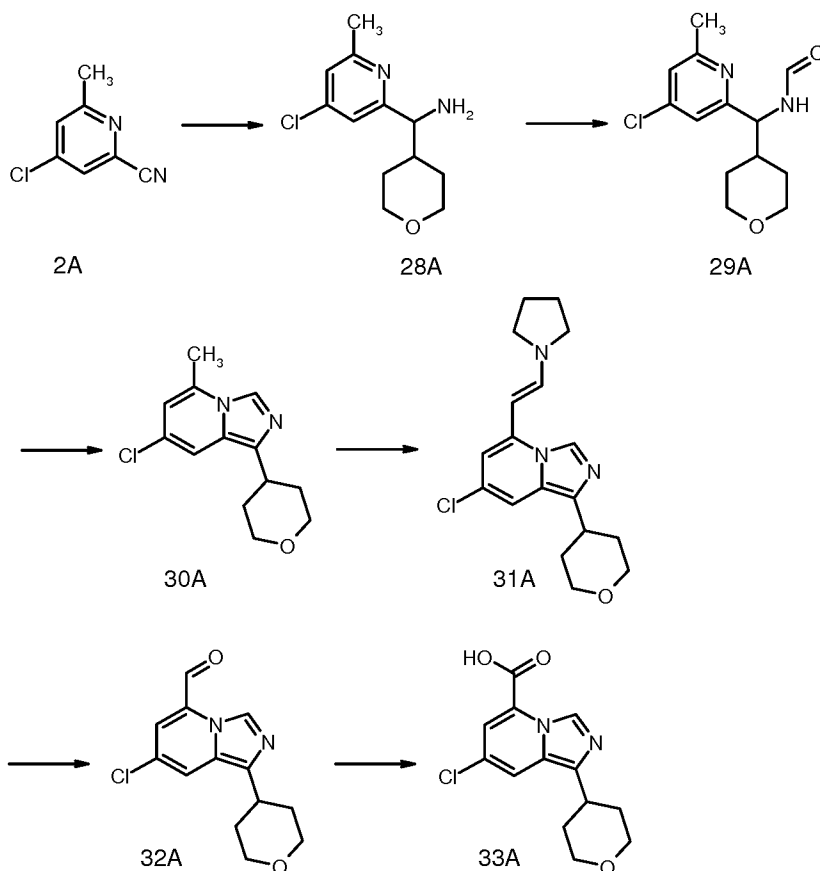
MS (ESIpos): m/z = 265 (M+H) $^+$.

10 **Intermediate 27A - 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carbonyl chloride**



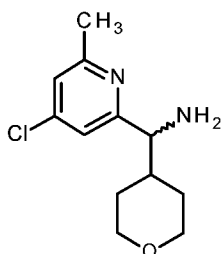
To a solution of 1.5 g 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carboxylic acid
15 (intermediate 26A) (5.66 mmol) in dichloromethane (100 ml) were added 2 drops of DMF. At 5°C were added 2.16g ethanedioyl dichloride (16.99 mmol, 3eq.). The reaction mixture stirred 1 h at 50 °C. The mixture was concentrated and dried in high vacuum to provide 1.6 g (100%) of the crude product which was used for the next reactions.

20 **Synthesis of 7-chloro-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxylic acid–intermediate 33A**
(Scheme Q)



Scheme Q

Intermediate 28A - *rac*-(4-Chloro-6-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanamine

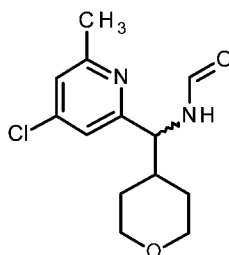


Preparation of the Grignard (carried out in flame dried glassware under argon) – Magnesium turnings 3.00 g (125 mmol) were stirred in tetrahydrofuran 75 mL, one flake of iodine was added. The mixture was stirred for 2 hours until the colour had dissipated. 4-Chlorotetrahydropyran (2.00 g) was added and the mixture was heated to 60 °C, and one drop of methyl iodide was added. The mixture turned cloudy and an exothermia was observed. A further portion of 4-chlorotetrahydropyran 8.00 g was added and the mixture was stirred at 60 °C for 2 hours.

To a solution of 4-chloro-6-methylpicolinonitrile (intermediate 2A, 8.50 g, 56.0 mmol) in tetrahydrofuran 400 mL was added the Grignard solution drop-wise, at -78 °C, under argon. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was then cooled to 5 °C and methanol 150 mL was added drop-wise followed by sodium borohydride 1.50 g (0.40 mmol) which was added portion-wise. After the addition was complete the mixture was stirred at room temperature for 2 hours. The reaction was then quenched by the addition of water and ethyl acetate. The phases were separated and the aqueous phase was extracted again with ethyl acetate. The organic phases were combined, washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness. The residue was purified by dry flash chromatography (silica gel, eluent: ethyl acetate/methanol 9:1 to 4:1) to yield 5.90 g (44%) of (4-chloro-6-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanamine.

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 1.14-1.45 (m, 4H), 1.83-1.93 (m, 1H), 2.51 (s, 3H), 3.33 (m, 2H), 3.61 (d, 1H), 3.90 (dd, 1H), 4.01 (dd, 1H), 7.02 (s, 1H), 7.04 (s, 1H).

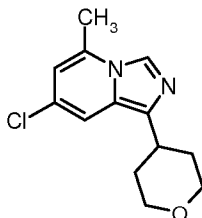
Intermediate 29A - *rac*-N-((4-Chloro-6-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)formamide



A mixture of (4-chloro-6-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanamine (intermediate 28A, 5.90 g, 24.5 mmol) and ethyl formate 18.0 mL was stirred at reflux for 3 hours. The reaction mixture was then evaporated to dryness, followed by co-evaporation with toluene (five times) to yield *N*-((4-chloro-6-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)formamide which was used without further purification in the next step.

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 1.80 (m, 2H), 2.10 (m, 2H), 2.52 (s, 3H), 3.13 (m, 1H), 3.56 (td, 2H), 4.10 (dd, 2H), 6.45 (s, 1H), 7.37 (s, 1H), 7.97 (s, 1H).

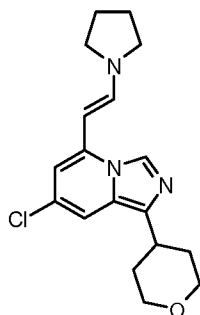
Intermediate 30A - 7-Chloro-5-methyl-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine



A solution of *N*-((4-chloro-6-methylpyridin-2-yl)(tetrahydro-2*H*-pyran-4-yl)methyl)formamide (intermediate 29A, 24.5 mmol) in toluene 100 mL was stirred at reflux and phosphoryl chloride (POCl₃; 2.75 mL; 29.4 mmol) was added drop-wise. The reaction mixture was stirred at reflux for 1 hour and 10 minutes then evaporated to dryness. The residue was dissolved in dichloromethane and was then added carefully to a mixture of dichloromethane and aqueous sodium carbonate solution. The aqueous phase was extracted with dichloromethane. The organic phases were combined, washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness to yield 7-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-*a*]pyridine which was used without further purification in the next step.

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Intermediate 31A - (E)-7-Chloro-5-(2-(pyrrolidin-1-yl)vinyl)-1-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-*a*] pyridine

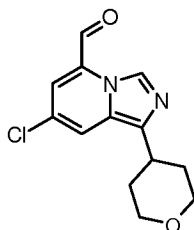


A mixture of 7-chloro-5-methyl-1-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-*a*]pyridine (intermediate 30A, 24.5 mmol) and pyrrolidine 6.14 mL (73.5 mmol) in *N,N*-dimethylformamide dimethyl acetal 6.50 mL (49.0 mmol) was stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature then was carefully poured onto a mixture of ice and dichloromethane. Brine was added and the phases were separated. The organic phase was dried over magnesium sulphate, filtered and evaporated to dryness to yield 7.70 g of (E)-7-chloro-5-(2-(pyrrolidin-1-yl)vinyl)-1-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-*a*]pyridine which was used without further purification in the next step.

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 1.68-2.15 (m, 8H), 3.27-3.60 (m, 7H), 4.10 (m, 2H), 4.90 (d, 1H), 6.25 (s, 1H), 7.09 (s, 1H), 7.33 (d, 1H), 8.01 (s, 1H).

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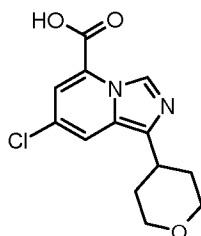
Intermediate 32A - 7-Chloro-1-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-*a*]pyridine-5-carbaldehyde



A solution of (E)-7-chloro-5-(2-(pyrrolidin-1-yl)vinyl)-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine (intermediate 31A, 24.5 mmol) in tetrahydrofuran 125 mL and water 25 mL was cooled to 0 °C, and sodium periodate 10.5 g (49.0 mmol) was added portion-wise over a period of 20 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was diluted with ethyl acetate, followed by filtration through celite. The filtrate was poured onto a saturated aqueous solution of sodium bicarbonate and the phases were separated. The organic phase was washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness to yield 7-chloro-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carbaldehyde which was used without further purification in the next step.

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 9.80 (s, 1H), 9.37 (s, 1H), 7.82 (s, 1H), 7.24 (s, 1H), 4.10 (m, 2H), 3.58 (m, 2H), 3.20-3.58 (m, 1H), 1.60-2.20 (m, 4H)

Intermediate 33A - 7-Chloro-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxylic acid



A mixture of 7-chloro-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carbaldehyde (intermediate 32A, 24.5 mmol) and formic acid 100 mL was cooled to 0 °C and hydrogen peroxide 1.76 mL (25.7 mmol) was added drop-wise. The mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was then cooled to 0 °C and quenched with brine 100 mL which was added slowly. The mixture was extracted with chloroform/2-isopropanol (7:1 mixture) three times. The organic phases were combined, washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness. The residue was triturated in diethyl ether and the resulting solid was slurried in cold 2-isopropanol for 30 minutes then filtered, washed with diethyl ether and dried to yield 1.15 g of 7-chloro-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxylic acid. The filtrates were combined and evaporated under vacuum. The aqueous phase was further extracted with dichloromethane/2-isopropanol (7:3 mixture) three times, the organic phases were combined dried over magnesium sulphate, filtered and evaporated to

dryness. The residue was combined with the residue from the filtrate along with the initial 1.15 g of 7-chloro-1-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-*a*]pyridine-5-carboxylic acid. The combined residues were then slurried in cold diethyl ether and dried to yield 1.64 g (24 % yield over 5 steps) of 7-chloro-1-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-*a*]pyridine-5-carboxylic acid.

5

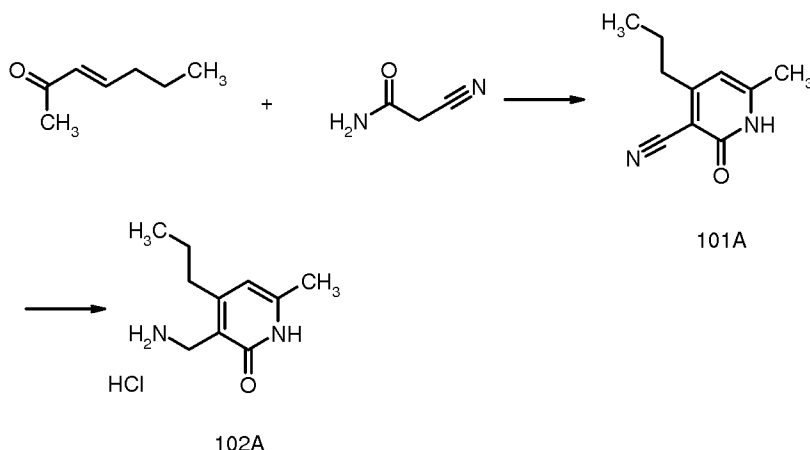
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 1.87 (m, 2H), 1.99 (m, 2H), 3.29 (m, 3H), 4.06 (m, 2H), 7.94 (s, 1H), 8.36 (s, 1H), 10.06 (s, 1H).

Synthesis of Intermediates – Part 2 – Pyridone building blocks

- 10 3-(Aminomethyl)-4,6-dimethylpyridin-2(1*H*)-one hydrochloride is commercially available from various vendors. The other pyridones were prepared as described in the subsequent paragraphs.

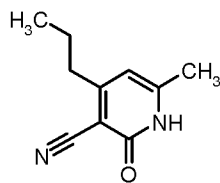
Synthesis of 3-(aminomethyl)-6-methyl-4-propylpyridin-2(1*H*)-one hydrochlorid acid salt - 102A

15 (Scheme E)



Scheme E

Intermediate 101A - 6-methyl-2-oxo-4-propyl-1,2-dihydropyridine-3-carbonitrile



20

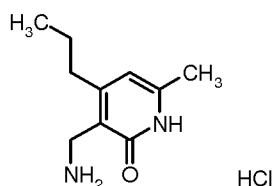
- To a stirred solution of potassium tert-butoxide (20 g, 0.178 mol) and cyano acetamide (16.49 g, 0.196 mol) in DMSO (300 ml) was added 3-hepten-2-one (20 g, 23.26 ml, 0.178 mol) under argon atmosphere at room temperature. Reaction was exothermic, and the temperature was maintained
- 25 between 25-30 °C using an ice-bath. The reaction mixture was stirred at room temperature for 30 min and then additional potassium tert-butoxide was added to the reaction mixture (exothermic

reaction; the temperature was maintained below 35 °C using a cold water bath). The argon was then displaced with air and the reaction mixture was stirred for 16 h. UPLC (conditions 1) showed essentially complete turnover. The reaction mixture was cooled to 0 °C under argon and the reaction was stopped by addition of water (50 ml), followed by 2N aqueous hydrochloric acid (350 ml) until the reaction mixture was acidic. The mixture was stirred for 30 min and then the solid was collected by filtration. The solid was washed with water (700 ml) and dried to afford the product 15 g (47.7%) as an off-white solid.

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 0.87 (t, 3H), 1.53-1.59 (m, 2H), 2.19 (s, 3H), 2.51 (m, 2H), 6.15 (s, 1H), 2.31 (br s, 1H).

UPLC-MS (conditions 1.1): R_t = 0.55 min, 98.77%. MS (ESIpos): m/z = 177 (M+H)⁺

Intermediate 102A – 3-(aminomethyl)-6-methyl-4-propylpyridin-2(1H)-one hydrochloride

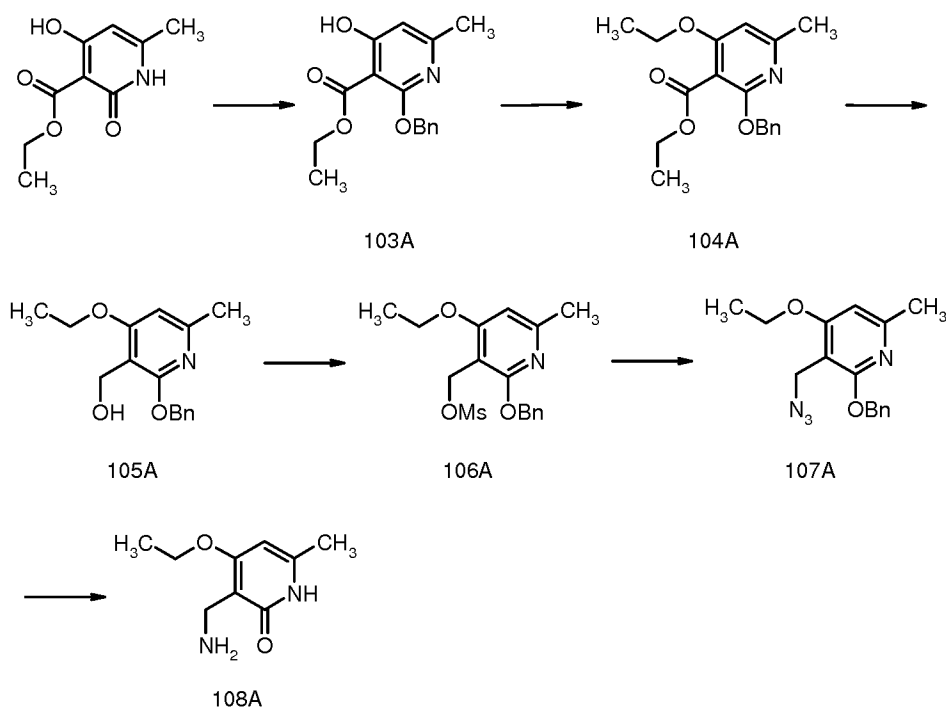


To a stirred solution of 6-methyl-2-oxo-4-propyl-1,2-dihydropyridine-3-carbonitrile (intermediate **101A**) (1 g, 5.67 mmol) in methanol (40 ml) and concentrated hydrogen chloride solution (1 ml) was added palladium hydroxide (0.95 g, 6.8 mmol). The mixture was stirred for 72 h under hydrogen pressure (34 bar). The reaction mixture was filtered and the filtrate concentrated under vacuum to give the crude product 1.2 g (97%).

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 0.85 (t, 3H), 1.48 (m, 2H), 2.12 (s, 3H), 2.41 (m, 2H), 3.72 (m, 2H), 5.95 (s, 1H), 8.05 (br s, 3H), 11.83 (br s, 1H).

LC-MS (conditions 1.1): R_t = 1.31 min, 96.6%. MS (ESIpos): m/z = 181 (M+H)⁺.

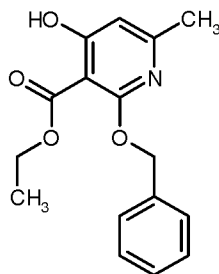
Synthesis of 3-(Aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-one - 108A (Scheme F)



Scheme F

Intermediate 103A - Ethyl 2-(benzyloxy)-4-hydroxy-6-methylpyridine-3-carboxylate

5



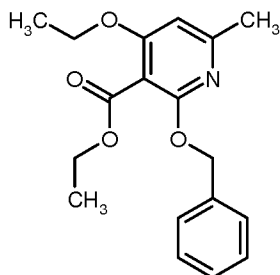
10 A mixture of ethyl 2,4-dihydroxy-6-methylnicotinate (CAS 10350-10-4) (175 g; 0.887 mol), benzyl bromide 110.8 ml (0.932 mol) and silver carbonate 129.7 g (0.470 mol) in toluene (2.6 l) was stirred at 60 °C (oil bath temperature) under an argon atmosphere for 24 h. The reaction mixture was filtered over celite then allowed to cool to room temperature and heptane (2 l) was added. A white precipitate formed which was collected by filtration, washed with heptane to recover unreacted 2,4-dihydroxy-6-methylnicotinate. The filtrate was evaporated *in vacuo* to yield an orange oil which crystallized upon standing at room temperature. The crude product was

15 recrystallized from a minimum of heptane under cooling to -18 °C over night to yield off-white crystals which were filtered, washed with a minimum of cold heptane and dried *in vacuo* to yield intermediate **103A**, 124.6 g (49 %).

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.34 (t, 3H), 2.38 (s, 3H), 4.38 (q, 2H), 5.43 (s, 2H), 6.40

(s, 1H), 7.28-7.39 (m, 3H), 7.51 (d, 2H), 12.30 (s, 1H).

Intermediate 104A - Ethyl 2-(benzyloxy)-4-ethoxy-6-methylpyridine-3-carboxylate



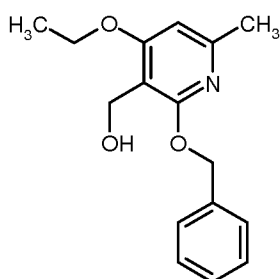
5

A mixture of intermediate **103A** (15.6 g, 54.3 mmol), potassium carbonate (22.5 g, 162.9 mmol) and iodoethane (4.34 ml, 54.3 mmol) in DMF (150 mL) was stirred at room temperature under an argon atmosphere for 18 h. The mixture was filtered over celite and the celite cake was washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was mixed with dichloromethane (0.60 l). The solids were filtered and washed with dichloromethane. The filtrate was concentrated *in vacuo* to give intermediate **104A**, 13.4 g (78 %) as yellow oil.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.24 (t, 3H), 1.30 (t, 3H), 2.33 (s, 3H), 3.99 (q, 2H), 4.28 (q, 2H), 5.35 (s, 2H), 6.30 (s, 1H), 7.16-7.36 (m, 5H).

UPLC-MS (conditions 1.1): R_t = 0.79 min, 91.97%. MS (ESIpos): m/z = 315 (M+H)⁺.

Intermediate 105A - [2-(Benzyloxy)-4-ethoxy-6-methylpyridin-3-yl]methanol



20

To sodium bis(2-methoxyethoxy)aluminum dihydride (109 ml; 3.5 M in toluene, 377 mmol) in toluene (1 l) was slowly added intermediate **104A** (119 g, 377 mmol) in toluene (1 l) at room temperature. The temperature rose to 30 °C and the mixture was stirred at 80 °C (oil bath temperature) for 2 h under an argon atmosphere; LC analysis indicated approximately 30% product formation. A further portion of sodium bis(2-methoxyethoxy)aluminum dihydride (218 ml, 754 mmol) was added slowly to the reaction mixture at room temperature, then the reaction mixture

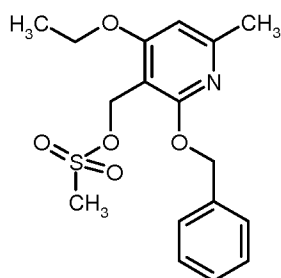
25

was heated at 80 °C (oil bath temperature) for 1.5 h after which time LC analysis indicated total consumption of the starting material. The reaction mixture was cooled to 5 °C in an ice bath and aqueous sodium hydroxide (2 M) was added dropwise until no further effervescence was observed. The organic partition was collected and washed with brine (2 x 250 mL), dried over sodium sulfate, filtered and concentrated to give a crude yellow solid. The crude product was recrystallized from heptane to yield intermediate **105A**, 79.4 g (77 %) as an off-white solid.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.42 (t, 3H), 2.41 (s, 3H), 4.07 (q, 2H), 4.72 (d, 2H), 5.41 (s, 2H), 6.36 (s, 1H), 7.28-7.45 (m, 5H).

UPLC-MS (conditions 1.1): R_t = 0.40 min, 98.54%. MS (ESIpos): m/z = 273 (M+H)⁺.

Intermediate 106A - [2-(Benzyloxy)-4-ethoxy-6-methylpyridin-3-yl]methyl methanesulfonate



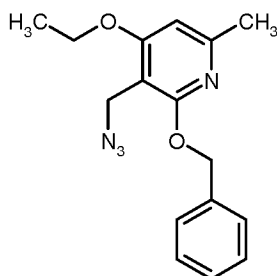
15

To ice-cooled intermediate **105A** (5 g, 18.29 mmol) in dichloromethane (200 ml) was added *N,N*-diisopropylethylamine (4.14 ml, 23.78 mmol) followed by methanesulfonyl chloride (1.56 ml, 20.12 mmol) in dichloromethane (50 ml) dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The solvent was removed *in vacuo* (water bath 20 °C) to yield intermediate **106A** as a pale yellow solid, 6.43 g (99 %), which was used in the next step without purification.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.49 (t, 3H), 2.42 (s, 3H), 2.77 (s, 3H), 4.11 (q, 2H), 4.69 (s, 2H), 5.44 (s, 2H), 6.36 (s, 1H), 7.28-7.49 (m, 5H).

UPLC-MS (conditions 1.1): R_t = 1.16 min, 97.53%. MS (ESIpos): m/z = 288 (mesylate reacts rapidly with methanol in MS solution).

Intermediate 107A - 3-(Azidomethyl)-2-(benzyloxy)-4-ethoxy-6-methylpyridine

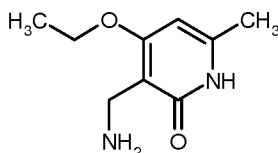


To intermediate **106A** (6.43 g, 18.29 mmol) in DMF (240 ml) was added diisopropylethylamine (4.14 ml, 23.78 mmol), followed by sodium azide (1.31 g, 20.12 mmol), and the reaction mixture was stirred under argon at room temperature for 1 h. The reaction mixture was quenched with dilute sodium hydroxide solution (200 ml, 2 M) and extracted with ethyl acetate (3 x 200 ml). The organic layer was collected and washed with brine solution, dried over sodium sulfate, filtered and the solution was concentrated *in vacuo* (water bath 20 °C) to one tenth of its original volume. This solution of intermediate **107A** was used in the next step.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 1.40 (t, 3H), 2.40 (s, 3H), 4.12 (q, 2H), 4.31 (s, 2H), 5.35 (s, 2H), 6.59 (s, 1H), 7.24-7.42 (m, 5H).

UPLC-MS (conditions 1.1): R_t = 0.92 min, 80.46%. MS (ESIpos): m/z = 299 (M+H)⁺.

15 Intermediate 108A - 3-(Aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-one



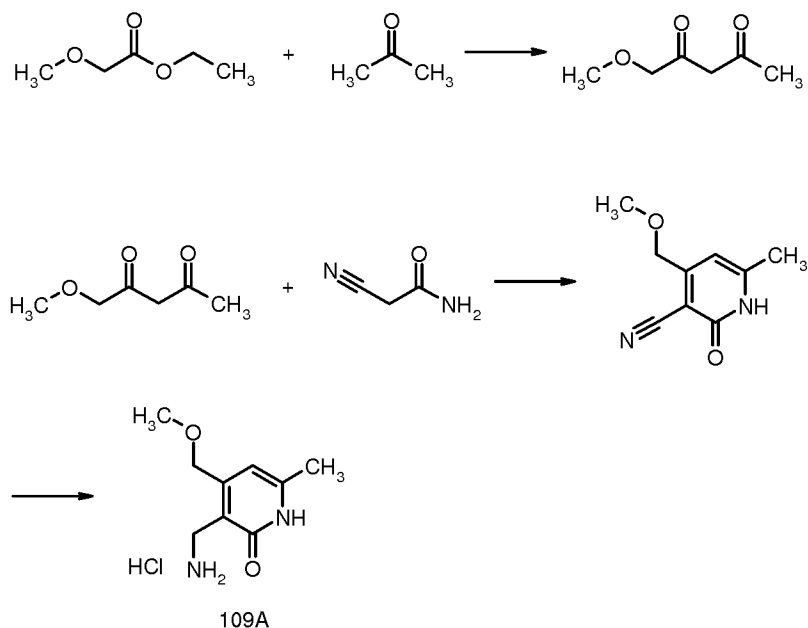
To intermediate **107A** in an autoclave was added industrial methylated spirits (denaturated ethanol) (190 ml) and acetic acid (2 ml; 36.59 mmol) followed by palladium hydroxide 0.55 g (3.9 mmol). The autoclave was pressurized with hydrogen (41 bar) and the reaction mixture was stirred for 18 h at room temperature. A further portion of palladium hydroxide was added (0.5 g, 3.56 mmol) and the reaction mixture was pressurized with hydrogen (41 bar) and stirred for 16 h. The reaction mixture was filtered through celite, washed with methanol and the solvent removed *in vacuo* to yield a dark brown solid. The crude solid was triturated with dichloromethane and the resulting grey solid was dissolved into sodium hydroxide solution (50 ml, 2M) and extracted into an isopropyl alcohol chloroform mixture (3:7; 5 x 100 ml) to yield after concentration intermediate **108A** as an off-white solid, 2.15 g (54% yield).

¹H NMR (400 MHz, methanol-d₄) δ [ppm] = 1.39 (t, 3H), 2.26 (s, 3H), 3.64 (s, 2H), 4.14 (q, 2H),

6.19 (s, 1H). UPLC-MS (conditions 1.1): $R_t = 0.44$ min, 84.27%. MS (ESIpos): $m/z = 183$ (M+H)⁺.

Synthesis of 3-(aminomethyl)-4-(methoxymethyl)-6-methylpyridin-2(1H)-one hydrochloride salt- 109A

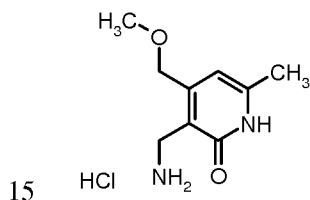
5 (Scheme G)



Scheme G

- 10 The synthesis of Intermediate 109A is described in WO2011/140324 and was used with slight modifications.

Intermediate 109A - 3-(aminomethyl)-4-(methoxymethyl)-6-methylpyridin-2(1H)-one hydrochloride salt



Step 1)

- To a suspension of sodium (17.52 g, 761.87 mmol) in anhydrous toluene (250 ml) was added ethyl 2-methoxyacetate (72.00 g, 609.49 mmol) at -5 °C. After stirring for 3 h, acetone (42.13 g, 725.30 mmol) was added slowly and the mixture became brown and viscous. Then *tert*-butyl methyl ether (252.0 ml) was added. The reaction mixture was stirred at 15 °C for 12 h. The formed sodium salt precipitate was collected, washed with *tert*-butyl methyl ether (200 ml), and dissolved in 20%
- 20

aqueous sulfuric acid (250 ml). The aqueous solution was extracted with *tert*-butyl methyl ether (150 ml x 3). The combined organic layers were concentrated to afford 1-methoxypentane-2,4-dione (45.0 g, 57%) as a red oil.

- 5 ¹H NMR (400 MHz, CDCl₃) δ [ppm] = 5.76 (s, 1H), 3.95 (s, 2H), 3.39 (s, 3H), 2.06 (s, 3H).

Step 2)

To a solution of 1-methoxypentane-2,4-dione (45.0 g, 345.78 mmol) and cyanoacetamide (29.07 g, 345.78 mmol) in ethanol (450 ml) was added slowly piperidine (29.44 g, 345.78 mmol) at 70 °C.

- 10 The mixture was stirred for 2 h at 80 °C, and then cooled to 20 °C. The contents were filtered to give a solid, which was triturated with ethanol (100 ml) to give 4-(methoxymethyl)-6-methyl-2-oxo-1H-pyridine-3-carbonitrile (45.0 g, 73%) as a gray solid.

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 6.29 (s, 1H), 4.43 (s, 2H), 3.35 (s, 3H), 2.28 (s, 3H).

15

Step 3)

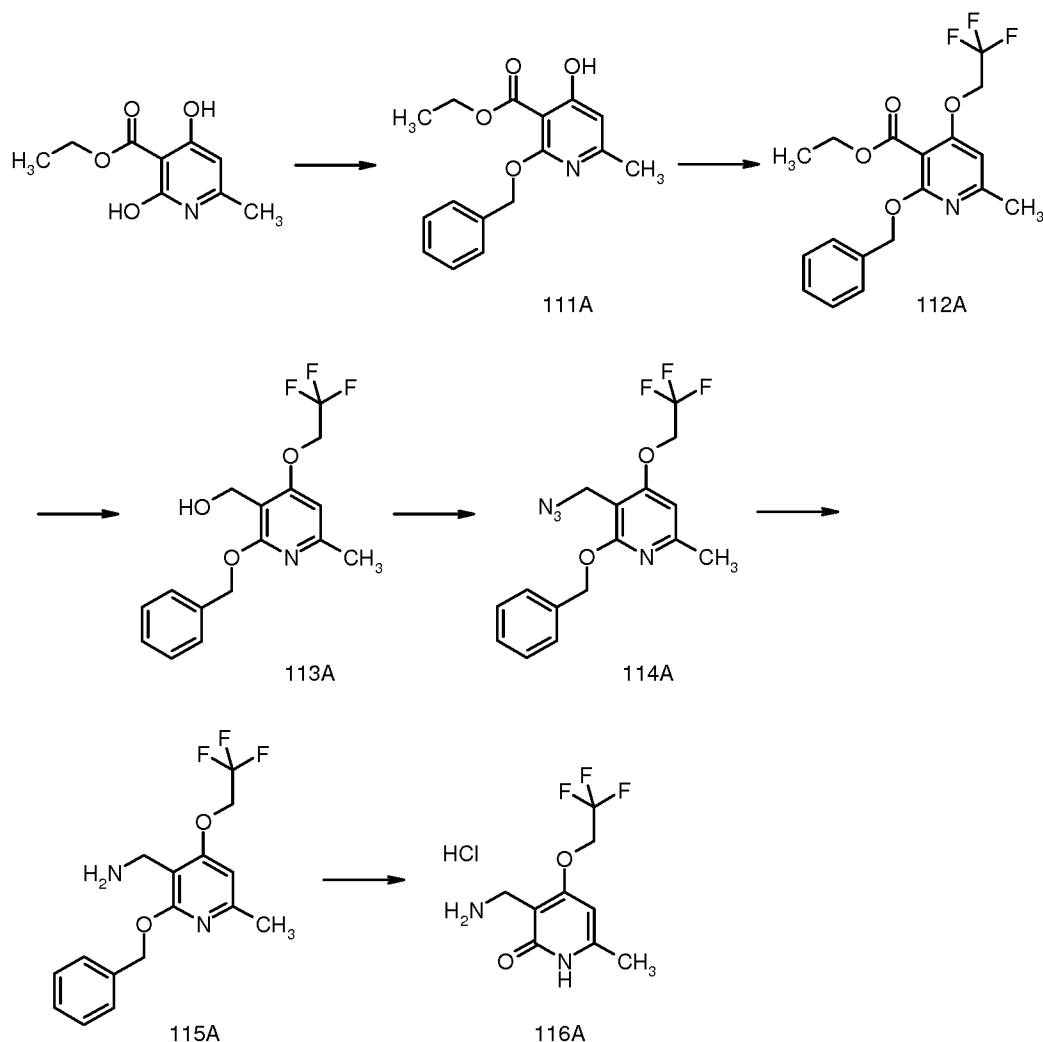
To a solution of 4-(methoxymethyl)-6-methyl-2-oxo-1H-pyridine-3-carbonitrile (45.0 g, 252.54 mmol) in methanol (500 ml) was added Raney-Nickel (147.9 g) and aqueous ammonia (70 mL) under a nitrogen atmosphere. The suspension was degassed under vacuum and purged with
20 hydrogen for three times. The mixture was stirred under hydrogen (1.8 bar) atmosphere at 15 °C for 6 h. Then the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by precipitation upon addition of hydrogen chloride in methanol (500.0 ml, 4.0 M), and the solid was filtered and dried to give 3-(aminomethyl)-4-(methoxymethyl)-6-methylpyridin-2(1H)-one hydrochloride (intermediate **109A**, 20.0 g, 36%) as white solid.

25

¹H NMR (400 MHz, DMSO-d₆): δ = 12.03 (br, 1H), 8.03 (br, 3H), 6.15 (s, 1H), 4.45 (s, 2H), 3.78-3.74 (m, 2H), 3.33 (s, 3H), 2.21 (s, 3H).

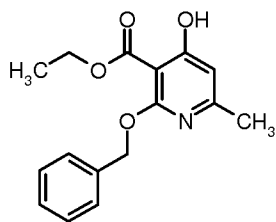
30

Synthesis of 3-(Aminomethyl)-6-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-ol hydrochloride - 116A
(Scheme H)



5 Scheme H

Intermediate 111A - Ethyl 2-(benzyloxy)-4-hydroxy-6-methylnicotinate

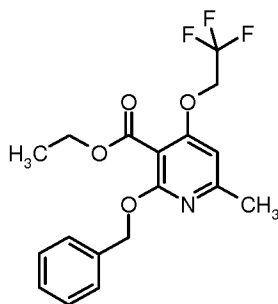


- 10 To a mixture of ethyl-2,4-dihydroxy-6-methylnicotinate (CAS 70254-52-3, 250 g, 1.27 mol) and silver carbonate (182 g, 0.66 mol) in tetrahydrofuran (3.0 l) was added benzyl bromide (260 g, 1.54 mol). The mixture was stirred at 60 °C for 12 h then cooled to room temperature and filtered. The filtrate was concentrated and the resulting residue was re-dissolved in heptane. The resulting solid

was filtered off and the filtrate cooled to -10 °C. The solid that formed was then filtered off and washed with cold heptane and dried to give intermediate **111A** (235 g, 64%).

¹H NMR (400MHz, CDCl₃) δ [ppm] = 12.29 (s, 1H), 7.26-7.53 (m, 5H), 6.40 (s, 1H), 5.43 (s, 2H),
5 4.38 (q, 2H), 2.38 (s, 3H), 1.35 (t, 1H).

Intermediate 112A - Ethyl 2-(benzyloxy)-6-methyl-4-(2,2,2-trifluoroethoxy)nicotinate



10 Step 1)

A mixture of trifluoroethanol (142 g, 1.42 mol) and triflic anhydride (350 g, 1.24 mol) was stirred at room temperature for 30 min then heated at reflux for 3 h. The mixture was then distilled at atmospheric pressure to give the corresponding triflate of trifluoroethanol (280 g, 100%, bp. 118 °C).

15

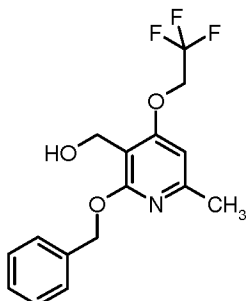
¹H NMR (400MHz, CDCl₃) δ [ppm] = 4.70 (q, 2H).

Step 2)

A mixture of intermediate **111A** (224 g, 0.78 mol), the crude product of step 1 (234 g, 1.02 mol)
20 and potassium carbonate (430 g, 3.11 mol) in acetone (2.2 l) was stirred at reflux, under argon, for 4 h. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated and the residue was triturated with heptane. The resulting solid was filtered then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulphate and concentrated to give intermediate **112A** (192 g). A second batch was isolated from the
25 initial filtrate to give a total of 251 g (88%) of intermediate **112A**.

¹H NMR (300MHz, CDCl₃) δ [ppm] = 7.28-7.45 (m, 5H), 6.32 (s, 1H), 5.43 (s, 2H), 4.36 (m, 4H),
2.43 (s, 3H), 1.31 (t, 3H).

30 **Intermediate 113A - (2-(Benzyloxy)-6-methyl-4-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol**

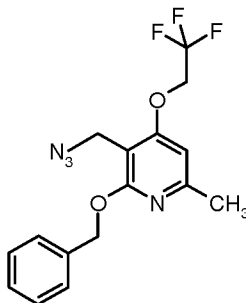


To a solution of intermediate **112A** (120 g, 0.32 mol) in tetrahydrofuran (1.0 l) at 0 °C was added lithium aluminium hydride (1M solution in tetrahydrofuran, 320 ml, 0.32 mol), under argon, whilst
 5 maintaining a temperature below -10 °C. Once the addition was complete the mixture was allowed to warm to room temperature and stirred under argon for 2 h. The mixture was then cooled to 10 °C and water was added (6 ml) dropwise followed by sodium hydroxide (15%, aq, 6 ml) then water (18 ml). The resulting mixture was stirred for 20 min then filtered. The filtrate was concentrated to give an oil which crystallized upon cooling to give intermediate **113A**.

10

¹H NMR (400MHz, CDCl₃) δ [ppm] = 7.30-7.46 (m, 5H), 6.32 (s, 1H), 5.40 (s, 2H), 4.72 (d, 2H), 4.37 (q, 2H), 2.43 (s, 3H), 2.29 (t, 1H).

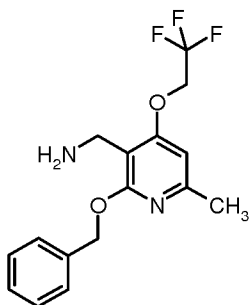
Intermediate 114A - 3-(Azidomethyl)-2-(benzyloxy)-6-methyl-4-(2,2,2-trifluoroethoxy)pyridine
 15



A solution of intermediate **113A** (165 g, 505 mmol) and diisopropylethylamine (132 ml, 757 mmol) in dichloromethane (1.5 l) was cooled to 0 °C and a solution of methanesulfonyl chloride (43.1 ml, 555 mmol) in dichloromethane (150 mL) was added dropwise over a period of 1 h. The
 20 mixture was stirred at room temperature for 2 h and then concentrated. The residue was re-dissolved in DMF (1.2 l) and sodium azide (39.4 g, 606 mmol) was added. The mixture was stirred at room temperature for 18 h. Water was added and the mixture was extracted with heptane/ethyl acetate (3:1). The organic layer was washed with water then brine, dried over magnesium sulfate
 25 then concentrated to give intermediate **114A** (165 g, 93%).

^1H NMR (400MHz, CDCl_3) δ [ppm] = 7.28-7.48 (m, 5H), 6.34 (s, 1H), 5.42 (s, 2H), 4.32-4.44 (m, 4H), 2.45 (s, 3H).

Intermediate 115A - **(2-(Benzyloxy)-6-methyl-4-(2,2,2-trifluoroethoxy)pyridine-3-yl)methanamine**

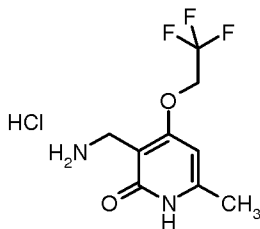


A mixture of intermediate **114A** (165 g, 468 mmol) and 5% Pd/C (8 g) in methanol was stirred at 50 C under 50 bar of hydrogen for 7 h. The mixture was filtered through celite and concentrated.
 10 The resulting yellow oil was triturated with diethyl ether/heptanes (1:1) to give intermediate **115A** (110 g, 72%) as a white solid.

^1H NMR (400MHz, CDCl_3) δ [ppm] = 7.27-7.47 (m, 5H), 6.29 (s, 1H), 5.42 (s, 2H), 4.39 (q, 2H), 3.84 (s, 2H), 2.41 (s, 3H), 1.70 (br. s., 2H).

15

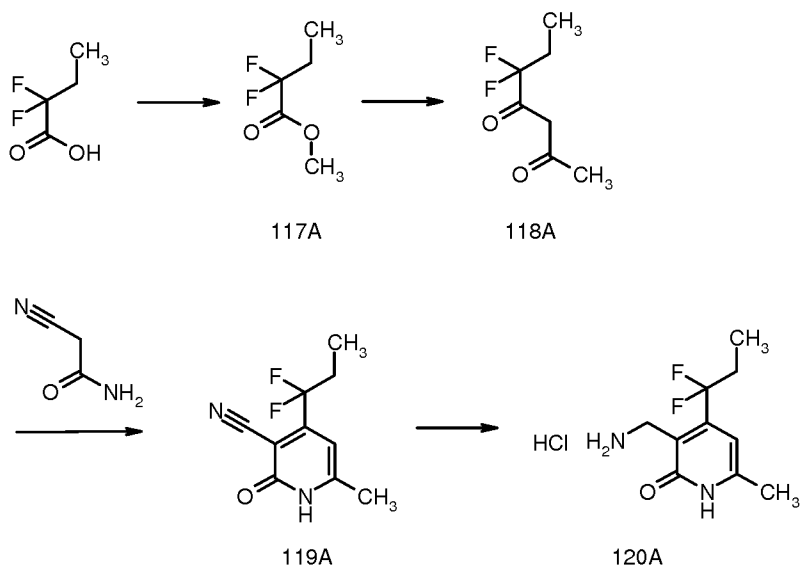
Intermediate 116A - **3-(Aminomethyl)-6-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-ol hydrochloride salt**



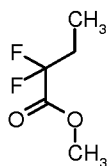
20 To a solution of intermediate **115A** (55 g, 164 mmol) in dioxane (500 ml) was added hydrochloric acid (6M, aq, 140 ml). The mixture was stirred at room temperature for 18 h and was then concentrated. The residue was subjected to repeated azeotropic distillation with toluene and was then triturated with diethyl ether to give intermediate **116A** (51.6 g, 99%) as a white solid.

25 ^1H NMR (400MHz, DMSO-d_6) δ [ppm] = 11.94 (br.s., 1H), 8.03 (br.s., 3H), 6.30 (s, 1H), 5.73 (br.s., 2H), 3.68 (m, 2H), 2.18 (s, 3H).

Synthesis of 3-(Aminomethyl)-4-(1,1-difluoropropyl)-6-methylpyridin-2(1H)-one

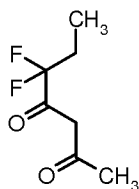
hydrochloride – Intermediate 120A (Scheme I)**Scheme I**

5

Intermediate 117A - Methyl 2,2-difluorobutanoate

To a solution of 2,2-difluorobutanoic acid (CAS 2366-62-3, 12.4 g, 100 mmol) in dichloromethane (300 ml) was added triethylamine (14.0 ml, 100 mmol) dropwise followed by methyl chloroformate (8.0 ml, 100 mmol) dropwise at 0 °C (effervescence was observed). The mixture was stirred at room temperature for 1 h then at reflux for 1 h. Water (200 ml) and 2M aqueous hydrochloric acid (100 ml) were added. The organic layer was separated, washed with saturated aqueous sodium bicarbonate solution (100 ml), dried over sodium sulfate and concentrated to give intermediate **117A** (9.7 g, 70%).

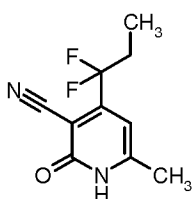
^1H NMR (300 MHz, CDCl_3) δ [ppm] = 3.87 (s, 3H), 2.10 (m, 2H), 1.03 (t, 3H).

Intermediate 118A - 5,5-Difluoroheptane-2,4-dione

20

To a suspension of sodium hydride (24.0 g, 600 mmol) in tetrahydrofuran (500 ml) was added a solution of intermediate **117A** (61.5 g, 446 mmol) in anhydrous acetone (45 ml) dropwise, at -10 °C, under argon. The mixture was allowed to warm to 0 °C (effervescence was observed) and stirred for 1 h. The reaction mixture was quenched by the addition of water (500 ml). Diethyl ether (500 ml) and 2M aqueous HCl (500 ml) were added and the organic layer was separated, washed with saturated aqueous sodium bicarbonate solution (100 ml), dried over sodium sulfate and concentrated to give intermediate **118A** (35.3 g, 48%) which was used in the subsequent reaction without further purification.

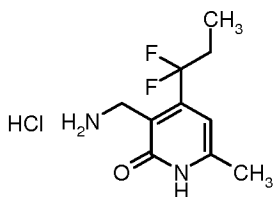
Intermediate 119A - 4-(1,1-Difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



To a hot solution of cyanoacetamide (19.3 g, 230 mmol) in IMS (1.5 l) was added intermediate **118A** (35.3 g, 216 mmol), followed by triethylamine (16.0 ml, 115 mmol), and the mixture was stirred at reflux overnight. The mixture was then concentrated. Water (500 ml) was added to the residue and the resulting solids were collected, washed with water and dried to give intermediate **119A** (45.9 g, 100%).

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 6.33 (s, 1H), 2.29 (s, 3H), 2.18 (m, 2H), 0.91 (t, 3H).
¹⁹F NMR (400 MHz, DMSO-d₆) δ [ppm] = -98.14 (t, 2F).
¹³C NMR (100 MHz, DMSO-d₆) δ [ppm] = 161.60, 155.24, 155.10, 122.00 (t), 115.16, 102.73, 96.50, 30.45 (t), 19.93, 6.69.

Intermediate 120A - 3-(Aminomethyl)-4-(1,1-difluoropropyl)-6-methylpyridin-2(1H)-one hydrochloride



To a solution of intermediate **119A** (55.2 g, 260 mmol) in methanol (1.0 l) was added concentrated aqueous hydrochloric acid (25 ml) followed by palladium hydroxide (10.0 g), and the mixture was stirred under hydrogen (28 bar) at room temperature for 7 d. The mixture was then stirred at 55 °C

for 2 d, then at 60 °C for a further 5 d. The mixture was then filtered and fresh catalyst was added to the filtrate. The mixture was then stirred under hydrogen (28 bar) at 60 °C for 18 h. The mixture was then cooled, filtered and the filtrate concentrated. The crude product was purified by recrystallization from methanol/isopropanol, followed by recrystallization from concentrated
 5 hydrochloric acid in ethanol to give intermediate **120A** (10.9 g, 20%).

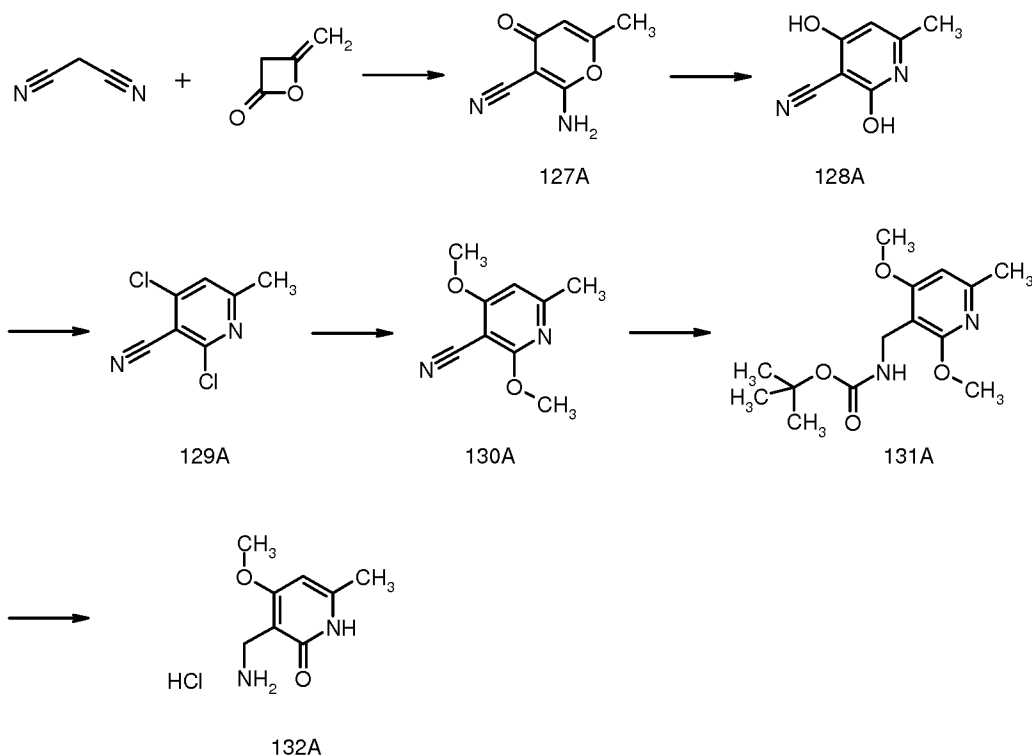
¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 8.14 (bs, 3H), 6.14 (s, 1H), 3.81 (s, 2H), 2.23 (s, 3H), 2.16 (m, 2H), 0.98 (t, 3H).

¹⁹F NMR (400 MHz, DMSO-d₆) δ [ppm] = -94.95 (m, 2F).

10 ¹³C NMR (100 MHz, DMSO-d₆) δ [ppm] = 163.58, 147.91 (t), 147.50, 123.46, 118.01, 102.02, 35.70, 31.55 (t), 19.15, 6.85.

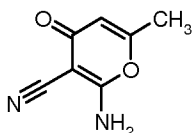
15 Synthesis of 3-(aminomethyl)-4-methoxy-6-methylpyridin-2(1H)-one hydrochloride salt - **132A** (Scheme K)

The synthesis of 3-(aminomethyl)-4-methoxy-6-methylpyridin-2(1H)-one is described in WO2013120104 and was used with slight adaptations:



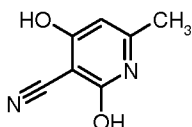
Scheme K

Intermediate **127A** – 2-amino-6-methyl-4-oxo-4H-pyran-3-carbonitrile



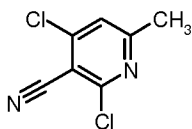
To a solution of malononitrile (30 g, 1.82 mol) in tetrahydrofuran (300 ml) was added sodium hydride (10.9 g, 1.82 mol) below 10 °C very carefully under a nitrogen atmosphere and then stirred for 0.5 h at 0 °C. Then 4-methyleneoxetan-2-one (38.18 g, 1.82 mol) was added dropwise below 0 °C and then the reaction was stirred at -10 °C for 1 h. The reaction was neutralized by 4N aqueous hydrochloric acid and concentrated *in vacuo* to give 2-amino-6-methyl-4-oxo-4H-pyran-3-carbonitrile, intermediate **127A** (combined yield from 4 batches: 240 g, 88% yield) as orange oil, which was used in the next step without purification.

10

Intermediate 128A - 2, 4-dihydroxy-6-methylnicotinonitrile

A solution of 2-amino-6-methyl-4-oxo-4H-pyran-3-carbonitrile (intermediate **127A**, 60 g, 1.60 mol) in 10 % HCl solution (800 ml) was refluxed for 5 hours with intensive stirring. After cooling to 18°C, the mixture was filtered, the filter cake was washed with water (800 ml) and ethanol (800 ml), methyl *tert*-butyl ether (800 ml) and dried *in vacuo* to give 2,4-dihydroxy-6-methylnicotinonitrile (intermediate **128A**, combined yield from 4 batches: 105 g, 58% yield) as yellow powder, which was used in the next step without purification.

20

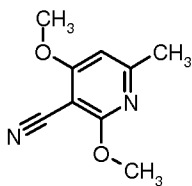
Intermediate 129A - 2, 4-dichloro-6-methylnicotinonitrile

To a solution of 2,4-dihydroxy-6-methylnicotinonitrile (intermediate **128A**, 30 g, 599.49 mmol) in POCl₃ (90 ml) was added DMF (730 mg, 29.97 mmol), then the mixture was heated at 95°C for 3 h. The mixture was concentrated *in vacuo*; the residue was dissolved in ethyl acetate (3 l) and neutralized by saturated aqueous sodium bicarbonate solution. Then the mixture was filtered and the organic layer was separated and dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 2,4-dichloro-6-methylnicotinonitrile (intermediate **129A**, combined yield from 3 batches: 90 g, 80% yield) as brown solid.

30

^1H NMR (400 MHz, methanol- d_4) δ [ppm] = 7.60 (s, 1 H), 2.58 (s, 3 H).

Intermediate 130A - 2,4-dimethoxy-6-methylnicotinonitrile

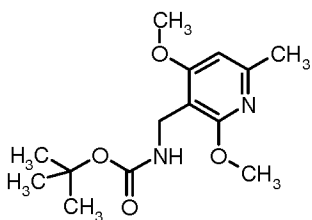


5

To a solution of 2,4-dichloro-6-methylnicotinonitrile (intermediate **129A**, 20 g, 427.73 mmol) in methanol (200 ml) was added sodium methanolate (11.55 g, 875.44 mmol) and stirred at 80 °C for 4 h. After cooling to 18 °C, the reaction was neutralized by acetic acid. The solvent was removed *in vacuo* and the residue was washed with water (800 ml) and methyl *tert*-butyl ether (800 ml). The resulting solid was concentrated in tetrahydrofuran (400 ml) to give 2,4-dimethoxy-6-methylnicotinonitrile (intermediate **130A**, combined yield from 4 batches: 72 g, 94% yield) as dark-yellow solid.

^1H NMR (400 MHz, methanol- d_4) δ [ppm] = 6.73 (s, 1 H), 3.99-4.00 (2 overlapping s, 6 H), 2.48(s, 3 H).

Intermediate 131A – *tert*-butyl((2,4-dimethoxy-6-methylpyridin-3-yl) methyl)carbamate

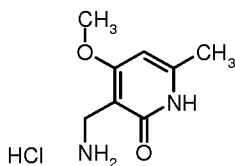


20

To a solution of 2,4-dimethoxy-6-methylnicotinonitrile (intermediate **130A**, 5 g, 224.48 mmol) in the mixture of tetrahydrofuran (80 ml) and methanol (80 ml) was added Raney Nickel (5 g), triethylamine (15 g, 1.19 mol) and di-*tert*-butyl dicarbonate (18.37 g, 673.44 mmol). Then the mixture was stirred under an atmosphere of hydrogen at 25°C for 16 h. The reaction was concentrated to give *tert*-butyl((2,4-dimethoxy-6-methylpyridin-3-yl)methyl)carbamate (intermediate **131A**, combined yield from 8 batches: 54.4 g, 86% yield) as yellow solid.

^1H NMR (400 MHz, methanol- d_4) δ [ppm] = 6.57 (s, 1 H), 4.21 (s, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.41 (s, 3 H), 1.45 (s, 9 H).

25

Intermediate 132A 3-(aminomethyl)-4-methoxy-6-methylpyridin-2(1H)-one hydrochloride

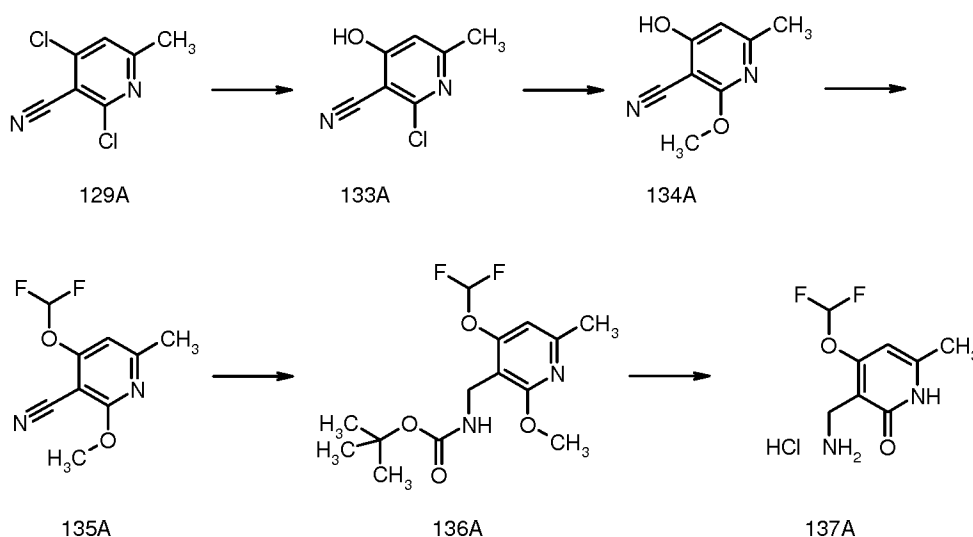
- 5 *tert*-Butyl((2,4-dimethoxy-6-methylpyridin-3-yl)methyl)carbamate (intermediate **131A**, 20 g, 10.63 mmol) was dissolved in 4N aqueous hydrochloric acid (400 ml) and refluxed at 110 °C for 5 h. Then the reaction was concentrated *in vacuo*. The residue was dissolved in ethanol (200 ml) and stirred for 15 min, filtered and washed with methyl *tert*-butyl ether (200 ml). The mixture was concentrated *in vacuo* to give 3-(aminomethyl)-4-methoxy-6-methylpyridin-2(1H)-one hydrochloride (intermediate **132A**, combined yield from 2 batches: 22 g, 76% yield) as white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ [ppm] = 11.76 (s, 1 H), 7.98 (br. s, 2 H), 6.20 (s, 1 H), 3.85 (s, 3 H), 3.73-3.72 (d, 2 H), 2.23 (s, 3 H).

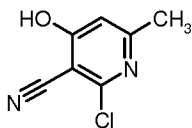
15 **Synthesis of 3-(aminomethyl)-4-(difluoromethoxy)-6-methylpyridin-2(1H)-one hydrochloride salt - 137A (Scheme L)**

The synthesis of 3-(aminomethyl)-4-(difluoromethoxy)-6-methylpyridin-2(1H)-one is described in WO2013120104 and was used with slight adaptations:

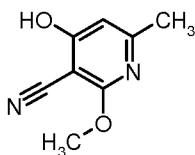
20



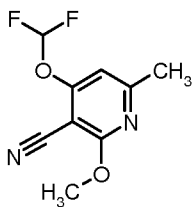
Scheme L

Intermediate 133A – 2-chloro-4-hydroxy-6-methylnicotinonitrile

A solution of 2,4-dichloro-6-methylnicotinonitrile (150 g, 3.21 mol) and potassium acetate (236.13 g, 9.64 mol) in DMF (700 ml) was stirred at 80 °C for 12 h under nitrogen after which target compound was detected and the starting material was consumed (based on TLC analysis). Then the mixture was concentrated in high vacuum to remove most of DMF and then dissolved in ethyl acetate (10 l) and filtered to remove the salt. The organic layer was washed with water (3x 800 ml) and dried over sodium sulfate, filtered and concentrated *in vacuo* to give 2-chloro-4-hydroxy-6-methylnicotinonitrile (intermediate **133A**, combined yield from 4 batches: 300 g, 49% yield) as brown oil which was used in the following step without further purification.

Intermediate 134A – 4-hydroxy-2-methoxy-6-methylnicotinonitrile

A mixture of 2-chloro-4-hydroxy-6-methylnicotinonitrile (intermediate **133A**, 100 g, 1.78 mol) and sodium methanolate (160.22 g, 8.91 mol) in methanol (500 ml) was stirred at 80 °C for 12 h under nitrogen. Then the reaction mixture was acidified with 1N aqueous hydrochloric acid to pH=2~3 and then concentrated *in vacuo* to remove most methanol. The residue was extracted with ethyl acetate (1 l) and water (1 l), the organic layer was dried with sodium sulfate, filtered and concentrated *in vacuo* to give 4-hydroxy-2-methoxy-6-methylnicotinonitrile (intermediate **134A**, combined yield from 3 batches: 120 g, 41% yield) as dark yellow solid, which was used in the subsequent step without further purification.

Intermediate 135A – 4-(difluoromethoxy)-2-methoxy-6-methylnicotinonitrile

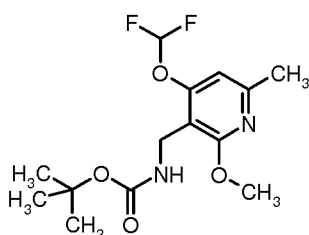
To a solution of 4-hydroxy-2-methoxy-6-methylnicotinonitrile (intermediate **134A**, 60 g, 731.0

mmol) in DMF (400 ml) was added sodium hydride (26.32 g, 2.2 mol) portionwise at 0 °C under nitrogen and the mixture was stirred for 30 min and then ethyl 2-chloro-2,2-difluoroacetate (CAS 383-62-0, 185.42 g, 2.34 mol) was added dropwise with vigorous stirring over the course of 30 min. Then the reaction was warmed to 80 °C and was stirred for 12 h under nitrogen. Then the reaction was quenched with saturated aqueous sodium carbonate solution, extracted with ethyl acetate (2 l) and water (2 l), the organic layer was dried with sodium sulfate and filtered and concentrated. The residue was purified by column chromatography on silica gel (petrol ether/ethyl acetate = 80/1) to give 4-(difluoromethoxy)-2-methoxy-6-methylnicotinonitrile (intermediate **135A**, combined yield from 2 batches: 21 g, 13% yield) as a yellow solid.

10

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 6.70 (t, 1 H), 6.67 (s, 1 H), 4.05 (s, 3 H), 2.52 (s, 3 H).

Intermediate 136A – *tert*-butyl((4-(difluoromethoxy)-2-methoxy-6-methylpyridin-3-yl)methyl)carbamate

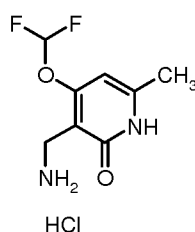


15

To a solution of 4-(difluoromethoxy)-2-methoxy-6-methylnicotinonitrile (intermediate **135A**, 1.40 g, 98.1 mmol) and di-*tert*-butyl dicarbonate (2.14 g, 147.15 mmol), triethylamine (992.67 mg, 147.15 mmol) in tetrahydrofuran (30 ml) was added Raney-Nickel (1.12 g) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (2 bar) at 30 °C for 12 h. The reaction mixture was filtered and the filtrate was concentrated to give *tert*-butyl((4-(difluoromethoxy)-2-methoxy-6-methylpyridin-3-yl)methyl)carbamate (intermediate **136A**, combined yield from 15 batches: 23 g, 74% yield) as a yellow oil which was used without further purification.

25

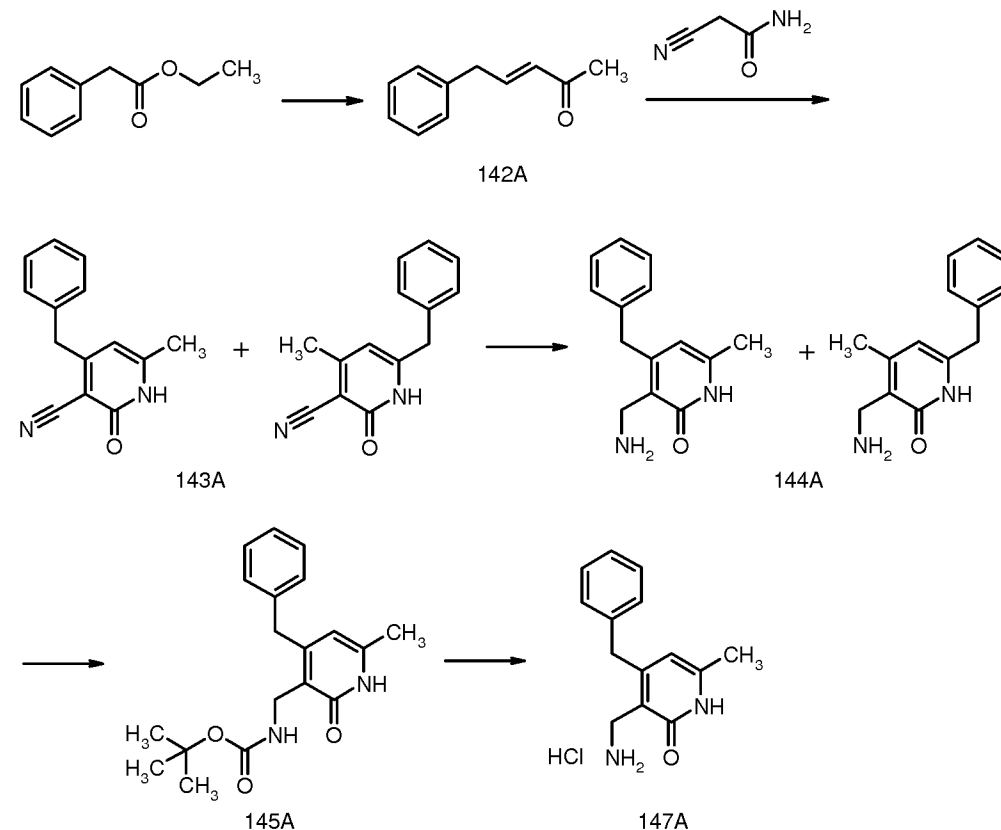
Intermediate 137A – 3-(aminomethyl)-4-(difluoromethoxy)-6-methylpyridin-2(1H)-one hydrochloride



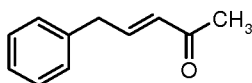
A solution of *tert*-butyl((4-(difluoromethoxy)-2-methoxy-6-methylpyridin-3-yl)methyl)carbamate (intermediate **136A**, 12 g, 50.26 mmol) in 4N aqueous hydrochloric acid (120 ml) was stirred at 120 °C for 4 h. The formed precipitate was filtered off and dried in high vacuum, washed with ethanol (200 ml), filtered and dried again *in vacuo* to give 3-(aminomethyl)-4-(difluoromethoxy)-6-methylpyridin-2(1H)-one hydrochloride (intermediate **137A**, combined yield from 2 batches: 18.1 g, 66%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 12.21 (s, 1 H), 8.15 (br. s, 3 H), 7.41 (t, 1 H), 6.18 (s, 1 H), 3.76-3.75 (d, 2 H), 2.26 (s, 3 H).

Synthesis of 3-(aminomethyl)-6-benzyl-4-methylpyridin-2(1H) -one hydrochloride salt - 147A - and 3-(aminomethyl)-4-benzyl-6-methylpyridin-2(1H) -one hydrochloride – 148A (Scheme M)



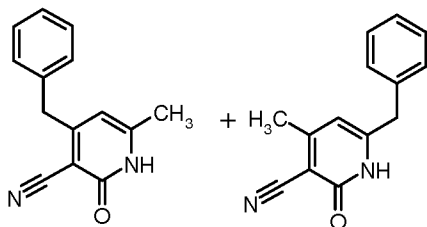
Scheme M

Intermediate 142A – (E)-5-phenylpent-3-en-2-one

- 5 To a mixture of sodium amide (228.07 g, 5.85 mol) in tetrahydrofuran (2 l) under nitrogen at -5 °C was added ethyl 2-phenylacetate (300.00 g, 1.83 mol) and acetone (106.11 g, 1.83 mol). The mixture was stirred at 20 °C for 12 h. Then the mixture was acidified to pH 4.0-5.0 with 1 N aqueous hydrochloric acid, and extracted with ethyl acetate (3x 2 l). The combined organic phases were washed with brine (2 x 2 l), dried with anhydrous sodium sulfate, filtered and concentrated *in*
- 10 *vacuo*. The residue was purified by silica gel chromatography (petrol ether/ethyl acetate 100:1 to 20:1) to afford (E)-5-phenylpent-3-en-2-one (150.00 g, 936.27 mmol, 51% yield) as orange oil.

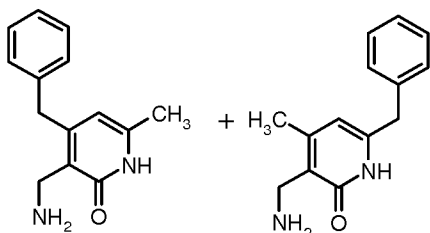
¹H NMR (400 MHz, CDCl₃) δ [ppm] = 7.33-7.35 (m, 5 H), 4.13-4.14 (m, 2 H), 3.60 (s, 2 H), 2.05 (d, 3 H).

15

Intermediate 143A – 4-benzyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile and 6-benzyl-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

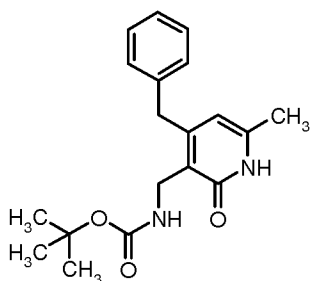
- 20 A solution of (E)-5-phenylpent-3-en-2-one (intermediate **142A**, 150.00 g, 936.27 mmol) and 2-cyanoacetamide (78.72 g, 936.27 mmol) in ethanol (1 l) was heated to 75 °C. Piperidine (79.72 g, 936.27 mmol) was added and the reaction mixture was heated to 80 °C for 30 min. The reaction was slowly quenched with water (500 ml) and stirred for 20 min. The mixture was filtered and concentrated to give the products 4-benzyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile and
- 25 6-benzyl-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (70.00 g, 312 mmol, 33% yield) in an approximately 1.5:1 mixture as yellow-green solid. This mixture was used in the subsequent reaction without further purification.

- Intermediate 144A – 3-(aminomethyl)-4-benzyl-6-methylpyridin-2(1H)-one and 3-(aminomethyl)-6-benzyl-4-methylpyridin-2(1H)-one**
- 30



To a solution of 4-benzyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile and 6-benzyl- 4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (intermediate **143A**, 5.0 g, 219.29 mmol) in DMF
 5 (100 ml) was added Raney-Nickel (5 g) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (3.5 bar) at 50 °C for 12 h. TLC showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated to give a mixture of crude 3-(aminomethyl)-4- benzyl-6-methylpyridin-2(1H)-one and 3-(aminomethyl)-6-benzyl-4-methylpyridin-2(1H)- one
 10 (combined yield from 28 batches: 160.00 g) as brown oil. This mixture was used in the subsequent step without further purification.

Intermediate 145A – tert-butyl ((4-benzyl-6-methyl-2-oxo-1,2-dihydropyridin -3-yl)methyl)carbamate

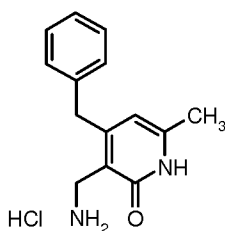


15

To a solution of 3-(aminomethyl)-4-benzyl-6-methylpyridin-2(1H)-one and 3-(aminomethyl) -6-benzyl-4-methylpyridin-2(1H)-one (intermediate **144A**, 80.00 g, 350.44 mmol) in dichloromethane (800 ml) was added triethylamine (35.46 g, 350.43 mmol) and di-*tert*-butyl dicarbonate (42.06 g,
 20 192.74 mmol) under nitrogen at 0 °C. The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was quenched with 1 N aqueous hydrochloric acid (300 ml); the mixture was extracted with dichloromethane (3x 500 ml). The combined organic layers were washed with brine (500 ml), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Separation of the two regioisomeric products was accomplished by preparative HPLC to yield the pure product
 25 *tert*-butyl ((4-benzyl-6-methyl-2-oxo- 1,2-dihydropyridin-3-yl)methyl)carbamate (combined yield from two batches: 7.4 g) as yellow solid.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 7.16 – 7.33 (m, 5 H), 5.89 (s, 1 H), 5.67 (br. s, 1 H), 4.28 (d, 2 H), 4.07 (s, 2 H), 2.25 (s, 3 H), 1.43 (s, 9 H).

5 **Intermediate 147A - 3-(aminomethyl)-4-benzyl-6-methylpyridin-2(1H)-one hydrochloride salt**

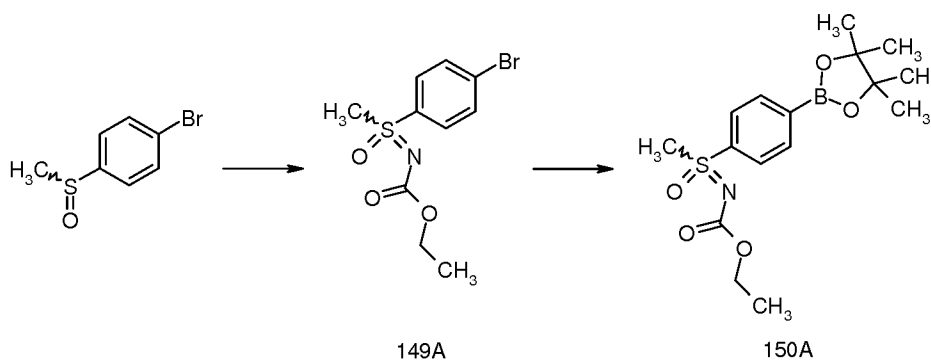


A solution of *tert*-butyl ((4-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl) methyl)carbamate (intermediate **145A**, 7.40 g, 31.57 mmol) in hydrochloric acid (4 N in ethyl acetate, 100 ml) was stirred at 20 °C for 3 h. Then the reaction was filtered and the filter cake was dried *in vacuo* to give the crude product 3-(aminomethyl)-4-benzyl-6-methyl pyridin-2(1H)-one hydrochloride (intermediate **147A**, 6.00 g) as yellow solid.

15 ¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 11.93 (s, 1 H), 8.061 (br. s, 3 H), 7.29-7.33 (m, 2 H), 7.19-7.24 (m, 3 H), 5.87 (s, 1 H), 3.94 (s, 2 H), 3.85 (d, 2 H), 2.13 (s, 3 H).

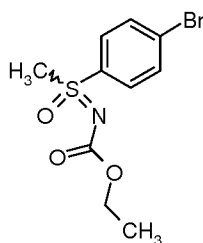
Synthesis of *rac*-ethyl {methyl(oxido)[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-λ⁶-sulfanylidene}carbamate – 150A (Scheme N)

20



Scheme N

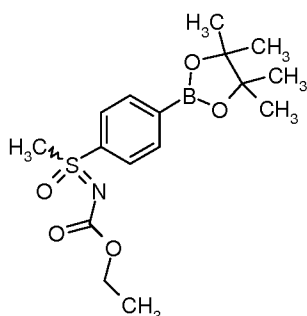
Intermediate 149A – *rac*-ethyl [(4-bromophenyl)(methyl)oxido-λ⁶-sulfanylidene]carbamate



To a suspension of *rac*-1-bromo-4-(methylsulfinyl)benzene (CAS 934-71-4, 100.0 g, 0.456 mol), ethyl carbamate (77.0 g, 0.864 mol), magnesium oxide (73.4 g, 1.821 mol) and dirhodium tetraacetate (4.7 g, 10.63 mmol) in dichloromethane (1.5 l) was added (diacetoxyiodo)benzene (CAS 3240-34-4, 221.5 g, 0.688 mol) carefully under nitrogen. The mixture was stirred at room temperature for 7 d. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (gradient of ethyl acetate in petroleum ether) to give the title compound (95.0 g, 68.0% of theory) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 7.87 - 7.85 (m, 2H), 7.76 - 7.74 (m, 2H), 4.13 - 4.08 (m, 2H), 3.30 (s, 3H), 1.28 - 1.22 (m, 3H).

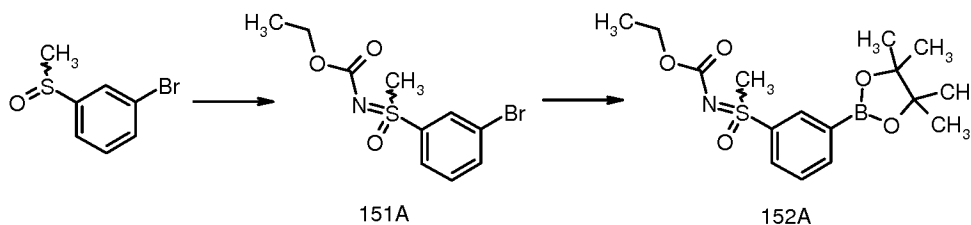
Intermediate 150A – *rac*-ethyl {methyl(oxido)[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-λ-sulfanylidene}carbamate



To a solution of intermediate **149A** (95.0 g, 0.310 mol) in anhydrous dioxane (1.5 l) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (95.0 g, 0.374 mol), potassium acetate (61.0 g, 0.622 mol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (CAS 95464-05-4, 7.0 g, 9.57 mmol) under nitrogen. After the addition, the mixture was stirred at 80 °C for 18 h. The mixture was filtered and to the filtrate was added acetic acid (18.0 g, 0.30 mol) and pinacol (18.0 g, 0.152 mol). The mixture was stirred at room temperature for 18 h. The mixture was concentrated and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 20: 1 ~ 5: 1) to give the crude, which was washed by petroleum ether/ethyl acetate (2 x 100 ml, petroleum ether/ethyl acetate = 1: 10) to give the title compound (87.0 g) as a white solid.

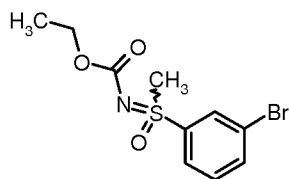
^1H NMR (400 MHz, methanol- d_4) δ [ppm] = 8.04 - 7.97 (m, 4H), 4.13 - 4.06 (m, 2H), 3.30 (s, 3H), 1.36 (s, 12H), 1.25 - 1.21 (m, 3H).

5 **Synthesis of *rac*-ethyl {methyl(oxido)[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]- λ^6 -sulfanylidene}carbamate – 152A (Scheme O)**



Scheme O

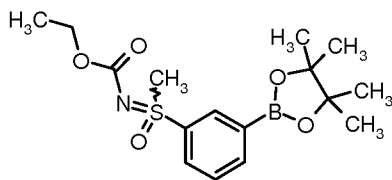
10 **Intermediate 151A – *rac*- ethyl [(3-bromophenyl)(methyl)oxido- λ^6 -sulfanylidene]carbamate**



To a suspension of *rac*-1-bromo-3-(methylsulfinyl)benzene (CAS 29959-92-0, 55.0 g, 0.251 mol), ethyl carbamate (45.0 g, 0.505 mol), magnesium oxide (40.3 g, 1.0 mol) and dirhodium tetraacetate (2.6 g, 7.6 mmol) in dichloromethane (600 ml) was added (diacetoxyiodo)benzene (CAS 3240-34-4, 122.0 g, 0.378 mol) carefully under nitrogen. The mixture was stirred at room temperature for 5 d. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude, which was purified by column chromatography on silica gel (gradient of ethyl acetate in petroleum ether) to give *rac*-ethyl[(3-bromophenyl)(methyl)oxido- λ^6 -sulfanylidene]carbamate (55.0 g, 81.4% of theory) as white solid.

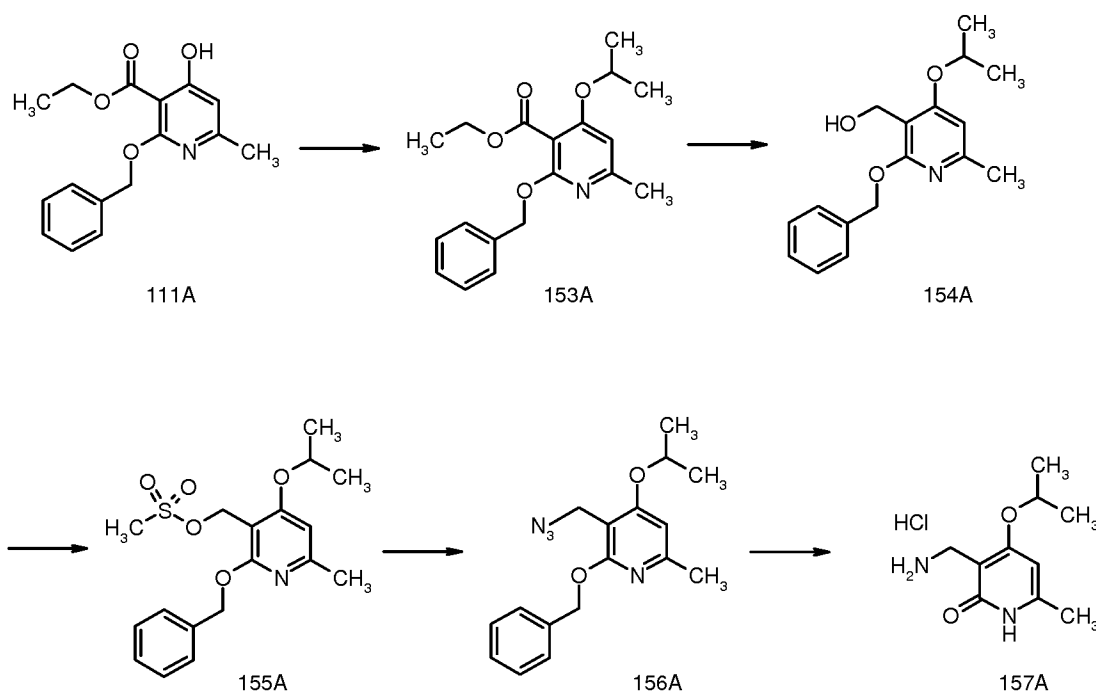
^1H NMR (400 MHz, CDCl_3) δ = 8.15 - 8.14 (m, 1H), 7.94 - 7.92 (m, 1H), 7.81 - 7.80 (m, 1H), 7.51 - 7.47 (m, 1H), 4.13 - 4.08 (m, 2H), 3.32 (s, 3H), 1.25 (t, 3H).

25 **Intermediate 152A: *rac*-ethyl {methyl(oxido)[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]- λ^6 -sulfanylidene}carbamate**

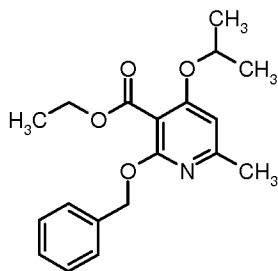


- To a solution of ethyl [(3-bromophenyl)(methyl)oxido-lambda⁶-sulfanylidene]carbamate (intermediate **151A**, 55.0 g, 0.18 mol) in anhydrous dioxane (600 ml) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (53.0 g, 0.209 mol), potassium acetate (35.3 g, 0.34 mol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (CAS 95464-05-4, 4.0 g, 5.47 mmol) under nitrogen. After the addition, the mixture was stirred at 80 °C for 4 h. The mixture was filtered and to the filtrate was added acetic acid (20.0 g, 0.33 mol) and pinacol (30.0 g, 0.253 mol). The mixture was stirred at room temperature for 18 h. The mixture was concentrated and purified by chromatography on silica gel (gradient of ethyl acetate in petroleum ether) to give the crude, which was washed with petroleum ether/ethyl acetate (2 x 100 ml, petroleum ether: ethyl acetate = 1: 10) to give *rac*-ethyl {methyl(oxido)[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-lambda⁶-sulfanylidene}carbamate (35.0 g) as white solid.
- ¹H NMR (400 MHz, methanol-d₄) δ [ppm] = 8.40 (s, 1H), 8.09 - 8.07 (m, 1H), 7.61 - 7.58 (m, 1H), 4.13 - 4.07 (m, 2H), 3.32 (s, 3H), 1.35 (s, 12H), 1.25 - 1.22 (m, 3H).

Synthesis of 3-(aminomethyl)-4-isopropoxy-6-methylpyridin-2(1H)-one hydrochloride - 157A (Scheme P)



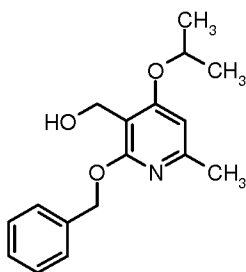
Scheme P

Intermediate 153A – ethyl 2-(benzyloxy)-4-isopropoxy-6-methylnicotinate

- 5 To a solution of ethyl 2-(benzyloxy)-4-hydroxy-6-methylnicotinate (intermediate **111A**, 2 g, 6.96 mmol), and potassium carbonate (2.89 g, 20.9 mmol) in DMF (60 ml) was added 2-iodopropane (0.76 ml, 7.66 mmol), and the reaction was stirred at room temperature for 12 h. Then, another 0.5 ml of 2-iodopropane were added and the mixture was stirred for 24 h. After this, the reaction mixture was filtered through a pad of Celite. The Celite was washed with ethyl acetate, and the combined filtrates were concentrated. The residue was treated with dichloromethane, and the resulting precipitate was filtered off and washed with dichloromethane. The combined filtrates were concentrated *in vacuo* to yield the title compound as a yellow oil (2.1 g, 90%),

¹H-NMR (400MHz, DMSO-d₆) δ [ppm] = 1.16 - 1.28 (m, 9H), 2.37 (s, 3H), 4.22 (q, 2H), 4.74 (spt, 1H), 5.35 (s, 2H), 6.75 (s, 1H), 7.23 - 7.43 (m, 5H).

MS (ESI): [M + H]⁺ = 330.2.

Intermediate 154A – [2-(benzyloxy)-4-isopropoxy-6-methylpyridin-3-yl]methanol

- 20 To a solution of ethyl 2-(benzyloxy)-4-isopropoxy-6-methylnicotinate (intermediate **153A**, 2.1 g, 6.38 mmol) in toluene (30 ml) was added sodium bis(2-methoxyethoxy)aluminum hydride (1.98 g, 6.38 mmol), and the reaction mixture was stirred at 80 °C for 12 h, after which additional sodium bis(2-methoxyethoxy)aluminum hydride was added and stirred at 80 °C for further 2 h. The reaction was then cooled to 0 °C and 2N aqueous sodium hydroxide was added. The organic phase was separated, washed with brine, dried with sodium sulfate and concentrated. The residue was stirred in hexane, filtered and dried to give [2-(benzyloxy)-4-isopropoxy-6-methylpyridin-3-

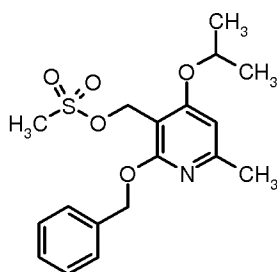
yl]methanol (1.6 g, 87%).

¹H-NMR (400MHz, DMSO-d₆) δ [ppm]= 1.28 (d, 6H), 2.33 (s, 3H), 4.30 (t, 1H), 4.41 (d, 2H), 4.68 (spt, 1H), 5.33 (s, 2H), 6.62 (s, 1H), 7.24 - 7.41 (m, 3H), 7.43 - 7.52 (m, 2H).

5

MS (ESI): [M + H]⁺ = 288,1.

Intermediate 155A – [2-(benzyloxy)-4-isopropoxy-6-methylpyridin-3-yl]methyl methanesulfonate

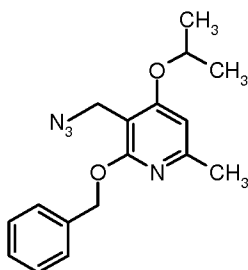


10

To a solution of [2-(benzyloxy)-4-isopropoxy-6-methylpyridin-3-yl]methanol (intermediate **154A**, 1.6 g, 5.57 mmol) in dichloromethane (40 ml) was added N-ethyl-diisopropylamine 1.26 ml, 7.24 mmol), and methanesulfonyl chloride (0.7 g, 6.13 mmol) at 0 °C. The cooling bath was removed and the reaction was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo* and used directly in the following step.

15

Intermediate 156A – 3-(azidomethyl)-2-(benzyloxy)-4-isopropoxy-6-methylpyridine

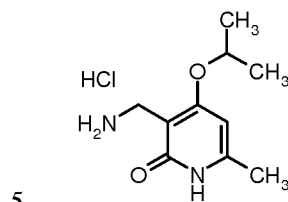


20

To a solution of crude [2-(benzyloxy)-4-isopropoxy-6-methylpyridin-3-yl]methyl methanesulfonate (Intermediate **155A**, 2.03 g) in DMF (60 ml) was added N-ethyl-diisopropylamine (1.26 ml, 7.22 mmol), followed by sodium azide (0.4 g, 6.11 mmol). The mixture was stirred at room temperature for 2 h. Then, 1 N aqueous sodium hydroxide was added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was used without purification in the following step.

25

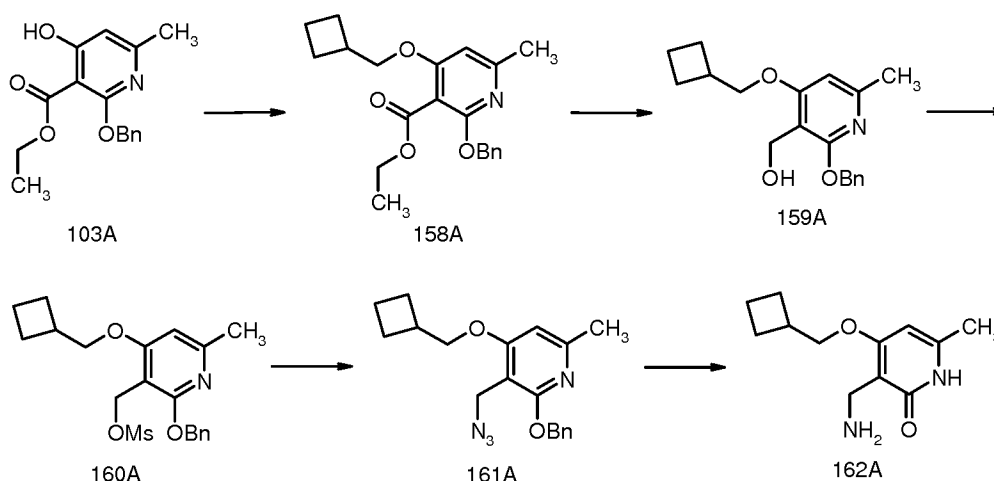
Intermediate 157A – 3-(aminomethyl)-4-isopropoxy-6-methylpyridin-2(1H)-one hydrochloride



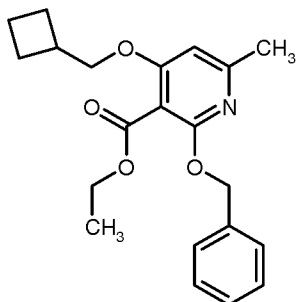
To a solution of crude 3-(azidomethyl)-2-(benzyloxy)-4-isopropoxy-6-methylpyridine (intermediate **156A**, 1.5 g) in ethanol (50 ml) was added glacial acetic acid (0.55 ml) and palladium dihydroxide on charcoal (20%) (400 mg). The reaction was put under hydrogen atmosphere at 40.12 bar and stirred for 24 h at 23 °C. The same amount of palladium catalyst was added and the hydrogenation was continued at 40.1 bar for further 24 h at 23 °C. The mixture was filtrated, the filter cake was washed with methanol (40 ml) and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol, triturated with hydrochloric acid (4 N in dioxane) and concentrated, re-dissolved and concentrated several times from ethanol, to yield 3-(aminomethyl)-4-isopropoxy-6-methylpyridin-2(1H)-one hydrochloride (760 mg, 58% over 3 steps).

¹H-NMR (400MHz, DMSO-d₆) δ [ppm]= 1.29 (d, 6H), 2.20 (s, 3H), 3.71 (q, 2H), 4.61 - 4.84 (m, 1H), 6.19 (s, 1H), 7.94 (br. s., 3H), 11.71 (br. s., 1H).

20 Synthesis of 3-(Aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-one - 162A (Scheme R)



Scheme R

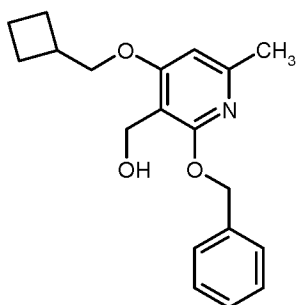
Intermediate 158A - Ethyl 2-(benzyloxy)-4-(cyclobutylmethoxy)-6-methylnicotinate

- 5 A mixture of intermediate **103A** (2.0 g, 6.96 mmol), potassium carbonate (2.89 g, 20.9 mmol) and (bromomethyl)cyclobutane (11.4 g, 7.66 mmol) in DMF (60 mL) was stirred at room temperature under an argon atmosphere for 18 h. The mixture was filtered over celite and the celite cake was washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was mixed with dichloromethane (0.60 l). The solids were filtered and washed with dichloromethane. The filtrate
10 was concentrated *in vacuo* to give intermediate **158A**, 1.62 g (65 %) as yellow oil.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.21 (t, 3H), 1.72 - 1.94 (m, 4H), 1.95 - 2.07 (m, 2H), 2.37 (s, 3H), 2.59 - 2.71 (m, 1H), 4.04 (d, 2H), 4.22 (q, 2H), 5.36 (s, 2H), 6.74 (s, 1H), 7.26 - 7.32 (m, 1H), 7.33 - 7.42 (m, 4H).

15

MS (ESI): [M + H]⁺ = 356.2.

Intermediate 159A - [2-(benzyloxy)-4-(cyclobutylmethoxy)-6-methylpyridin-3-yl]methanol

20

- To sodium bis(2-methoxyethoxy)aluminum dihydride (1.54 ml; 65% in toluene, 5.1 mmol) in toluene (1 l) was slowly added intermediate **158A** (1.8 g, 5.1 mmol) in toluene (30 ml) at room temperature. The temperature rose to 30 °C and the mixture was stirred at room temperature for 12 h under an argon atmosphere; A further portion of sodium bis(2-methoxyethoxy)aluminum dihydride (1.54 ml, 5.1 mmol) was added slowly to the reaction mixture, then the reaction mixture
25 was heated at 80 °C (oil bath temperature) for 2 h. The reaction mixture was cooled to 5 °C in an

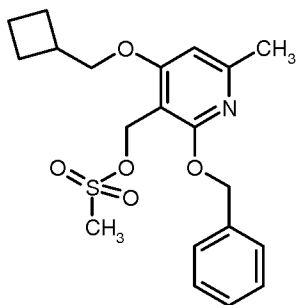
ice bath, and aqueous sodium hydroxide (2 M) was added dropwise. The organic partition was collected and washed with brine (2 x 20 mL), dried over sodium sulfate, filtered and concentrated to give a crude yellow solid. The crude product was suspended in hexane and filtered to yield intermediate **105A**, 1.1 g (44 %).

5

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.79 - 1.96 (m, 4H), 2.01 - 2.13 (m, 2H), 2.34 (s, 3H), 2.62 - 2.80 (m, 1H), 4.01 (d, 2H), 4.44 (br. s., 2H), 5.34 (s, 2H), 6.62 (s, 1H), 7.21 - 7.41 (m, 4H), 7.46 (m, 1H).

10 MS (ESI): [M + H]⁺ = 314.2.

Intermediate 160A - [2-(benzyloxy)-4-(cyclobutylmethoxy)-6-methylpyridin-3-yl]methyl methanesulfonate

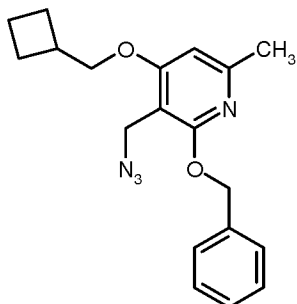


15

To an ice-cooled solution of intermediate **159A** (1.1 g, 3.5 mmol) in dichloromethane (40 ml) was added *N,N*-diisopropylethylamine (0.80 ml, 4.56 mmol), followed by methanesulfonyl chloride (0.30 ml, 3.86 mmol) being added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The solvent was removed *in vacuo* (water bath 20 °C) to yield intermediate **160A**, which was used in the next step without purification.

20

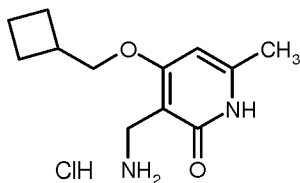
Intermediate 161A - 3-(azidomethyl)-2-(benzyloxy)-4-(cyclobutylmethoxy)-6-methylpyridine



25 To intermediate **160A** (1.37 g, crude product from the previous reaction) in DMF (40 ml) was added diisopropylethylamine (0.79 ml, 4.55 mmol), followed by sodium azide (0.25 g, 3.85 mmol),

and the reaction mixture was stirred under argon at room temperature for 2 h. The reaction mixture was quenched with dilute sodium hydroxide solution (40 ml, 1 M) and extracted with ethyl acetate. The organic layer was collected and washed with brine solution, dried over sodium sulfate, filtered and the solution was concentrated *in vacuo*, to yield intermediate **107A** (1 g crude), which was used in the next step without purification.

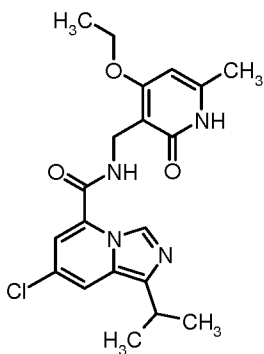
Intermediate 162A - 3-(aminomethyl)-4-(cyclobutylmethoxy)-6-methylpyridin-2(1H)-one hydrochloride



To intermediate **161A** (crude material from the previous reaction) in an autoclave was added ethanol (50 ml) and acetic acid (0.34 ml; 5.91 mmol) followed by palladium hydroxide (20% on charcoal, 207 mg, 0.3 mmol). The autoclave was pressurized with hydrogen (40 bar) and the reaction mixture was stirred for 42 h at room temperature. A further portion of palladium hydroxide was added (210 mg) and the reaction mixture was pressurized with hydrogen (40 bar) and stirred for 20 h. The reaction mixture was filtered through celite, washed with methanol and the solvent removed *in vacuo*. The residue was triturated with hydrochloric acid (4N in dioxane) and concentrated *in vacuo*. The crude material was then redissolved in ethanol and concentrated several times to yield after final concentration intermediate **162A** (657 mg, 72% over three steps).

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.81 - 1.91 (m, 4H), 2.00 - 2.09 (m, 2H), 2.21 (s, 3H), 2.63 - 2.75 (m, 1H), 3.73 (m, 2H), 4.05 (d, 2H), 6.19 (s, 1H), 7.86 (br. s., 2H), 11.74 (br. s., 1H).

Intermediate 201A – 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide

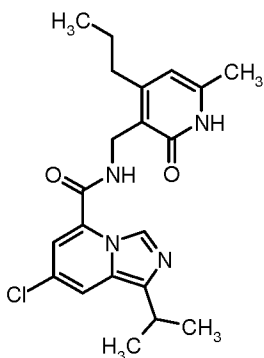


5 6 g 7-Chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylic acid (intermediate **8A**, 25.1 mmol), 5.04 g 3-(aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-on (intermediate **108A**, 27.65 mmol) and 12.4 g O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 32.68 mmol) were dissolved in 180 ml anhydrous DMF and treated with 10.9 ml *N,N*-diisopropylethylamine (62.85 mmol, 2.5 eq.). The resulting mixture was stirred at room
10 temperature overnight. The mixture was then poured into water and the solid material was filtered off. The filter cake was triturated with methanol, filtered and the solid was dried *in vacuo* to yield 4.5 g (46%) of the target compound.

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 11.44 (br. s, 1 H), 8.77 (s, 1 H), 8.69 (t, 1 H), 7.91 (s, 1
15 H), 7.08 (s, 1 H), 6.08 (s, 1 H), 4.28 (d, 2 H), 4.08 (q, 2 H), 2.17 (s, 3 H), 1.23 – 1.27 (m, 9 H).

MS (ESI): [M + H]⁺ = 403.

Intermediate 202A – 7-chloro-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide



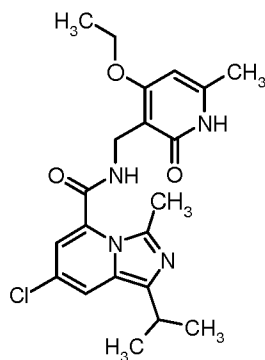
600 mg 7-Chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylic acid (intermediate **8A**, 2.5 mmol), 498 mg 3-(aminomethyl)-6-methyl-4-propylpyridin-2(1H)-one hydrochloride (intermediate

102A, 2.7 mmol) and 1.15 g O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 3.02 mmol) were dissolved in 12 ml anhydrous DMF and treated with 1.09 ml *N,N*-diisopropylethylamine (6.28 mmol). The resulting mixture was stirred at room temperature overnight. The mixture was then poured into water and the solid material was filtered off to yield 718 mg (72%) of the target compound.

¹H NMR (400 MHz, DMSO) δ [ppm] = 11.53 (br. s, 1 H), 8.91 (t, 1 H), 8.81 (s, 1 H), 7.94 (s, 1 H), 7.12 (s, 1 H), 5.89 (s, 1 H), 4.34 (d, 2 H), 2.12 (s, 3 H), 1.44 – 1.57 (m, 2 H), 1.20 – 1.28 (d, 6 H), 0.88 (t, 3 H) (3 H obscured by solvent signal).

MS (ESI): $[M + H]^+ = 403$.

Intermediate 203A - 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methylimidazo[1,5-a]pyridine-5-carboxamide

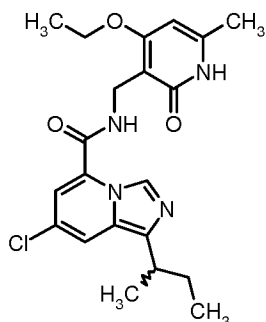


265 mg Lithium 7-chloro-3-methyl-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylate (intermediate **12A**, 1.025 mmol) were dissolved in 5ml anhydrous DMF. 178 μ l *N,N*-diisopropylethylamine (6.28 mmol) and 389.59 mg O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 3.02 mmol) were added 205 mg 3-(aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-one (intermediate **108A**, 1.13 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. 10 ml water was added. The mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic layers were washed with brine, dried over sodium sulphate, filtered and the solvent was removed *in vacuo*. The crude product was dissolved into a minimum volume of hot ethyl acetate and cooled to room temperature to yield a yellow precipitate which was collected and washed with diethyl ether to yield 363 mg (42%) of the title compound as a yellow solid.

¹H NMR (400 MHz, methanol-*d*₄) δ [ppm] = 1.29 (d, 6H), 1.40 (t, 3H), 2.29 (s, 3H), 2.52 (s, 3H), 3.24 (sept, 1H), 4.18 (q, 2H), 4.44 (s, 2H), 6.22 (s, 1H), 6.65 (d, 1H), 7.58 (d, 1H) (2 H obscured by solvent signal).

MS (ESI): $[M + H]^+ = 417$

Intermediate 204A – *rac*-1-sec-butyl-7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide



5

200 mg *rac*-1-sec-butyl-7-chloroimidazo[1,5-a]pyridine-5-carboxylic acid (intermediate **19A**, 0.79 mmol) were dissolved in 7.5ml anhydrous dimethylformamide. 414 μ l N,N-diisopropylethylamine (2.37 mmol) and 451.4 mg O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 1.19 mmol) were added 216 mg 3-(aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-one (intermediate **108A**, 1.5 mmol) was added. The resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated. The residue was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The crude was purified by flash chromatography on a NH-Silica Phase with dichloromethane 100% to dichloromethane/ methanol 80%/20% as eluent to yield 230.8 mg (70%) of the title compound.

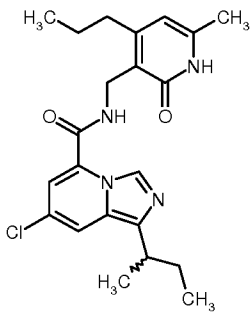
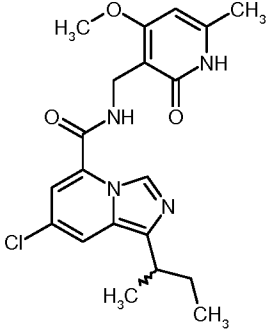
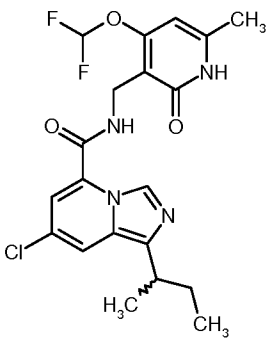
$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ [ppm]= 0.72 (t, 3H), 1.21 - 1.30 (m, 6H), 1.54 - 1.74 (m, 2H), 2.18 (s, 3H), 3.06 (sxt, 1H), 4.09 (q, 2H), 4.29 (d, 2H), 6.09 (s, 1H), 7.08 (d, 1H), 7.90 (d, 1H), 8.70 (t, 1H), 8.80 (s, 1H), 11.46 (s, 1H).

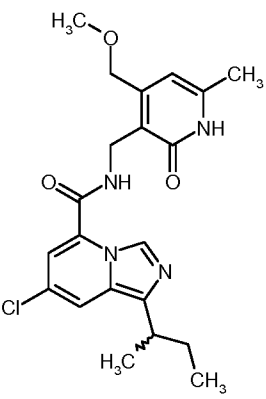
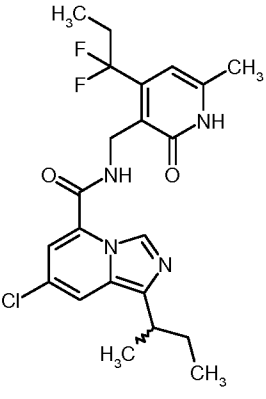
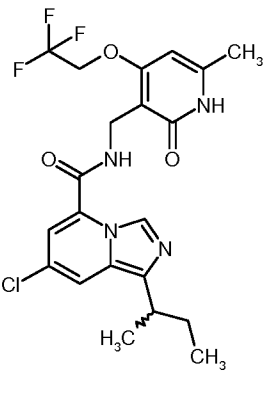
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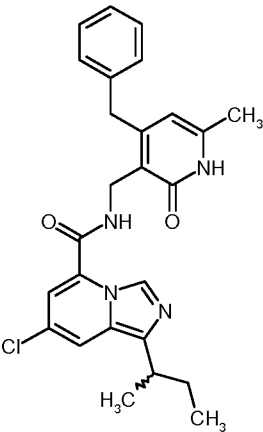
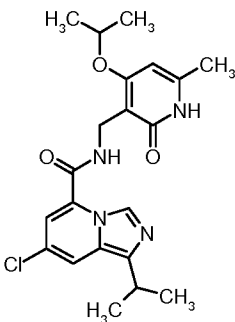
MS (ESI): $[M + H]^+ = 417.1$

The following intermediates were prepared in analogy to intermediates **201A**, **202A**, **203A**, and **204A** by amide coupling of the respective carboxylic acids (intermediate **8A** or intermediate **19A**) derivatives with respective aminomethylpyridone derivatives, which are described above.

25

Intermediate	Starting materials	Name	Structure	Analytics
205A	19A; 102A	<i>rac</i> -1-sec-butyl-7-chloro-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 0.73 (br. t, 3H), 0.90 (br. t, 3H), 1.24 (d, 3H), 1.46 - 1.57 (m, 2H), 1.58 - 1.74 (m, 2H), 2.13 (s, 3H), 3.01 - 3.12 (m, 1H), 4.35 (d, 2H), 5.91 (s, 1H), 7.11 (s, 1H), 7.91 (s, 1H), 8.80 (s, 1H), 8.86 - 8.93 (m, 1H), 11.53 (br. s, 1H) (2 H obscured by solvent signal). MS (ESD): [M + H] ⁺ = 415.2
206A	19A; 132A	<i>rac</i> -1-sec-butyl-7-chloro-N-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 0.72 (t, 3H), 1.24 (d, 3H), 1.55 - 1.74 (m, 2H), 2.19 (s, 3H), 3.06 (sxt, 1H), 3.81 (s, 3H), 4.27 (d, 2H), 6.12 (s, 1H), 7.09 (d, 1H), 7.90 (d, 1H), 8.70 (t, 1H), 8.80 (s, 1H), 11.49 (br. s, 1H). MS (ESD): [M + H] ⁺ = 403.1
207A	19A; 137A	<i>rac</i> -1-sec-butyl-7-chloro-N-{[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 0.72 (t, 3H), 1.24 (d, 3H), 1.54 - 1.74 (m, 2H), 2.21 (s, 3H), 3.06 (sxt, 1H), 4.31 (d, 2H), 6.09 (s, 1H), 7.10 (d, 1H), 7.30 (t, 1H), 7.92 (d, 1H), 8.79 (s, 1H), 8.87 (t, 1H), 11.90 (br. s, 1H). MS (ESD): [M + H] ⁺ = 439.1

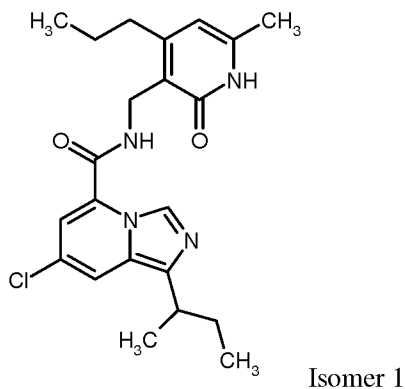
Intermediate	Starting materials	Name	Structure	Analytics
208A	19A; 109A	<i>rac</i> -1-sec-butyl-7-chloro-N-{[4-(methoxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ [ppm]= 0.72 (t, 3H), 1.24 (d, 3H), 1.55 - 1.73 (m, 2H), 2.17 (s, 3H), 3.06 (sxt, 1H), 3.31 (s, 3H), 4.31 (d, 2H), 4.45 (s, 2H), 6.09 (s, 1H), 7.13 (d, 1H), 7.91 (d, 1H), 8.80 (s, 1H), 8.93 (t, 1H), 11.70 (br. s., 1H). MS (ESD): $[\text{M} + \text{H}]^+ = 417.2$
209A	19A; 120A	<i>rac</i> -1-sec-butyl-7-chloro-N-{[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ [ppm]= 0.72 (t, 3H), 0.97 (t, 3H), 1.24 (d, 3H), 1.54 - 1.74 (m, 2H), 2.12 - 2.30 (m, 5H), 3.05 (sxt, 1H), 4.37 (d, 2H), 6.09 (s, 1H), 7.08 (d, 1H), 7.92 (d, 1H), 8.78 (s, 1H), 8.80 (t, 1H), 12.08 (br. s, 1H). MS (ESD): $[\text{M} + \text{H}]^+ = 451.2$
210A	19A; 116A	<i>rac</i> -1-sec-butyl-7-chloro-N-{[6-methyl-2-oxo-4-(2,2,2-trifluoroethoxy)-1,2-dihydropyridin-3-yl]methyl}imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ [ppm]= 0.72 (t, 3H), 1.24 (d, 3H), 1.57 - 1.72 (m, 2H), 2.20 (s, 3H), 3.06 (sxt, 1H), 4.31 (d, 2H), 4.82 (q, 2H), 6.18 (s, 1H), 7.08 (d, 1H), 7.90 (d, 1H), 8.72 (t, 1H), 8.80 (s, 1H), 11.65 (s, 1H). MS (ESD): $[\text{M} + \text{H}]^+ = 471$

Intermediate	Starting materials	Name	Structure	Analytics
211A	19A; 147A	<i>rac</i> -N-[(4-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-sec-butyl-7-chloroimidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 0.72 (t, 3H), 1.23 (d, 3H), 1.56 - 1.73 (m, 2H), 2.10 (s, 3H), 3.05 (sxt, 1H), 3.93 (s, 2H), 4.41 (d, 2H), 5.82 (s, 1H), 7.02 (d, 1H), 7.09 - 7.34 (m, 5H), 7.87 - 7.91 (m, 1H), 8.77 (s, 1H), 8.92 (t, 1H), 11.64 (br. s., 1H). MS (ESI): [M + H] ⁺ = 463.2
212A	8A; 157A	7-chloro-N-[(4-isopropoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm] = 1.22 (d, 6H), 1.27 (d, 6H), 2.18 (s, 3H), 3.35 - 3.44 (m, 1H, obscured by water signal), 4.29 (d, 2H), 4.66 (spt, 1H), 6.11 (s, 1H), 7.21 (s, 1H), 8.03 (s, 1H), 8.69 - 8.82 (m, 1H), 9.09 (br. s., 1H), 11.42 (br. s., 1H). MS (ESI): [M + H] ⁺ = 417.2

Intermediates 205.1A and 205.2A were obtained from separation of enantiomers of Intermediate 205A by chiral SFC:

System:	Sepiatec: Prep SFC100,
Column:	Chiralpak ID 5μm 250x20 mm
Solvent:	CO ₂ / 2-Propanol 77/23
flow:	80 ml/min
pressure(outlet):	150 bar
temperature:	40°C
detection:	UV 254 nm
fraction	Rt in min

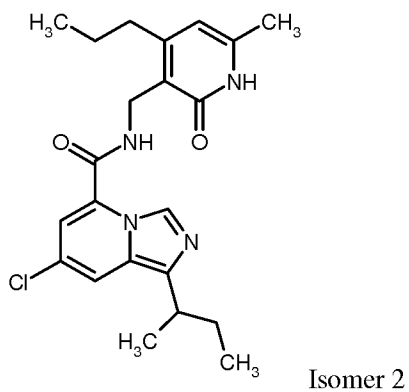
Intermediate 205.1	8 – 9
Intermediate 205.2	10 – 12

Intermediate 205.1A

Analytic chiral SFC:

<i>System:</i>	Agilent: 1260 AS, MWD, Aurora SFC-Modul:
<i>Column:</i>	Chiralpak ID 5µm 100x4.6 mm
<i>Solvent:</i>	CO ₂ / 2-Propanol 77/23
<i>Flow:</i>	4.0 ml/min
<i>Pressure:</i>	100 bar
<i>Temperature:</i>	37,5°C
<i>Detection:</i>	DAD 254 nm

5

R_t: 4.77 min**Intermediate 205.2A**

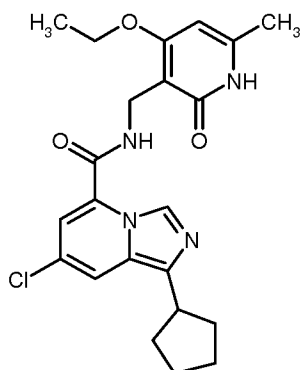
10 Analytic chiral SFC:

<i>System:</i>	Agilent: 1260 AS, MWD, Aurora SFC-Modul:
<i>Column:</i>	Chiralpak ID 5µm 100x4.6 mm
<i>Solvent:</i>	CO ₂ / 2-Propanol 77/23

<i>Flow:</i>	4.0 ml/min
<i>Pressure:</i>	100 bar
<i>Temperature:</i>	37,5°C
<i>Detection:</i>	DAD 254 nm

R_t: 6.15 min

Intermediate 213A – 7-chloro-1-cyclopentyl-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide



160 mg 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carbonyl chloride (intermediate **27A**, 0.79 mmol, 1 eq) were dissolved in 7.5 ml anhydrous dichloromethane. N,N-diisopropylethylamine (344 μ l; 1.98 mmol) and 451.4 mg 3-(aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-one (intermediate **108A**) were added. The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with dichloromethane. The remaining precipitate was filtered to provide 60 mg (25%) of the title compound as a solid. The dichloromethane layer was purified by flash chromatography to yield further 60 mg (25%).

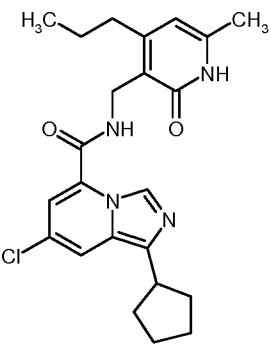
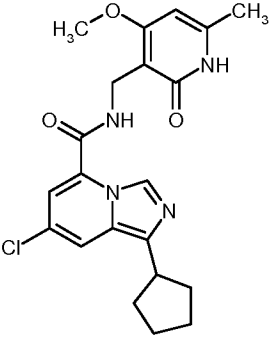
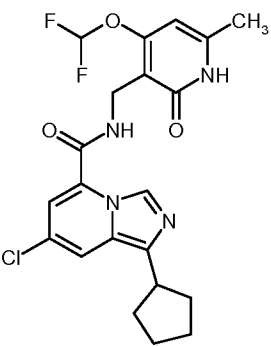
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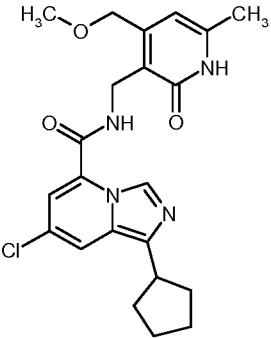
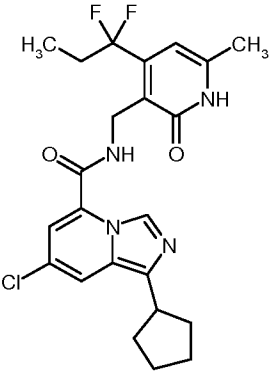
¹H-NMR (400MHz, DMSO-d₆) δ [ppm]= 1.26 (t, 3H), 1.57 - 1.69 (m, 2H), 1.78 (br. s., 4H), 1.89 - 2.01 (m, 2H), 2.18 (s, 3H), 3.38 - 3.46 (m, 1H), 4.09 (q, 2H), 4.29 (d, 2H), 6.09 (s, 1H), 7.08 (s, 1H), 7.89 (s, 1H), 8.66 - 8.73 (m, 1H), 8.79 (s, 1H), 11.45 (br. s, 1H).

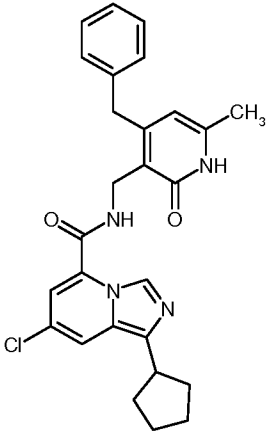
20 MS (ESI): [M + H]⁺ = 429.2

The following intermediates were prepared in analogy to intermediate **212A** by amide coupling of the respective carboxylic acid chloride (intermediate **27A**) with respective aminomethylpyridone derivatives, which are described above.

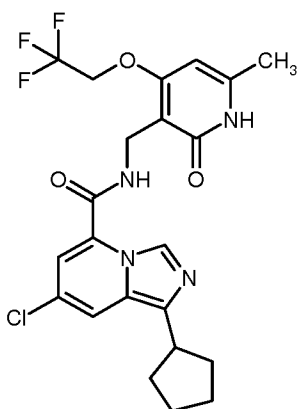
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Intermediate	Starting materials	Name	Structure	Analytics
214A	27A; 102A	7-chloro-1-cyclopentyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 0.90 (t, 3H), 1.51 (sxt, 2H), 1.60 - 1.70 (m, 2H), 1.70 - 1.84 (m, 4H), 1.89 - 2.00 (m, 2H), 2.13 (s, 3H), 3.36 - 3.46 (m, 1H), 4.35 (d, 2H), 5.91 (s, 1H), 7.12 (d, 1H), 7.90 (d, 1H), 8.79 (s, 1H), 8.89 (t, 1H), 11.52 (br. s, 1H) (2 H obscured by solvent signal). MS (ESI): [M + H] ⁺ = 427.2
215A	27A; 132A	7-chloro-1-cyclopentyl-N-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 1.60 - 1.69 (m, 2H), 1.70 - 1.85 (m, 4H), 1.90 - 2.00 (m, 2H), 2.20 (s, 3H), 3.41 (quin, 1H), 3.81 (s, 3H), 4.27 (d, 2H), 6.12 (s, 1H), 7.09 (d, 1H), 7.89 (d, 1H), 8.69 (t, 1H), 8.79 (s, 1H), 11.48 (s, 1H). MS (ESI): [M + H] ⁺ = 415.2
216A	27A; 137A	7-chloro-1-cyclopentyl-N-[[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO-d ₆) δ [ppm]= 1.59 - 1.70 (m, 2H), 1.71 - 1.84 (m, 4H), 1.91 - 2.00 (m, 2H), 2.21 (s, 3H), 3.41 (quin, 1H), 4.30 (d, 2H), 6.08 (s, 1H), 7.10 (d, 1H), 7.29 (t, 1H), 7.91 (d, 1H), 8.78 (s, 1H), 8.85 (t, 1H), 11.90 (s, 1H). MS (ESI): [M + H] ⁺ = 451

		idazo[1,5-a]pyridine-5-carboxamide		
217A	27A; 109A	7-chloro-1-cyclopentyl-N-{{[4-(methoxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 1.59 - 1.69 (m, 2H), 1.70 - 1.84 (m, 4H), 1.90 - 2.02 (m, 2H), 2.17 (s, 3H), 3.41 (quin, 1H), 4.31 (d, 2H), 4.45 (s, 2H), 6.09 (s, 1H), 7.13 (d, 1H), 7.90 (d, 1H), 8.78 (s, 1H), 8.92 (t, 1H), 11.68 (br. s, 1H) (3 H obscured by solvent signal). MS (ESI): [M + H] ⁺ = 429.2
218A	27A; 120A	7-chloro-1-cyclopentyl-N-{{[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆) δ [ppm]= 0.97 (t, 3H), 1.59 - 1.69 (m, 2H), 1.70 - 1.84 (m, 4H), 1.88 - 2.05 (m, 2H), 2.11 - 2.28 (m, 5H), 3.37 - 3.46 (m, 1H), 4.37 (d, 2H), 6.10 (s, 1H), 7.08 (d, 1H), 7.91 (d, 1H), 8.75 - 8.81 (m, 2H), 12.09 (br. s, 1H). MS (ESI): [M + H] ⁺ = 463.21

219A	27A; 147A	N-[(4-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO-d ₆) δ [ppm]= 1.60 - 1.68 (m, 2H), 1.71 - 1.83 (m, 4H), 1.90 - 1.99 (m, 2H), 2.11 (s, 3H), 3.37 - 3.44 (m, 1H), 3.92 (s, 2H), 4.41 (d, 2H), 5.82 (s, 1H), 7.01 (d, 1H), 7.12 - 7.25 (m, 5H), 7.88 (d, 1H), 8.75 (s, 1H), 8.91 (t, 1H), 11.61 (s, 1H). MS (ESI): [M + H] ⁺ = 475
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220A – **7-chloro-1-cyclopentyl-N-[[6-methyl-2-oxo-4-(2,2,2-trifluoroethoxy)-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide**



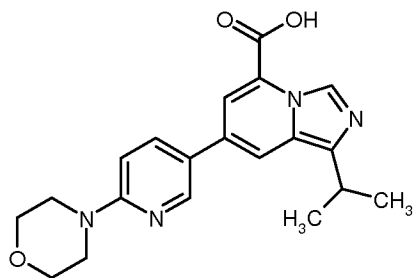
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100 mg 7-chloro-1-cyclopentylimidazo[1,5-a]pyridine-5-carboxylic acid (intermediate **26A**, 0.378 mmol), 133.9 mg 3-(aminomethyl)-6-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2(1H)-one hydrochloride (1:1) (intermediate **116A**, 0.49 mmol, 1.3 eq.) and 186.7 mg O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 0.49 mmol, 1.3 eq.) were dissolved in 2.14 mL anhydrous dimethylformamide and treated with 0.197 mL N,N-diisopropylethylamine (1.133 mmol, 3 eq.). The resulting mixture was stirred at room temperature overnight. The mixture was filtered and purified by preparative HPLC (condition 1) to yield 75 mg (41%) of the title compound.

15 ¹H-NMR (400MHz, DMSO-d₆) δ [ppm]= 1.61 - 1.69 (m, 2H), 1.70 - 1.85 (m, 4H), 1.93 - 2.01 (m, 2H), 2.20 (s, 3H), 3.42 - 3.50 (m, 1H), 4.31 (d, 2H), 4.82 (q, 2H), 6.19 (s, 1H), 7.06 - 7.08 (m, 1H), 7.16 (d, 1H), 7.95 (d, 1H), 8.96 (s, 1H), 11.66 (s, 1H).

MS (ESI): $[M + H]^+ = 483$.

Intermediate 221A – 1-isopropyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxylic acid



5

A mixture of 7-chloro-1-(propan-2-yl)imidazo[1,5-a]pyridine-5-carboxylic acid, (intermediate **8A**, 1 g, 4.19 mmol), [6-(morpholin-4-yl)pyridin-3-yl]boronic acid, 1.74 g (8.38 mmol), and sodium carbonate (0.88 g, 8.38 mmol) in 1,2-dimethoxyethane (12 ml), ethanol (4 ml) and water (4 ml) was degassed by bubbling argon for 20 mins, then tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol) was added. The mixture was heated in a Biotage Initiator® microwave oven at 140 °C for 60 minutes. The mixture was partitioned between water and ethyl acetate. The aqueous layer was acidified using concentrated aqueous hydrogen chloride and adjusted to pH 8 by adding saturated sodium bicarbonate solution. The resulting solid was collected by filtration to give the crude product. Sequential trituration (two times) from hot methanol gave the desired pure product (0.78 g, 50%). A small sample was solved in warm DMSO for NMR analysis.

10
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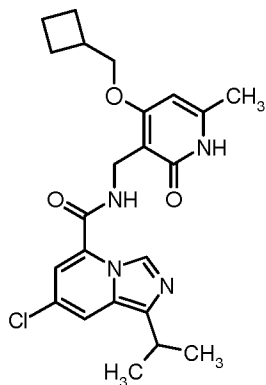
¹H NMR (400 MHz, DMSO-d₆) [ppm]= 1.28 (d, 6H), 3.43-3.48 (m, 5H), 3.66-3.68 (m, 4H), 6.88 (d, 1H), 7.76 (s, 1H), 8.01 (d, 1H), 8.13 (s, 1H), 8.55 (s, 1H), 9.02 (s, 1H).

20

MS (ESI): $m/z = (M+H)^+ 367$.

Intermediate 222A – 7-chloro-N-{[4-(cyclobutylmethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide

25

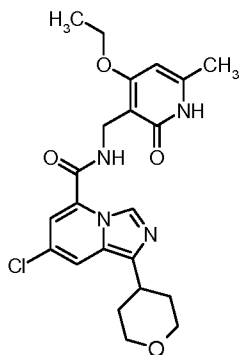


260 mg 7-chloro-1-isopropylimidazo[1,5-a]pyridine-5-carboxylic acid (intermediate **8A**, 1.09 mmol), 291 mg 3-(aminomethyl)-4-(cyclobutylmethoxy)-6-methylpyridin-2(1H)-one hydrochloride (intermediate **162A**, 1.1 mmol) and 538.5 mg O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 1.4 mmol) were dissolved in 2.7 mL anhydrous dimethylformamide and treated with 0.57 mL *N,N*-diisopropylethylamine (3.27 mmol). The resulting mixture was stirred at room temperature overnight. To the mixture was added water and the resulting mixture was extracted with ethyl acetate. The organic phasesd were washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, gradient of methanol in dichloromethane) to yield 190 mg (40%) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.26 (d, 6H), 1.75 - 1.86 (m, 4H), 1.89 - 2.01 (m, 2H), 2.18 (s, 3H), 2.61 - 2.70 (m, 1H), 3.32 - 3.41 (m, 1H, overlain by water signal), 4.00 (d, 2H), 4.30 (d, 2H), 6.11 (s, 1H), 7.18 (s, 1H), 7.98 (s, 1H), 8.72 (t, 1H), 8.97 (br. s., 1H), 11.47 (br. s., 1H).

MS (ESI): [M + H]⁺ = 443.2.

Intermediate 223A – 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxamide



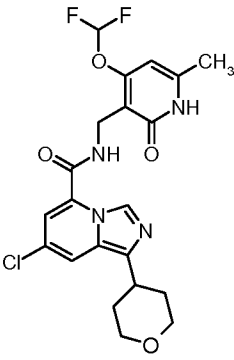
100 mg 7-chloro-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxylic acid (intermediate **33A**, 0.36 mmol), 78 mg 3-(Aminomethyl)-4-ethoxy-6-methylpyridin-2(1H)-one (intermediate **108A**, 0.43 mmol) and 176 mg O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 0.46 mmol) were dissolved in 3 ml anhydrous DMF and treated with 155 μ l *N,N*-diisopropylethylamine (0.89 mmol). The resulting mixture was heated in a microwave oven at 110 °C for 1 h. The mixture was then poured into water and the solid material was filtered off to yield 79 mg (50%) of the target compound.

10 ¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.26 (t, 3H), 1.61 - 1.71 (m, 2H), 1.78 - 1.96 (m, 2H), 2.14 - 2.21 (s, 3H), 3.18 - 3.30 (m, 1H, overlain by water signal), 3.41 - 3.52 (m, 2H), 3.94 (dd, 2H), 4.09 (q, 2H), 4.29 (d, 2H), 6.09 (s, 1H), 7.10 (d, 1H), 7.98 (d, 1H), 8.71 (t, 1H), 8.81 (s, 1H), 11.45 (br. s., 1H).

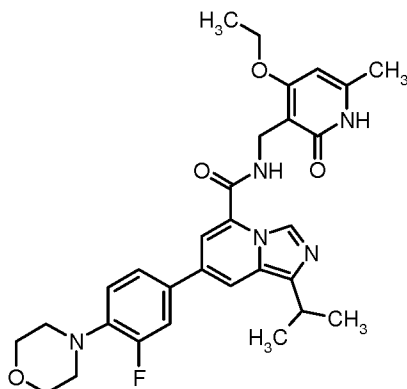
15 MS (ESI): [M + H]⁺ = 445.1.

The following intermediates were prepared in analogy to intermediate **223A** by amide coupling of the respective carboxylic acid (intermediate **33A**) with respective aminomethylpyridone derivatives, which are described above.

Intermediate	Starting materials	Name	Structure	Analytics
224A	33A; 116A	7-chloro-N- {[6-methyl- 2-oxo-4- (2,2,2- trifluoroethoxy)-1,2- dihydropyridin-3- yl)methyl]- 1- (tetrahydro- 2H-pyran-4- yl)imidazo[1, 5- a]pyridine-5- carboxamide		1H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.59 - 1.71 (m, 2H), 1.80 - 1.94 (m, 2H), 2.19 (s, 3H), 3.21 - 3.27 (m, 1H, overlain by water signal), 3.42 - 3.51 (m, 2H), 3.94 (dd, 2H), 4.30 (d, 2H), 4.82 (q, 2H), 6.19 (s, 1H), 7.10 (d, 1H), 7.98 (d, 1H), 8.73 (t, 1H), 8.80 (s, 1H), 11.67 (s, 1H). MS (ESI): [M + H] ⁺ = 499.1
225A	33A; 132A, reaction was carried out at room temperature overnight instead under microwave heating.	7-chloro-N- [(4- methoxy-6- methyl-2- oxo-1,2- dihydropyridin-3- yl)methyl]- 1- (tetrahydro- 2H-pyran-4- yl)imidazo[1, 5- a]pyridine-5- carboxamide		1H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.54 - 1.72 (m, 2H), 1.80 - 1.95 (m, 2H), 2.19 (s, 3H), 3.26 (m, 1H), 3.41 - 3.54 (m, 2H), 3.81 (s, 3H), 3.94 (dd, 2H), 4.26 (d, 2H), 6.12 (s, 1H), 7.11 (d, 1H), 7.98 (d, 1H), 8.71 (t, 1H), 8.81 (s, 1H), 11.50 (s, 1H). MS (ESI): [M + H] ⁺ = 431.1

226A	33A, 137A, reaction was carried out at room temperatu re overnight instead under microwav e heating.	7-chloro-N- {[4- (difluoromet hoxy)-6- methyl-2- oxo-1,2- dihydropyrid in-3- yl]methyl}- 1- (tetrahydro- 2H-pyran-4- yl)imidazo[1 ,5- a]pyridine-5- carboxamide		¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.61 - 1.69 (m, 2H), 1.79 - 1.94 (m, 2H), 2.21 (s, 3H), 3.22 - 3.29 (m, 1H, overlain by water signal), 3.42 - 3.51 (m, 2H), 3.94 (dd, 2H), 4.30 (d, 2H), 6.09 (s, 1H), 7.12 (d, 1H), 7.30 (t, 1H), 7.99 (d, 1H), 8.80 (s, 1H), 8.87 (t, 1H), 11.92 (s, 1H).
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Example 1 - N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[3-fluoro-4-(morpholin-4-yl)phenyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide

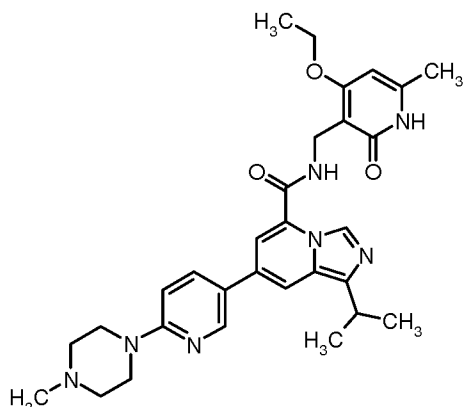


5 100 mg (0.25mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 83.9 mg (0.27 mmol) 4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]morpholine and 29 mg (25 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.25 ml (0.5 mmol) aqueous sodium carbonate solution (2N), 1.5 ml toluene und 1.5 ml
10 1,2-dimethoxyethane was added and the resulting mixture heated for 45 min to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue was re-dissolved in dimethylformamide, filtered and purified by HPLC (preparative HPLC conditions 1) to yield 37 mg (26%) of the target compound.

15 ¹H NMR (300 MHz, DMSO-d₆) δ [ppm] = 1.24 (t, 3 H), 1.29 (d, 6 H), 2.17 (s, 3 H), 3.04 (m, 4 H), 3.46 (sept., 1 H), 3.75 (m, 4 H), 4.08 (q, 2 H), 4.33 (d, 2 H), 6.09 (s, 1 H), 7.09 (t, 1 H), 7.43 (s, 1 H), 7.62 (dd, 1 H), 7.72 (dd, 1 H), 8.03 (s, 1 H), 8.72 (t, 1 H), 8.83 (s, 1 H), 11.46 (s, 1 H).
LCMS (conditions 2.2): Rt 0,87min; MS (ESI): [M + H]⁺ = 546.3.

20

Example 2 – N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



150 mg (0.37 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 124.2 mg (0.41 mmol) 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine and 43 mg (37
 5 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.37 ml (0.75 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol und 2 ml toluene were added and the resulting mixture heated for 1h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography (eluent: gradient of methanol in dichloromethane) to
 10 yield 92 mg of the slightly impure target compound. Further purification by preparative HPLC (see subsequent box for details) provided 49 mg (24%) of the target compound in pure form.

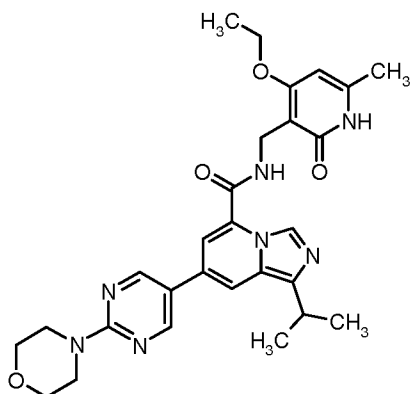
System:	Waters Autopurificationsystem: Pump 254, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD 3100
Column:	XBrigde C18 5 μ m 100x30 mm
Solvent:	A = H ₂ O + 0.1% HCOOH (99%)
	B = acetonitrile
Gradient:	0-8 min 1-99% B
Flow:	70 ml/min
Temperature:	room temperature

¹H NMR (300 MHz, DMSO-d₆) δ [ppm] = 1.24 (t, 3 H), 1.29 (d, 6 H), 2.17 (s, 3 H), 2.21 (s, 3 H),
 15 2.38-2.41 (m, 4 H), 3.43 (m, 1H), 3.51-3.54 (m, 4 H), 4.08 (q, 2H), 4.33 (d, 2 H), 6.08 (s, 1 H), 6.91 (d, 1 H), 7.44 (s, 1 H), 7.95 (s, 1 H), 8.01 (dd, 1H), 8.59 (d, 1H), 8.69 (t, 1 H), 8.82 (s, 1 H), 11.45 (s, 1 H).

LCMS (conditions 2.2): R_t 0.51min; MS (ESI): [M + H]⁺ = 544.2.

20

Example 3 N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[2-(morpholin-4-yl)pyrimidin-5-yl]imidazo[1,5-a]pyridine-5-carboxamide

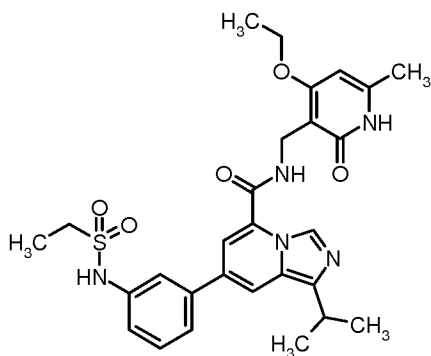


100 mg (0.25mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 79,5 mg (0.27 mmol) 4-[5-
 5 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]morpholine and 29 mg (25 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.25 ml (0.5 mmol) aqueous sodium carbonate solution (2N), 0.8 ml ethanol und 1.5 ml 1,2-dimethoxyethane was added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue re-
 10 dissolved in DMSO, filtered and purified by HPLC (preparative HPLC conditions 1) to yield 37.5 mg (28%) of the target compound.

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] = 1.23 (t, 3 H), 1.29 (d, 6 H), 2.17 (s, 3 H), 3.43 (sept, 1 H), 3.67-3.75 (m, 8 H), 4.09 (q, 2 H), 4.34 (d, 2 H), 6.08 (s, 1 H), 7.46 (s, 1 H), 8.04 (s, 1 H), 8.61
 15 (t, 1 H), 8.86 (s, 1 H), 8.88 (s, 2 H), 11.44 (s, 1 H).

LCMS (conditions 2.1): R_t 0,9 min; MS (ESI): $[M + H]^+ = 532$.

Example 4 N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-{3-
 20 [(ethylsulfonyl)-amino]phenyl}-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide



100 mg (0.25mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-

isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 62.5 mg (0.27 mmol) {3-[(ethylsulfonyl)amino]phenyl}boronic acid and 29 mg (25 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.25 ml (0.5 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane was added and the resulting mixture heated for 1h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue re-dissolved in dimethylsulfoxide, filtered and purified by HPLC (preparative HPLC conditions 1) to yield 50 mg (36%) of the target compound.

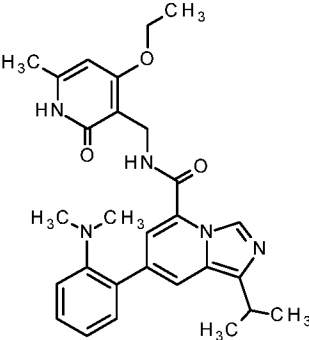
10 ¹H NMR (400 MHz, DMSO-d₆) δ [ppm] = 1.22 (t, 3 H), 1.26 (q, 3 H), 1.32 (d, 6 H), 2.17 (s, 3 H), 3.14 (q, 2 H), 3.44 (sept., 1 H), 4.1 (q, 2 H), 4.35 (dd, 2 H), 6.09 (s, 1 H), 7.24 (d, 1 H), 7.37 (s, 1 H), 7.43 (t, 1 H), 7.54 (d, 1 H), 7.92 (s, 1 H), 8.77 (t, 1 H), 8.82 (s, 1 H), 9.84 (s, 1 H), 11.46 (s, 1 H)

LCMS (condition 2.3): R_t 0,94 min; MS (ESI): $[M + H]^+ = 552$.

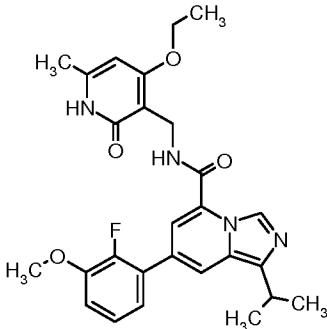
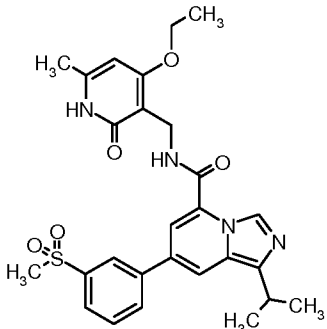
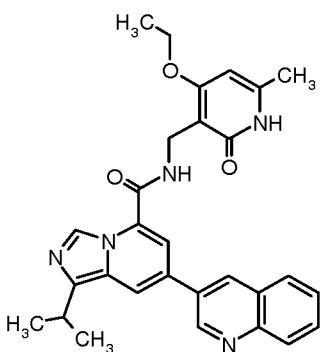
15

The following example compounds were synthesized in analogy to example compounds **1** to **4** by Suzuki coupling of intermediate **201A** with the respective commercially available boronic acids (or their pinacolate esters) employing a palladium catalyst in the presence of a base in a suitable solvent system under microwave heating (110 to 140 °C). Temperature and reaction time were individually modified in order to achieve maximum turnover of starting material. The target compounds were in general isolated by preparative HPLC conditions, for example preparative HPLC conditions 1 or 2.

25

Example	Name	Structure	Analytical data
5	7-[2-(dimethylamino)phenyl]-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.98 min MS (ESI): [M + H] ⁺ = 488.6

Example	Name	Structure	Analytical data
6	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-{3-[(methylsulfonyl)amino]phenyl}imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.83 min MS (ESI): [M + H] ⁺ = 538.6
7	7-(2,3-dihydro-1,4-benzodioxin-6-yl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.92 min MS (ESI): [M + H] ⁺ = 503.6
8	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[4-(pyrrolidin-1-ylcarbonyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (300MHz, DMSO-d ₆): δ [ppm] = 1.4 (t, 3 H), 1.30 (d, 6H), 2.19 (s, 3H), 2.23 – 2.40 (m, 4 H), 3.4-3.67 (m, 5 H), 4.08 (q, 2 H), 4.33 (d, 2H), 6.09 (s, 1 H), 7.45-7.49 (m, 3 H), 7.9 (d, 2 H), 8.11 (s, 1 H), 8.76 (t, 1 H), 8.87 (s, 1 H), 11.46 (s, 1 H). LCMS (conditions 2.4): R _t 0.88 min MS (ESI): [M + H] ⁺ = 542.7

Example	Name	Structure	Analytical data
9	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(2-fluoro-3-methoxyphenyl)-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.96 min MS (ESI): [M + H] ⁺ = 493.6
10	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[3-(methylsulfonyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H NMR (300 MHz, DMSO-d ₆) δ [ppm] = 1.26 (t, 3 H), 1.33 (d, 6 H), 2.19 (s, 3 H), 3.31 (s, 3 H), 3.53 (m, 1 H), 4.11 (q, 2 H), 4.36 (d, 2 H), 6.01 (s, 1 H), 7.5 (s, 1 H), 7.76 (t, 1 H), 7.91 (d, 1 H), 8.18-8.23 (m, 2 H), 8.35 (s, 1 H), 8.8 (t, 1 H), 8.86 (s, 1 H), 11.46 (s, 1 H). LCMS (conditions 2.4): R _t 0.84 min MS (ESI): [M + H] ⁺ = 523.6
11	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(quinolin-3-yl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.91 min MS (ESI): [M + H] ⁺ = 496.6

Example	Name	Structure	Analytical data
12	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(6-methoxypyridin-3-yl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.89 min MS (ESI): [M + H] ⁺ = 476.6
13	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(quinolin-4-yl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.84 min MS (ESI): [M + H] ⁺ = 496.6
14	7-(4-carbamoylphenyl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.74 min MS (ESI): [M + H] ⁺ = 488.6

Example	Name	Structure	Analytical data
15	7-[4-(tert-butylcarbamoyl)phenyl]-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.97 min MS (ESI): [M + H] ⁺ = 544.7
16	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[4-(methylsulfinyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.77 min MS (ESI): [M + H] ⁺ = 507.6
17	7-[3-(dimethylcarbamoyl)phenyl]-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.83 min MS (ESI): [M + H] ⁺ = 516.6
18	7-(3-acetamidophenyl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-		¹ H NMR (400 MHz, DMSO-d ₆) δ [ppm] = 1.26 (t, 3 H), 1.32 (d, 6 H), 2.07 (s, 3 H), 2.18 (s, 3 H), 3.44 (m, 1 H), 4.1 (q, 2 H), 4.35 (d, 2 H), 6.1 (s, 1 H), 7.37-7.41 (m, 2 H), 7.48 (d, 1 H), 7.64 (d, 1 H),

Example	Name	Structure	Analytical data
	-a]pyridine-5-carboxamide		7.85 (s, 1 H), 7.91 (s, 1 H), 8.77 (t, 1 H), 8.84 (s, 1 H), 10.04 (d, 1 H), 11.46 (s, 1 H). LCMS (conditions 2.3): R _t 0.88 min MS (ESI): [M + H] ⁺ = 502
19	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		¹ H NMR (300 MHz, DMSO-d ₆) δ [ppm] = 1.24 (t, 3 H), 1.29 (d, 6 H), 2.17 (s, 3 H), 3.44 (m, 1 H), 3.79 (s, 3 H), 4.08 (q, 2 H), 4.33 (d, 2 H), 6.08 (s, 1 H), 7.02 (d, 2 H), 7.42 (s, 1 H), 7.76 (d, 2 H), 7.93 (s, 1 H), 8.74 (t, 1 H), 8.88 (s, 1 H), 11.45 (s, 1 H). LCMS (conditions 2.4): R _t 0.93 min MS (ESI): [M + H] ⁺ = 475.6
20	7-(2,3-dihydro-1-benzofuran-5-yl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.93 min MS (ESI): [M + H] ⁺ = 487.6
21	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(pyridin-3-yl)imidazo[1,5-a]pyridine-5-carboxamide		¹ H NMR (300 MHz, DMSO-d ₆) δ [ppm] = 1.24 (t, 3 H), 1.30 (d, 6 H), 2.17 (s, 3 H), 3.48 (m, 1 H), 4.08 (q, 2 H), 4.34 (d, 2 H), 6.09 (s, 1 H), 7.48 (dd, 1 H), 7.53 (s, 1 H), 8.18 (s, 1 H), 8.23 (d, 1 H), 8.54 (d, 1 H), 8.72 (t, 1 H), 8.92 (s, 1 H), 9.08 (d, 1H),

Example	Name	Structure	Analytical data
			11.46 (s, 1 H). LCMS (conditions 2.2): R _t 0.64 min MS (ESI): [M + H] ⁺ = 444
22	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(quinolin-5-yl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.81 min MS (ESI): [M + H] ⁺ = 496.6
23	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(3-methylphenyl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 1.01 min MS (ESI): [M + H] ⁺ = 459.6
24	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[3-(methoxymethyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.94 min MS (ESI): [M + H] ⁺ = 489.6

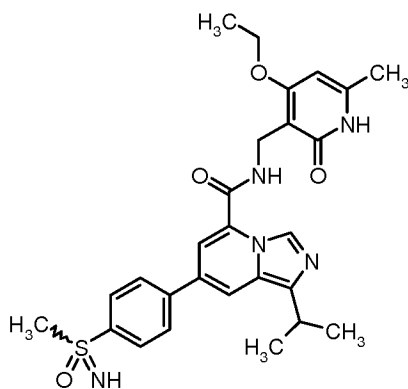
Example	Name	Structure	Analytical data
25	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3-isopropoxyphenyl)-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 1.07 min MS (ESI): [M + H] ⁺ = 503.6
26	7-[3-(dimethylamino)phenyl]-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS conditions 2.4): R _t 0.95 min MS (ESI): [M + H] ⁺ = 488.6
27	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-phenylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.94 min MS (ESI): [M + H] ⁺ = 445.5
28	7-(2,3-dimethoxyphenyl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-		LCMS (conditions 2.4): R _t 0.94 min MS (ESI): [M + H] ⁺ = 505.6

Example	Name	Structure	Analytical data
	carboxamide		
29	7-(4-cyano-3-fluorophenyl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 1.01 min MS (ESI): [M + H] ⁺ = 488.5
30	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[2-(methylsulfonyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.84 min MS (ESI): [M + H] ⁺ = 523.6
31	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(2-furylmethyl)-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R _t 0.86 min MS (ESI): [M + H] ⁺ = 449.5
32	7-[3-(benzyloxy)phenyl]-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-		LCMS (conditions 2.4): R _t 1.14 min MS (ESI): [M + H] ⁺ = 551.7

Example	Name	Structure	Analytical data
	-a]pyridine-5-carboxamide		
33	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(4-fluorophenyl)-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R_t 0.96 min MS (ESI): $[M + H]^+ = 463.5$
34	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(1-methyl-1H-indol-5-yl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R_t 0.96 min MS (ESI): $[M + H]^+ = 498.6$
35	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(2,3,5-trifluorophenyl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R_t 1.08 min MS (ESI): $[M + H]^+ = 499.5$
36	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(1-naphthyl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R_t 1.06 min MS (ESI): $[M + H]^+ = 495.6$

Example	Name	Structure	Analytical data
	-a]pyridine-5-carboxamide		
37	7-(biphenyl-2-yl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R_t 1.08 min MS (ESI): $[M + H]^+ = 521.6$
38	7-(4-chloro-3-methylphenyl)-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R_t 1.11 min MS (ESI): $[M + H]^+ = 494$
39	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-(2-propoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		LCMS (conditions 2.4): R_t 1.04 min MS (ESI): $[M + H]^+ = 503.6$

Example 40 *rac*-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[4-(S-methylsulfonimidoyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide



Step 1)

100 mg (0.224 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 95 mg (0.268 mmol) *rac*-ethyl {methyl(oxido)[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-lambda⁶-sulfanylidene}carbamate (intermediate **152A**) and 26 mg (22 μmol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 1 ml ethanol, 1 ml 1,2-dimethoxyethane and 0.22 ml (0.45 mmol) aqueous sodium carbonate solution (2N), were added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography (eluent: gradient of ethyl acetate in hexane) to yield 100 mg (71%) of the title compound.

MS (ESI): [M + H]⁺ = 594.

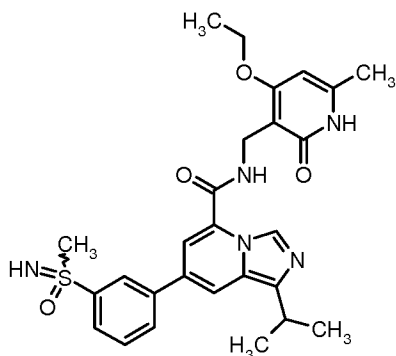
Step 2)

To a solution of the product of step 1 (100 mg, 0.17 mmol) in ethanol (3 ml) was added a solution of sodium ethanolate in ethanol (0.23 ml, 0.61 mmol) and the reaction was stirred at 70 °C overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (conditions 1) to yield 25 mg (29%) of *rac*-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[4-(S-methylsulfonimidoyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 1.25 (t, 3H), 1.32 (d, 6H), 2.18 (s, 3H), 3.10 (s, 3H), 3.50 (dt, 1H), 4.10 (q, 2H), 4.26 (br. s., 1H), 4.35 (d, 2H), 6.10 (s, 1H), 7.52 (d, 1H), 7.99 (d, 2H), 8.07 (d, 2H), 8.20 (s, 1H), 8.77 (t, 1H), 8.88 (s, 1H).

MS (ESI): [M + H]⁺ = 522.

Example 41 *rac*-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[3-(S-methylsulfonimidoyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide



5

Step 1) 100 mg (0.224 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 95 mg (0.268 mmol) *rac*-ethyl {methyl(oxido)[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-lambda⁶-sulfanylidene}carbamate (intermediate **152A**) and 26 mg (22 μmol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 1 ml ethanol, 1 ml 1,2-dimethoxyethane and 0.22 ml (0.45 mmol) aqueous sodium carbonate solution (2N), were added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography (eluent: gradient of ethyl acetate in hexane) to yield 100 mg (71%) of the title compound.

MS (ESI): [M + H]⁺ = 594.

Step 2)

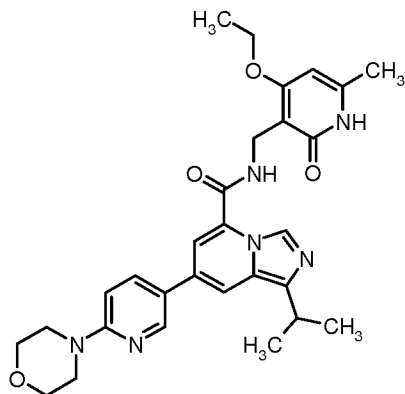
To a solution of the product of step 1 (100 mg, 0.17 mmol) in ethanol (3 ml) was added a solution of sodium ethanolate in ethanol (0.23 ml, 0.61 mmol) and the reaction was stirred at 70 °C for 3 days. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (conditions 1) to yield 25 mg (29%) of *rac*-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[4-(S-methylsulfonimidoyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.26 (t, 3H), 1.32 (d, 6H), 2.18 (s, 3H), 3.16 (s, 3H), 3.51 (m, 1H), 4.10 (q, 2H), 4.30 (s, 1H), 4.35 (d, 2H), 6.09 (s, 1H), 7.47 (d, 1H), 7.69 (t, 1H), 7.91 (d, 1H), 8.10 (d, 1H), 8.17 (s, 1H), 8.33 (s, 1H), 8.80 (t, 1H), 8.84 (s, 1H), 11.46 (br. s., 1H).

30

MS (ESI): [M + H]⁺ = 522.

Example 42 N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



5

100 mg (0.25 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 79.2 mg (0.27 mmol) 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine, 0.25 ml (0.50 mmol) aqueous sodium carbonate solution (2N), 29 mg (25 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 1 ml ethanol und 2 ml toluene was added and the resulting mixture heated for 45 min to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (conditions 1) provided 24 mg (18%) of the target compound in pure form.

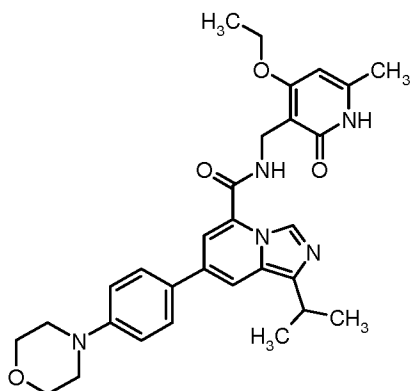
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¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 1.25 (t, 3H), 1.30 (d, 6H), 2.18 (s, 3H), 3.39 - 3.47 (m, 1H), 3.48 - 3.53 (m, 4H), 3.68 - 3.75 (m, 4H), 4.09 (q, 2H), 4.34 (d, 2H), 6.10 (s, 1H), 6.94 (d, 1H), 7.46 (s, 1H), 7.98 (s, 1H), 8.06 (dd, 1H), 8.64 (d, 1H), 8.70 (t, 1H), 8.83 (s, 1H), 11.47 (br. s., 1H).

MS (ESI): [M + H]⁺ = 531.

Example 43 N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[4-(morpholin-4-yl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide

25



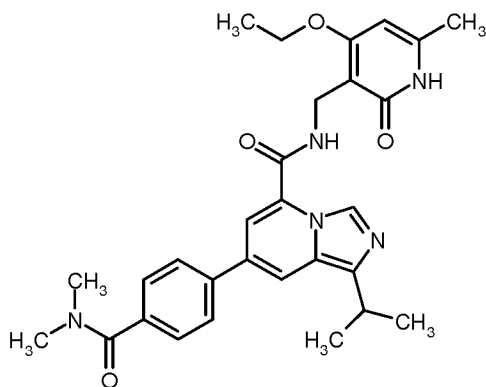
100 mg (0.25 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 50.9 mg (0.25 mmol) [4-(morpholin-4-yl)phenyl]boronic acid, 0.22 ml (0.50 mmol) aqueous solution of sodium carbonate (2N), 26 mg (22 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane was added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (see box below) provided 22 mg (18%) of the target compound in pure form.

<i>System:</i>	Waters Autopurificationsystem: Pump 254, Sample Manager 2767, CFO, DAD 2996, SQD 3100
<i>Column:</i>	XBrigde C18 5 μ m 100x30 mm
<i>Solvent:</i>	A = H ₂ O + 0.2% NH ₃ (32%)
	B = acetonitrile
<i>Gradient:</i>	0–0.5 min 25 mL/min to 70 mL/min 34% B; 0.5–5.5 min 34–54% B
<i>Flow:</i>	70 ml/min
<i>Temperature:</i>	room temperature

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.25 (t, 3H), 1.30 (d, 6H), 2.18 (s, 3H), 3.11 - 3.21 (m, 4H), 3.44 (spt, 1H), 3.71 - 3.80 (m, 4H), 4.09 (q, 2H), 4.33 (d, 2H), 6.09 (s, 1H), 6.96 - 7.06 (m, 2H), 7.43 (d, 1H), 7.67 - 7.76 (m, 2H), 7.87 - 7.94 (m, 1H), 8.75 (t, 1H), 8.80 (s, 1H), 11.46 (s, 1H).

MS (ESI): [M + H]⁺ = 530.

Example 44 - 7-[4-(dimethylcarbamoyl)phenyl]-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide

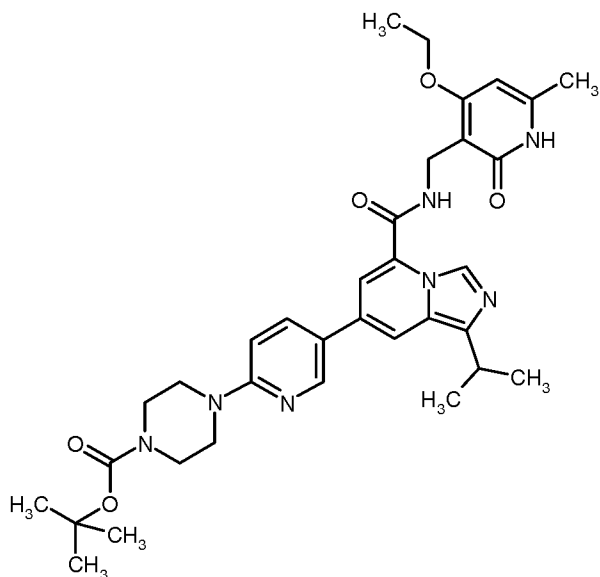


100 mg (0.25 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 52.7 mg (0.273 mmol) [4-(dimethylcarbamoyl)phenyl]boronic acid and 28.7 mg (25 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.25 ml (0.50 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (condition 1) provided 57.7 mg (45%) of the target compound in pure form.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 1.25 (t, 3H), 1.31 (d, 6H), 2.18 (s, 3H), 2.90 - 3.07 (m, 6H), 3.49 (spt, 1H), 4.09 (q, 2H), 4.34 (d, 2H), 6.09 (s, 1H), 7.46 - 7.55 (m, 3H), 7.91 (d, 2H), 8.13 (s, 1H), 8.78 (t, 1H), 8.88 (s, 1H), 11.47 (s, 1H).

MS (ESI): [M + H]⁺ = 516.

Example 45 - tert-butyl 4-[5-(5-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl)-1-isopropylimidazo[1,5-a]pyridin-7-yl)pyridin-2-yl]piperazine-1-carboxylate

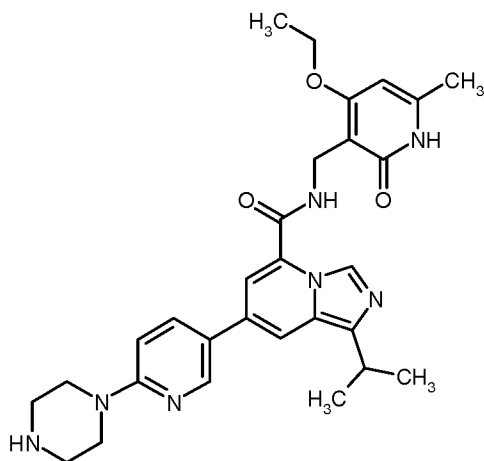


200 mg (0.5 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 212.6 mg (0.546 mmol) *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine-1-carboxylate and 57.4 mg (50 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.5 ml (1.0 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol und 2 ml toluene were added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography (eluent: gradient of dichloromethane and dichloromethane/methanol) to yield 162 mg (52%) of the target compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.26 (t, 3H), 1.30 (d, 6H), 1.43 (s, 9H), 2.18 (s, 3H), 3.40 - 3.48 (m, 5H), 3.52 - 3.59 (m, 4H), 4.09 (q, 2H), 4.34 (d, 2H), 6.09 (s, 1H), 6.94 (d, 1H), 7.45 (d, 1H), 7.96 (d, 1H), 8.05 (dd, 1H), 8.63 (d, 1H), 8.69 (t, 1H), 8.83 (s, 1H), 11.45 (s, 1H).

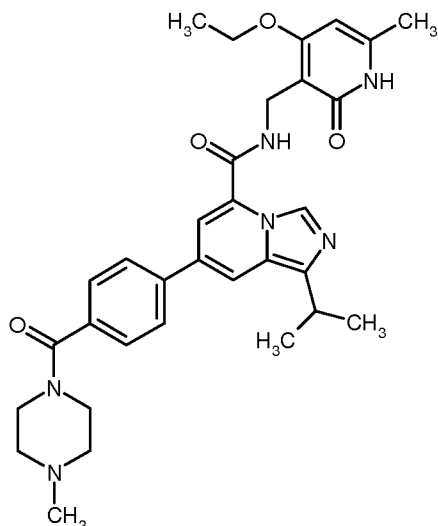
MS (ESI⁺): [M + H]⁺ = 631.

Example 46 - N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[6-(piperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



- 130 mg (0,206 mmol) tert-butyl 4-[5-(5-[[4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl]-1-isopropylimidazo[1,5-a]pyridin-7-yl)pyridin-2-yl]piperazine-1-carboxylate (Example 45) were dissolved in dichloromethane (5 ml). 0.16 ml (2.064 mmol) trifluoroacetic acid was added. The reaction stirred at room temperature over night. The mixture was concentrated. The residue was purified by preparative HPLC (condition 1) to provided 54 mg (49%) of the target compound.
- 10 ¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 1.25 (t, 3H), 1.31 (d, 6H), 2.18 (s, 3H), 3.17 - 3.26 (m, 4H), 3.42 - 3.52 (m, 1H), 3.73 - 3.81 (m, 4H), 4.09 (q, 2H), 4.34 (d, 2H), 6.10 (s, 1H), 7.04 (d, 1H), 7.49 (s, 1H), 8.02 (s, 1H), 8.12 (dd, 1H), 8.68 (d, 1H), 8.72 (br. t, 1H), 8.76 - 8.85 (m, 1H), 8.91 (br. s, 1H), 11.47 (br. s, 1H).
- 15 MS (ESI): [M + H]⁺ = 530.

Example 47 – N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}imidazo[1,5-a]pyridine-5-carboxamide



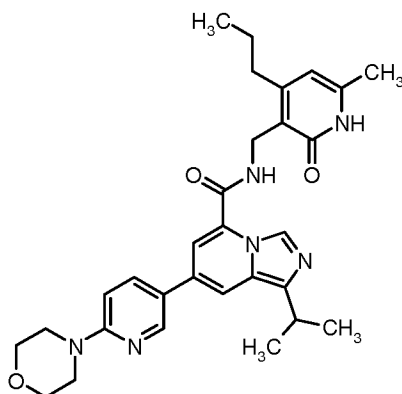
100 mg (0.25 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **201A**), 90.2 mg (0.273 mmol) (4-methylpiperazin-1-yl)[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanone and 28.7 mg (25 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.25 ml (0.50 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol and 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (condition 1) provided 52.4 mg (37%) of the target compound in pure form.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 1.22 - 1.28 (m, 3H), 1.31 (d, 6H), 1.76 - 1.95 (m, 4H), 2.18 (s, 3H), 3.39 - 3.55 (m, 5H), 4.09 (q, 2H), 4.34 (d, 2H), 6.10 (s, 1H), 7.51 (s, 1H), 7.61 (d, 2H), 7.91 (d, 2H), 8.13 (s, 1H), 8.78 (d, 1H), 8.88 (s, 1H), 11.47 (s, 1H) (3 H obscured by solvent signal).

MS (ESI): [M + H]⁺ = 571.5.

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Example 48 – 1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



Example 48 was independently prepared by two methods:

Method 48-I

- 5 100 mg (0.25mmol) 7-chloro-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide (intermediate **202A**), 86.9 mg (0.3 mmol) 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine, 0.25 ml (0.5 mmol) aqueous sodium carbonate solution (2N), 29 mg (25 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.5 ml ethanol und 1.5 ml 1,2-
- 10 toluene was added and the resulting mixture heated for 45 min to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered, concentrated *in vacuo* and the residue re-dissolved in dimethylformamide, filtered and purified by HPLC (for HPLC conditions see box below) to yield 20 mg (15%) of the target compound.

<i>System:</i>	Agilent: Prep 1200
<i>Column:</i>	XBridge C18 5 μ m 100x30mm
<i>Solvent:</i>	A: H ₂ O + 0.1% trifluoroacetic acid (99%); B = acetonitrile
<i>Gradient:</i>	0-10 min 1-99% B
<i>Flow:</i>	60 ml/min
<i>Temperature:</i>	RT
<i>Detection:</i>	UV 254 nm

15

Method 48-II

- To a solution of 1-isopropyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxylic acid (intermediate **221A**) (135 mg, 0.37 mmol) and N-ethyl-diisopropylamine (289 μ l, 1.66 mmol) in DMF (1.5 ml) were subsequently added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 211 mg, 0.55 mmol), and 3-(aminomethyl)-6-methyl-4-propylpyridin-2(1H)-one hydrochloride (intermediate **102A**, 120 mg, 0.55 mmol), and the mixture was stirred for 12 h at room temperature. The reaction mixture was then partitioned between water and ethyl acetate, the aqueous phase was extracted twice with ethyl acetate, and the
- 20

combined organic phases were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was pre purified by chromatography (Biotage KP-Sil, dichloromethane, methanol), to obtain 1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide (157 mg, 54%).

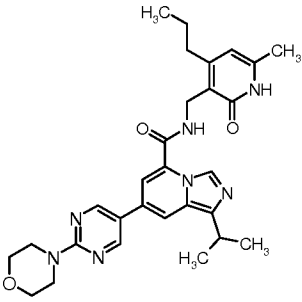
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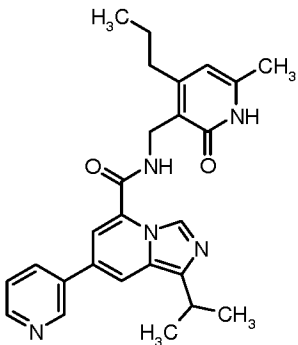
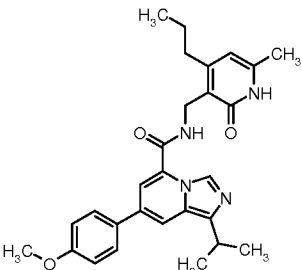
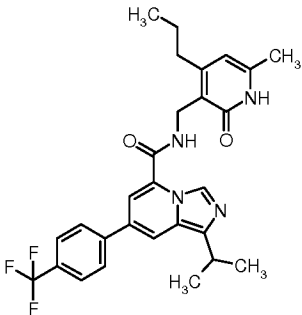
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 0.88 (t, 3H), 1.30 (d, 6H), 1.52 (m, 2H), 2.13 (s, 3H), 3.43 - 3.54 (m, 5H), 3.67 - 3.77 (m, 4H), 4.40 (d, 2H), 5.92 (s, 1H), 6.94 (d, 1H), 7.55 (s, 1H), 8.03 (s, 1H), 8.06 (dd, 1H), 8.65 (d, 1H), 8.95 (m, 2H), 11.56 (br. s., 1H), (2 H obscured by solvent signal).

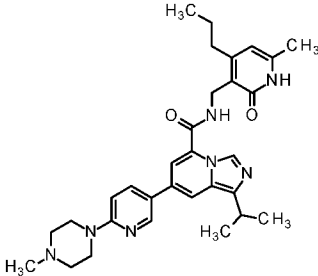
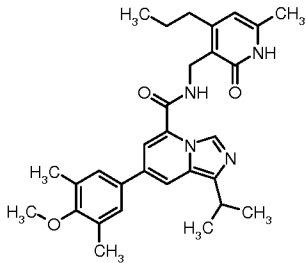
10 LCMS (Methode 2): R_t 0.83 min; MS (ESI): [M + H]⁺ = 529.

The following example compounds were synthesized in analogy to example compound **48** by Suzuki coupling (Method 48-I) of intermediate **202A** or intermediate **212A** with the respective commercially available boronic acids (or their pinacolate esters) employing a palladium catalyst in the presence of a base in a suitable solvent system under microwave heating (usually 110 °C). The reaction time and temperature was individually adapted in order to achieve maximum turnover of starting material. The target compounds were in general isolated by preparative HPLC, for example preparative HPLC conditions 1 or 2.

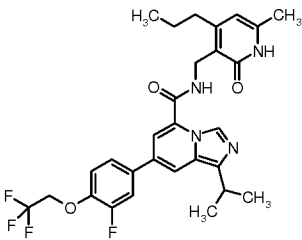
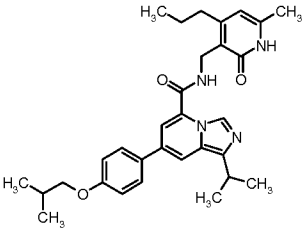
20

Example	Name	Structure	Analytical data
49	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[2-(morpholin-4-yl)pyrimidin-5-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.52 (sxt, 2H), 2.13 (s, 3H), 3.38 - 3.49 (m, 1H), 3.68 (d, 4H), 3.75 (d, 4H), 4.40 (d, 2H), 5.92 (s, 1H), 7.50 - 7.52 (m, 1H), 8.07 (d, 1H), 8.84 - 8.88 (m, 2H), 8.89 (s, 2H), 11.57 (br. s, 1H). (2 H obscured by solvent signal). MS (ESI): [M + H] ⁺ = 530.3

Example	Name	Structure	Analytical data
50	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-(pyridin-3-yl)imidazo[1,5-a]pyridine-5-carboxamide		^1H NMR (300 MHz, DMSO- d_6) δ [ppm] = 0.88 (t, 3 H), 1.23 (d, 6 H), 1.51 (m, 2 H), 2.12 (s, 3 H), 3.48 (m, 1 H), 4.41 (d, 2 H), 5.91 (s, 1 H), 7.49 (dd, 1 H), 7.57 (s, 1 H), 8.2 (s, 1 H), 8.23 (dd, 1 H), 8.55 (d, 1 H), 8.88 (s, 1 H), 8.95 (t, 1 H), 9.07 (d, 1 H), 11.55 (s, 1 H) (2 H obscured by solvent signal). LCMS (conditions 2.2): R_t 0.77 min MS (ESI): $[M + H]^+ = 442.2$
51	1-isopropyl-7-(4-methoxyphenyl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		^1H NMR (300 MHz, DMSO- d_6) δ [ppm] = 0.88 (t, 3 H), 1.29 (d, 6 H), 1.51 (m, 2 H), 2.17 (s, 3 H), 3.44 (m, 1 H), 3.79 (s, 3 H), 4.40 (d, 2 H), 5.91 (s, 1 H), 7.02 (d, 2 H), 7.46 (s, 1 H), 7.77 (d, 2 H), 7.94 (s, 1 H), 8.80 (s, 1 H), 8.97 (t, 1 H), 11.46 (s, 1 H) (2 H obscured by solvent signal). LCMS (conditions 2.2): R_t 0.97 min MS (ESI): $[M + H]^+ = 473.2$
52	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[4-(trifluoromethyl)]		^1H -NMR (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.31 (d, 6H), 1.46 - 1.58 (m, 2H), 2.14 (s, 3H), 3.50 (spt, 1H), 4.42 (d, 2H), 5.92 (s, 1H), 7.55 (d, 1H), 7.84 (d, 2H), 8.07 (s, 2H), 8.22 (d, 1H), 8.88 (s, 1H), 9.01 (t, 1H), 11.56 (s,

Example	Name	Structure	Analytical data
	)phenyl]imidazo [1,5-a]pyridine- 5-carboxamide		1H) (2 H obscured by solvent signal). LCMS (conditions 2.6): R _t 1.37 min MS (ESI): [M + H] ⁺ = 511.3
53	1-isopropyl-N- [(6-methyl-2- oxo-4-propyl- 1,2- dihydropyridin- 3-yl)methyl]-7- [6-(4- methylpiperazin- -1-yl)pyridin-3- yl]imidazo[1,5- a]pyridine-5- carboxamide		¹ H-NMR (400MHz, DMSO- d ₆): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.47 - 1.59 (m, 2H), 2.13 (s, 3H), 2.22 (s, 3H), 2.37 - 2.44 (m, 4H), 3.39 - 3.49 (m, 1H), 3.50 - 3.58 (m, 4H), 4.41 (d, 2H), 5.92 (s, 1H), 6.93 (d, 1H), 7.50 (d, 1H), 7.97 (d, 1H), 8.02 (dd, 1H), 8.61 (d, 1H), 8.82 (s, 1H), 8.92 (t, 1H), 11.55 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.6): R _t 1.13 min MS (ESI): [M + H] ⁺ = 542.4
54	1-isopropyl-7- (4-methoxy-3,5- dimethylphenyl) -N-[(6-methyl- 2-oxo-4-propyl- 1,2- dihydropyridin- 3- yl)methyl]imida zo[1,5- a]pyridine-5- carboxamide		¹ H-NMR (400MHz, DMSO- d ₆): δ [ppm]= 0.90 (t, 3H), 1.30 (d, 6H), 1.54 (sxt, 2H), 2.13 (s, 3H), 2.29 (s, 6H), 3.45 (spt, 1H), 3.68 (s, 3H), 4.41 (d, 2H), 5.91 (s, 1H), 7.43 (d, 1H), 7.49 (s, 2H), 7.95 (d, 1H), 8.79 (s, 1H), 8.94 (t, 1H), 11.53 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.14 min MS (ESI): [M + H] ⁺ = 501.4

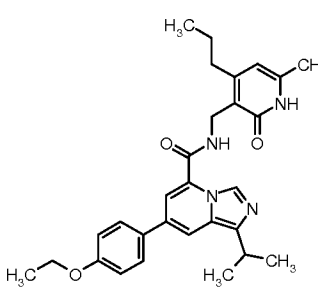
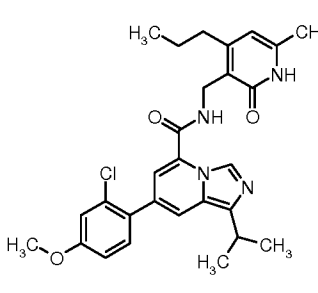
Example	Name	Structure	Analytical data
55	7-(2,4-dimethoxyphenyl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.29 (d, 6H), 1.52 (sxt, 2H), 2.12 (s, 3H), 3.31 - 3.39 (m, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.38 (d, 2H), 5.90 (s, 1H), 6.63 (dd, 1H), 6.67 (d, 1H), 7.26 (d, 1H), 7.38 (d, 1H), 7.74 (d, 1H), 8.77 (s, 1H), 8.81 (t, 1H), 11.51 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 1.05 min MS (ESI): $[\text{M} + \text{H}]^+ = 503.4$
56	7-(3-chloro-4-methoxyphenyl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.53 (sxt, 2H), 2.14 (s, 3H), 3.49 (spt, 1H), 3.91 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 7.24 (d, 1H), 7.46 (d, 1H), 7.80 (dd, 1H), 7.97 (d, 1H), 8.06 (d, 1H), 8.82 (s, 1H), 8.97 (t, 1H), 11.54 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 1.12 min MS (ESI): $[\text{M} + \text{H}]^+ = 507.3$
57	7-(4-ethoxy-3-fluorophenyl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.37 (t, 3H), 1.53 (sxt, 2H), 2.14 (s, 3H), 3.47 (spt, 1H), 4.16 (q, 2H), 4.41 (d, 2H), 5.92 (s, 1H), 7.24 (t, 1H), 7.47 (d, 1H), 7.59 - 7.64 (m, 1H), 7.78 (d, 1H), 8.04 (d, 1H), 8.83 (s, 1H), 8.95 (t, 1H),

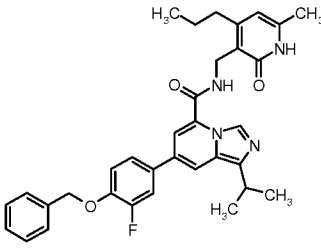
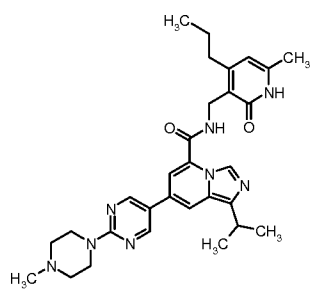
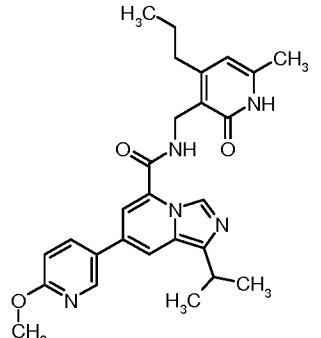
Example	Name	Structure	Analytical data
	alpyridine-5-carboxamide		11.54 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.14 min MS (ESI): [M + H] ⁺ = 505.3
58	7-[3-fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.89 (s, 3H), 1.30 (d, 6H), 1.53 (sxt, 2H), 2.14 (s, 3H), 3.48 (spt, 1H), 4.41 (d, 2H), 4.91 (q, 2H), 5.92 (s, 1H), 7.40 (t, 1H), 7.49 (d, 1H), 7.66 - 7.71 (m, 1H), 7.86 (dd, 1H), 8.10 (d, 1H), 8.84 (s, 1H), 8.94 (t, 1H), 11.54 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.19 min MS (ESI): [M + H] ⁺ = 559.3
59	7-(4-isobutoxyphenyl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.89 (t, 3H), 1.00 (d, 6H), 1.30 (d, 6H), 1.53 (sxt, 2H), 2.03 (spt, 1H), 2.14 (s, 3H), 3.45 (spt, 1H), 3.79 (d, 2H), 4.41 (d, 2H), 5.92 (s, 1H), 7.00 - 7.05 (m, 2H), 7.46 (d, 1H), 7.73 - 7.78 (m, 2H), 7.94 (d, 1H), 8.81 (s, 1H), 8.97 (t, 1H), 11.53 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.27 min MS (ESI): [M + H] ⁺ = 515.4

Example	Name	Structure	Analytical data
60	1-isopropyl-7-(3-methoxyphenyl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.31 (d, 6H), 1.53 (sxt, 2H), 2.13 (s, 3H), 3.49 (spt, 1H), 3.84 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 6.92 - 6.97 (m, 1H), 7.37 - 7.41 (m, 3H), 7.47 (d, 1H), 8.06 (d, 1H), 8.83 (s, 1H), 8.98 (t, 1H), 11.53 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 1.07 min MS (ESI): $[M + H]^+ = 515.4$
61	1-isopropyl-7-(4-methoxy-2-methylphenyl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.88 (t, 3H), 1.28 (d, 6H), 1.51 (sxt, 2H), 2.11 (s, 3H), 2.28 (s, 3H), 3.34 - 3.43 (m, 1H), 3.77 (s, 3H), 4.36 (d, 2H), 5.89 (s, 1H), 6.84 (dd, 1H), 6.89 (d, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.61 (d, 1H), 8.82 (t, 1H), 8.85 (s, 1H), 11.51 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 1.10 min MS (ESI): $[M + H]^+ = 487.3$
62	7-(3-fluoro-4-methoxyphenyl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.52 (sxt, 2H), 2.14 (s, 3H), 3.47 (spt, 1H), 3.88 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 7.25 (t, 1H), 7.47 (d, 1H), 7.62 - 7.67 (m, 1H), 7.79 (dd, 1H), 8.05 (d, 1H), 8.83 (s, 1H), 8.96 (t, 1H), 11.55 (s, 1H)

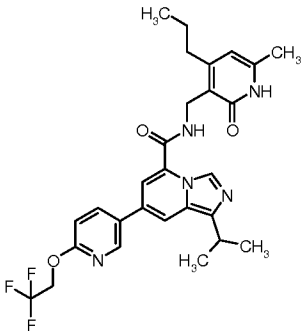
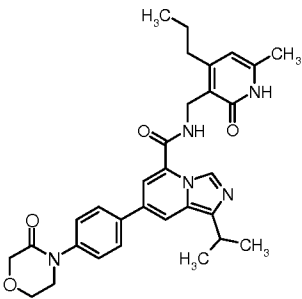
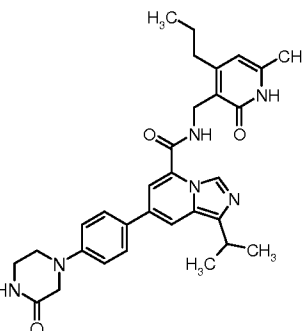
Example	Name	Structure	Analytical data
	zo[1,5-a]pyridine-5-carboxamide		(2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.07 min MS (ESI): [M + H] ⁺ = 491.3
63	1-isopropyl-7-(4-methoxy-3-methylphenyl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imida- zo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.53 (sxt, 2H), 2.13 (s, 3H), 2.23 (s, 3H), 3.45 (spt, 1H), 3.83 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 7.02 (d, 1H), 7.45 (d, 1H), 7.64 (s, 2H), 7.94 (d, 1H), 8.79 (s, 1H), 8.97 (t, 1H), 11.54 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.13 min MS (ESI): [M + H] ⁺ = 487.3
64	7-(2-fluoro-4-methoxyphenyl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imida- zo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.52 (sxt, 2H), 2.13 (s, 3H), 3.39 (spt, 1H), 3.82 (s, 3H), 4.39 (d, 2H), 5.91 (s, 1H), 6.88 - 6.99 (m, 1H), 7.30 (s, 1H), 7.59 - 7.66 (m, 2H), 7.83 (s, 1H), 8.83 (s, 1H), 8.85 - 8.90 (m, 1H), 11.52 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.09 min MS (ESI): [M + H] ⁺ = 491.3

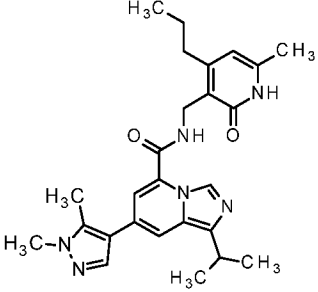
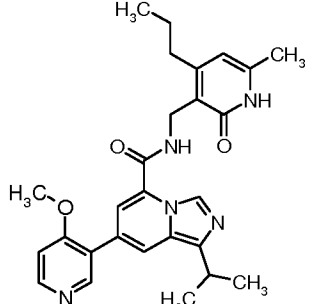
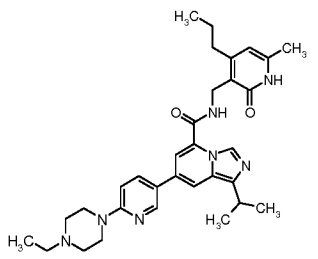
Example	Name	Structure	Analytical data
65	7-(3,4-dimethoxyphenyl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.53 (sxt, 2H), 2.13 (s, 3H), 3.48 (spt, 1H), 3.80 (s, 3H), 3.87 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 7.05 (d, 1H), 7.32 - 7.38 (m, 2H), 7.44 (d, 1H), 7.98 (d, 1H), 8.78 (s, 1H), 8.96 (t, 1H), 11.53 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 0.99 min MS (ESI): $[M + H]^+ = 503.3$
66	1-isopropyl-7-[4-(2-methoxyethoxy)phenyl]-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.53 (sxt, 2H), 2.14 (s, 3H), 3.32 (s, 3H), 3.44 (spt, 1H), 3.66 - 3.70 (m, 2H), 4.12 - 4.16 (m, 2H), 4.41 (d, 2H), 5.92 (s, 1H), 7.04 (d, 2H), 7.47 (d, 1H), 7.76 (d, 2H), 7.95 (d, 1H), 8.81 (s, 1H), 8.96 (t, 1H), 11.53 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 1.03 min MS (ESI): $[M + H]^+ = 517.3$
67	1-isopropyl-7-(4-methoxy-2,5-dimethylphenyl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.28 (d, 6H), 1.51 (sxt, 2H), 2.11 (s, 3H), 2.14 (s, 3H), 2.27 (s, 3H), 3.33 - 3.41 (m, 1H), 3.81 (s, 3H), 4.37 (d, 2H), 5.89 (s, 1H), 6.87 (s, 1H), 7.10 (s, 1H), 7.14 (d, 1H), 7.58 (d,

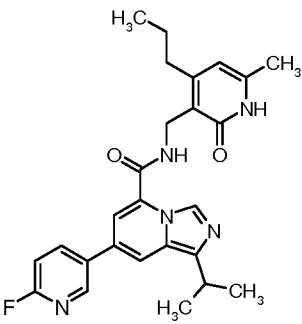
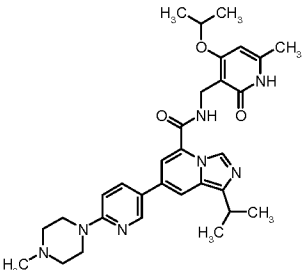
Example	Name	Structure	Analytical data
	yl)methyl]imida zo[1,5- a]pyridine-5- carboxamide		1H), 8.80 (t, 1H), 8.84 (s, 1H), 11.50 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.18 min MS (ESI): [M + H] ⁺ = 501.3
68	7-(4- ethoxyphenyl)- 1-isopropyl-N- [(6-methyl-2- oxo-4-propyl- 1,2- dihydropyridin- 3- yl)methyl]imida zo[1,5- a]pyridine-5- carboxamide		¹ H-NMR (400MHz, DMSO- d ₆): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.35 (t, 3H), 1.52 (sxt, 2H), 2.13 (s, 3H), 3.45 (spt, 1H), 4.07 (q, 2H), 4.40 (d, 2H), 5.92 (s, 1H), 6.99 - 7.04 (m, 2H), 7.47 (d, 1H), 7.73 - 7.78 (m, 2H), 7.95 (d, 1H), 8.81 (s, 1H), 8.97 (t, 1H), 11.55 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.12 min MS (ESI): [M + H] ⁺ = 487.3
69	7-(2-chloro-4- methoxyphenyl)- 1-isopropyl-N- [(6-methyl-2- oxo-4-propyl- 1,2- dihydropyridin- 3- yl)methyl]imida zo[1,5- a]pyridine-5- carboxamide		¹ H-NMR (400MHz, DMSO- d ₆): δ [ppm]= 0.88 (t, 3H), 1.29 (d, 6H), 1.51 (sxt, 2H), 2.12 (s, 3H), 3.35 - 3.41 (m, 2H), 3.82 (s, 3H), 4.37 (d, 2H), 5.88 - 5.91 (m, 1H), 7.03 (dd, 1H), 7.16 (d, 1H), 7.22 (d, 1H), 7.48 (d, 1H), 7.75 (d, 1H), 8.82 (t, 1H), 8.86 (s, 1H), 11.52 (br. s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.15 min MS (ESI): [M + H] ⁺ = 507.3

Example	Name	Structure	Analytical data
70	7-[4-(benzyloxy)-3-fluorophenyl]-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.52 (sxt, 2H), 2.13 (s, 3H), 3.47 (spt, 1H), 4.40 (d, 2H), 5.24 (s, 2H), 5.92 (s, 1H), 7.30 - 7.38 (m, 2H), 7.39 - 7.44 (m, 2H), 7.46 - 7.50 (m, 3H), 7.60 - 7.64 (m, 1H), 7.80 (dd, 1H), 8.05 (d, 1H), 8.83 (s, 1H), 8.94 (t, 1H), 11.53 - 11.57 (m, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 1.28 min MS (ESI): $[\text{M} + \text{H}]^+ = 567.3$
71	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.88 (t, 3H), 1.29 (d, 6H), 1.52 (sxt, 2H), 2.13 (s, 3H), 2.21 (s, 3H), 2.37 (br. t, 4H), 3.38 - 3.49 (m, 1H), 3.78 (t, 4H), 4.40 (d, 2H), 5.92 (s, 1H), 7.21 - 7.27 (m, 1H), 7.38 - 7.42 (m, 1H), 7.50 (d, 1H), 8.05 (d, 1H), 8.83 - 8.88 (m, 2H), 11.56 (br. s, 1H) (2 H obscured by solvent signal). MS (ESI): $[\text{M} + \text{H}]^+ = 543.3$
72	1-isopropyl-7-(6-methoxypyridin-3-yl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.52 (sxt, 2H), 2.14 (s, 3H), 3.46 (spt, 1H), 3.90 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 6.93 (d, 1H), 7.51 (d, 1H), 8.06 (d, 1H), 8.17 (dd, 1H), 8.64 (d, 1H), 8.85 (s, 1H),

Example	Name	Structure	Analytical data
	yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		8.91 (t, 1H), 11.54 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 0.99 min MS (ESI): [M + H] ⁺ = 474.3
73	7-(5-fluoro-6-methoxypyridin-3-yl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.89 (t, 3H), 1.31 (d, 6H), 1.53 (sxt, 2H), 2.14 (s, 3H), 3.46 (spt, 1H), 3.99 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 7.53 (d, 1H), 8.15 (d, 1H), 8.24 (dd, 1H), 8.50 (d, 1H), 8.85 - 8.91 (m, 2H), 11.51 - 11.58 (m, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 1.07 min MS (ESI): [M + H] ⁺ = 492.3
74	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[(4-(methylsulfonyl)amino)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.89 (t, 3H), 1.31 (d, 6H), 1.53 (spt, 2H), 2.13 (s, 3H), 3.01 (s, 3H), 3.40 - 3.50 (m, 2H), 4.41 (d, 2H), 5.92 (s, 1H), 7.30 (d, 2H), 7.48 (d, 1H), 7.80 (d, 2H), 7.99 (d, 1H), 8.82 (s, 1H), 8.95 (t, 1H), 9.83 (br. s, 1H), 11.53 (br. s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 0.91 min MS (ESI): [M + H] ⁺ = 536.3

Example	Name	Structure	Analytical data
75	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.31 (d, 6H), 1.52 (sxt, 2H), 2.14 (s, 3H), 3.47 (spt, 1H), 4.41 (d, 2H), 5.05 (q, 2H), 5.92 (s, 1H), 7.11 (d, 1H), 7.53 (d, 1H), 8.12 (d, 1H), 8.29 (dd, 1H), 8.68 (d, 1H), 8.85 - 8.94 (m, 2H), 11.54 (br. s., 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 1.17 min MS (ESI): $[M + H]^+ = 542.3$
76	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[4-(3-oxomorpholin-4-yl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (s, 3H), 1.31 (d, 6H), 1.46 - 1.59 (m, 2H), 2.13 (s, 3H), 3.48 (spt, 1H), 3.78 (t, 2H), 4.00 (t, 2H), 4.23 (s, 2H), 4.41 (d, 2H), 5.92 (s, 1H), 7.52 (d, 3H), 7.88 (d, 2H), 8.08 (d, 1H), 8.85 (s, 1H), 9.00 (t, 1H), 11.57 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 0.90 min MS (ESI): $[M + H]^+ = 542.3$
77	1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[4-(3-oxopiperazin-1-yl)phenyl]imidazo[1,5-a]		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.29 (d, 6H), 1.46 - 1.58 (m, 3H), 2.13 (s, 3H), 3.40 - 3.50 (m, 4H), 3.78 (s, 2H), 4.40 (s, 2H), 5.91 (s, 1H), 7.01 (d, 2H), 7.47 (s, 1H), 7.73 (d, 2H), 7.92 (s, 1H), 8.10 (s, 1H), 8.80 (s, 1H), 9.11 (br. s, 1H), 11.50 (br. s, 1H) (2 H obscured by

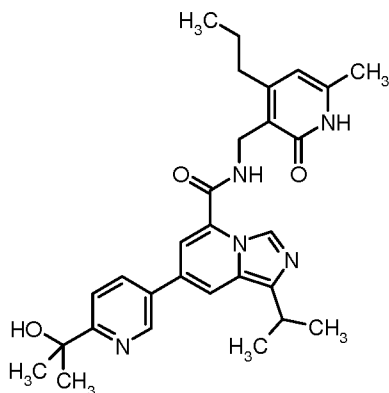
Example	Name	Structure	Analytical data
	alpyridine-5-carboxamide		solvent signal). UPLC (conditions 1.1): R_t 0.67 min MS (ESI): $[M + H]^+ = 541$
78	7-(1,5-dimethyl-1H-pyrazol-4-yl)-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidozo[1,5-alpyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.29 (d, 6H), 1.52 (sxt, 2H), 2.13 (s, 3H), 2.41 (s, 3H), 3.78 (s, 3H), 4.38 (d, 2H), 5.91 (s, 1H), 7.22 (d, 1H), 7.59 (d, 1H), 7.69 (s, 1H), 8.76 (s, 1H), 8.87 (t, 1H), 11.55 (s, 1H) (3 H obscured by solvent signal). LCMS (conditions 2.5): R_t 0.86 min MS (ESI): $[M + H]^+ = 461.3$
79	1-isopropyl-7-(4-methoxypyridin-3-yl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidozo[1,5-alpyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.89 (t, 3H), 1.30 (d, 6H), 1.52 (sxt, 2H), 2.12 (s, 3H), 3.91 (s, 3H), 4.38 (d, 2H), 5.91 (s, 1H), 7.21 (d, 1H), 7.34 (d, 1H), 7.93 (s, 1H), 8.47 (d, 1H), 8.58 (s, 1H), 8.80 - 8.88 (m, 2H), 11.54 (s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.6): R_t 1.05 min MS (ESI): $[M + H]^+ = 472.3$
80	1-isopropyl-7-(4-methoxypyridin-3-yl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.88 (t, 3H), 1.03 (t, 3H), 1.27 - 1.33 (m, 6H), 1.52 (sxt, 2H), 2.13 (s, 3H), 2.37 (q, 2H), 3.40 - 3.48 (m, 1H), 3.54 (br. t, 4H), 4.40 (d, 2H), 5.92 (s, 1H), 6.90 -

Example	Name	Structure	Analytical data
	3- yl)methyl]imida zo[1,5- a]pyridine-5- carboxamide		6.95 (m, 1H), 7.49 (d, 1H), 7.96 (d, 1H), 8.02 (dd, 1H), 8.61 (d, 1H), 8.82 (s, 1H), 8.91 (t, 1H), 11.55 (br. s, 1H). (6 H obscured by solvent signal). LCMS (conditions 2.6): R _t 0.76 min MS (ESI): [M + H] ⁺ = 556.4
81	7-(6- fluoropyridin-3- yl)-1-isopropyl- N-[(6-methyl-2- oxo-4-propyl- 1,2- dihydropyridin- 3- yl)methyl]imida zo[1,5- a]pyridine-5- carboxamide		¹ H-NMR (400MHz, DMSO- d ₆): δ [ppm]= 0.89 (t, 3H), 1.31 (d, 6H), 1.52 (sxt, 2H), 2.13 (s, 3H), 3.47 (spt, 1H), 4.41 (d, 2H), 5.92 (s, 1H), 7.33 (dd, 1H), 7.55 (d, 1H), 8.21 (d, 1H), 8.46 (dt, 1H), 8.74 (d, 1H), 8.89 (s, 1H), 8.94 (t, 1H), 11.57 (s, 1H). (2 H obscured by solvent signal). MS (ESI): [M + H] ⁺ = 462.2
82	N-[(4- isopropoxy-6- methyl-2-oxo- 1,2- dihydropyridin- 3-yl)methyl]-1- isopropyl-7-[6- (4- methylpiperazin -1-yl)pyridin-3- yl]imidazo[1,5- a]pyridine-5- carboxamide		¹ H-NMR (400MHz, DMSO- d ₆): d [ppm] = 1.21 (d, 6H), 1.30 (d, 6H), 2.17 (s, 3H), 2.22 (s, 3H), 2.36 - 2.44 (m, 4H), 3.44 (m, 1H), 3.50 - 3.59 (m, 4H), 4.33 (d, 2H), 4.65 (m, 1H), 6.11 (s, 1H), 6.93 (d, 1H), 7.45 (d, 1H), 7.96 (d, 1H), 8.02 (dd, 1H), 8.60 (d, 1H), 8.69 (t, 1H), 8.84 (s, 1H), 11.42 (br. s., 1H). LCMS (conditions 2.6): R _t 1.08 min MS (ESI): [M + H] ⁺ = 558.4

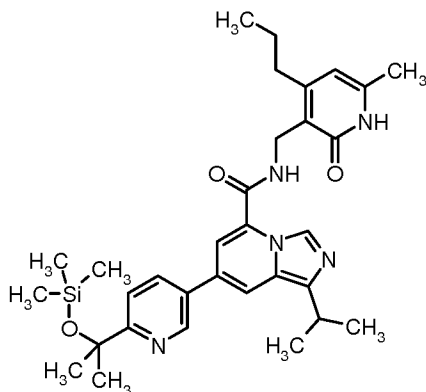
Example	Name	Structure	Analytical data
83	N-[(4-isopropoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): d [ppm] = 1.21 (d, 6H), 1.30 (d, 6H), 2.17 (s, 3H), 3.40 - 3.48 (m, 1H), 3.48 - 3.53 (m, 4H), 3.67 - 3.77 (m, 4H), 4.33 (d, 2H), 4.66 (spt, 1H), 6.11 (s, 1H), 6.94 (d, 1H), 7.46 (d, 1H), 7.98 (d, 1H), 8.05 (dd, 1H), 8.63 (d, 1H), 8.69 (t, 1H), 8.85 (s, 1H), 11.43 (br. s., 1H). LCMS (conditions 2.6): R_t 1.09 min MS (ESI): $[\text{M} + \text{H}]^+ = 545.3$

Example 84 – 7-[6-(2-hydroxypropan-2-yl)pyridin-3-yl]-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide

5



Step 1 – 1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-(6-{2-[(trimethylsilyl)oxy]propan-2-yl}pyridin-3-yl)imidazo[1,5-a]pyridine-5-carboxamide



To a solution of 7-chloro-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide (intermediate **202A**) (250 mg, 0.62 mmol) and 5-
 5 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-{2-[(trimethylsilyl)oxy]propan-2-yl}pyridine (241 mg, 0.75 mmol) in tetrahydrofuran (10 ml) under an atmosphere of nitrogen was added potassium phosphate (0.5 M, 4.2 ml), followed by a solution of (2'-aminobiphenyl-2-yl)(chloro)dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)palladium (2nd generation Ruphos precatalyst) (98 mg, 125 mmol) in tetrahydrofuran (0.5 ml), and the reaction was stirred at 50 °C
 10 for 2 h. Water was added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was taken to the next step without purification.

LCMS (conditions 2.4): Rt 1.40 min; MS (ESI): [M + H]⁺ = 574.5.

15

Step 2

To a solution of crude 1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-(6-{2-[(trimethylsilyl)oxy]propan-2-yl}pyridin-3-yl)imidazo[1,5-a]pyridine-5-carboxamide (crude from the previous step) in dichloromethane (10 ml) was added formic acid (5 ml) and the
 20 mixture was stirred for 1 h at room temperature. The mixture was concentrated and pre-purified by chromatography (Biotage KP-NH, dichloromethane, methanol). After HPLC purification (preparative conditions 1), 7-[6-(2-hydroxypropan-2-yl)pyridin-3-yl]-1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide (229 mg, 73%) was obtained.

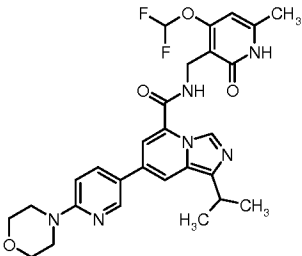
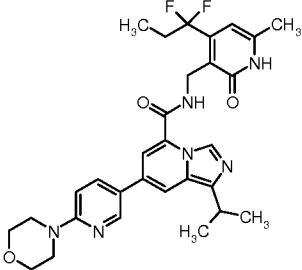
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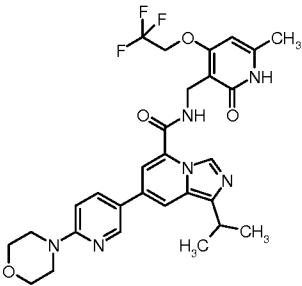
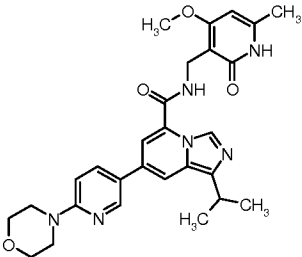
¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 0.89 (t, 3H), 1.34 (d, 6H), 1.45 - 1.59 (m, 8H), 2.14 (s, 3H), 3.59 (dt, 1H), 4.42 (d, 2H), 5.93 (s, 1H), 7.80 (d, 2H), 8.30 (dd, 1H), 8.34 (s, 1H), 8.98 (d, 1H), 9.05 (t, 1H), 9.37 (br. s., 1H), 11.58 (br. s., 1H). (2 H obscured by solvent signal)

30 LCMS (conditions 2.4): Rt 0.88 min; MS (ESI): [M + H]⁺ = 502.3.

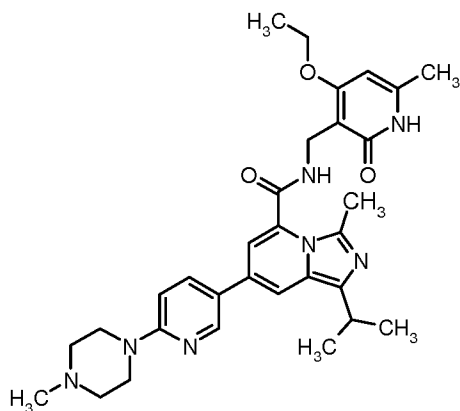
The following examples were prepared as described for example **48**, method 48-II, by amide coupling of intermediate **221A** with the respective aminomethylpyridone derivatives, which are

5 described above.

Example	Name	Structure	Analytical data
85	N-{[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-1-isopropyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): d [ppm] = 1.30 (d, 6H), 2.21 (s, 3H), 3.41 - 3.49 (m, 1H), 3.49 - 3.55 (m, 4H), 3.68 - 3.76 (m, 4H), 4.35 (d, 2H), 6.10 (s, 1H), 6.95 (d, 1H), 7.31 (t, 1H), 7.51 (m, 1H), 8.01 (s, 1H), 8.06 (dd, 1H), 8.64 (d, 1H), 8.88 (m, 2H), 11.93 (s, 1H). MS (ESI): [M + H] ⁺ = 553
86	N-{[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-1-isopropyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): d [ppm] = 0.98 (t, 3H), 1.37 (d, 6H), 2.14 - 2.30 (m, 5H), 3.50 - 3.62 (m, 4H, obscured by water signal), 3.65 - 3.68 (m, 1H, obscured by water signal), 3.68 - 3.79 (m, 4H, obscured by water signal), 4.44 (d, 2H), 6.13 (s, 1H), 7.03 (d, 1H), 7.90 (s, 1H), 8.15 (dd, 1H), 8.32 (s, 1H), 8.70 (d, 1H), 9.05 (m, 1H), 9.82 (br. s., 1H), 12.15 (br. s., 1H). LCMS (conditions 2.5): Rt 0.93 min; MS (ESI): [M + H] ⁺ = 565.3

Example	Name	Structure	Analytical data
87	1-isopropyl-N- {[6-methyl-2-oxo-4-(2,2,2-trifluoroethoxy)-1,2-dihydropyridin-3-yl]methyl}-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): d [ppm] = 1.30 (d, 6H), 2.20 (s, 3H), 3.39 - 3.48 (m, 1H), 3.48 - 3.54 (m, 4H), 3.66 - 3.76 (m, 4H), 4.35 (d, 2H), 4.82 (q, 2H), 6.20 (s, 1H), 6.93 (d, 1H), 7.46 (d, 1H), 7.97 (d, 1H), 8.05 (dd, 1H), 8.63 (d, 1H), 8.72 (t, 1H), 8.82 (s, 1H), 11.68 (s, 1H). LCMS (conditions 2.5): Rt 0.88 min; MS (ESI): $[\text{M} + \text{H}]^+ = 585.3$
88	1-isopropyl-N- [(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): d [ppm] = 1.30 (d, 6H), 2.20 (s, 3H), 3.40 - 3.48 (m, 1H), 3.48 - 3.53 (m, 4H), 3.69 - 3.74 (m, 4H), 3.81 (s, 3H), 4.31 (d, 2H), 6.13 (s, 1H), 6.93 (d, 1H), 7.46 (d, 1H), 7.98 (d, 1H), 8.06 (dd, 1H), 8.64 (d, 1H), 8.70 (t, 1H), 8.83 (s, 1H), 11.50 (s, 1H). LCMS (conditions 2.4): Rt 0.75 min; MS (ESI): $[\text{M} + \text{H}]^+ = 517.4$

Example 89 – N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methyl-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



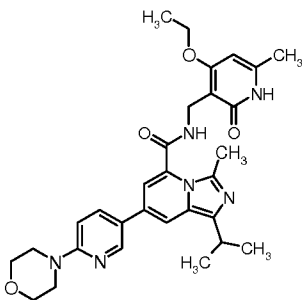
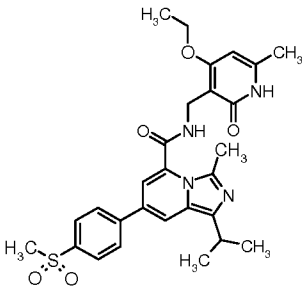
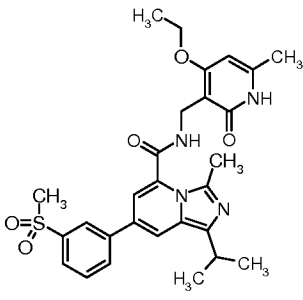
80 mg (0.19 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **203A**, 68.82 mg, 0.23
 5 mmol) 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine and 22 mg (19 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.192 ml (0.384 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol and 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and
 10 the residue purified by preparative HPLC (Preparative HPLC conditions 2 (basic)) provided 60.7 mg (52%) of the target compound in pure form.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 1.22 - 1.34 (m, 9H), 2.17 (s, 3H), 2.22 (s, 3H), 2.37 - 2.43 (m, 4H), 2.46 (s, 3H), 3.35 - 3.44 (m, 1H), 3.48 - 3.57 (m, 4H), 4.10 (q, 2H), 4.29 (d, 2H),
 15 6.08 (s, 1H), 6.86 - 6.93 (m, 2H), 7.78 (d, 1H), 7.94 (dd, 1H), 8.51 (d, 1H), 8.67 (t, 1H), 11.44 (s, 1H).

MS (ESI): [M + H]⁺ = 558.4.

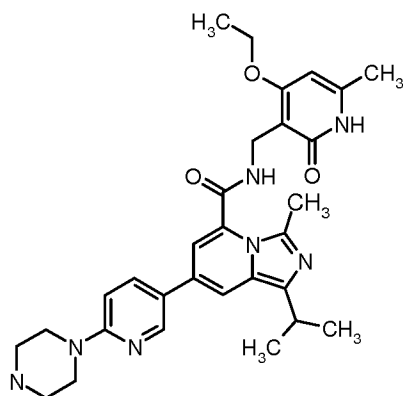
20

The following example compounds were synthesized in analogy to example compound **89** by Suzuki coupling of intermediate intermediate **203A** with the respective commercially available boronic acids (or their pinacolate esters) employing a palladium catalyst in the presence of a base in suitable solvent system under microwave heating (usually 110 °C). The reaction time and
 25 temperature was individually adapted in order to achieve maximum turnover of starting material. The target compounds were in general isolated by preparative HPLC conditions, for example preparative HPLC conditions 1 or 2.

Example	Name	Structure	Analytical data
90	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.25 - 1.33 (m, 9H), 2.17 (s, 3H), 2.47 (s, 3H), 3.39 (spt, 1H), 3.46 - 3.53 (m, 4H), 3.69 - 3.75 (m, 4H), 4.11 (q, 2H), 4.29 (d, 2H), 6.08 (s, 1H), 6.87 - 6.94 (m, 2H), 7.80 (d, 1H), 7.97 (dd, 1H), 8.54 (d, 1H), 8.66 (t, 1H), 11.42 (s, 1H). LCMS (conditions 2.6): R _t 1.01 min MS (ESI): [M + H] ⁺ = 545.37
91	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methyl-7-[4-(methylsulfonyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, Pyr): δ [ppm]= 1.29 (t, 3H), 1.50 (d, 6H), 2.24 (s, 3H), 3.04 (s, 3H), 3.34 (s, 3H), 3.37 - 3.48 (m, 1H), 4.02 (q, 2H), 5.17 (d, 2H), 5.96 (s, 1H), 7.30 (d, 1H), 7.80 (d, 2H), 7.92 (d, 1H), 8.15 (d, 2H), 9.71 (t, 1H), 12.83 (br. s., 1H). MS (ESI): [M + H] ⁺ = 537
92	N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methyl-7-[3-(methylsulfonyl)phenyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.26 - 1.35 (m, 9H), 2.17 (s, 3H), 3.31 (s, 3H), 3.41 - 3.52 (m, 1H), 4.11 (q, 2H), 4.30 (d, 2H), 6.09 (s, 1H), 7.01 (d, 1H), 7.68 - 7.75 (m, 1H), 7.85 (s, 1H), 8.07 (d, 1H), 8.14 (d, 1H), 8.26 (s, 1H), 8.72 - 8.80 (m, 1H), 11.41 (br. s, 1H) (3H obscured by solvent signal). LCMS (conditions 2.6):

Example	Name	Structure	Analytical data
			R _t 0.97 min MS (ESI): [M + H] ⁺ = 537.3

Example 93 -N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methyl-7-[6-(piperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



5

Step 1)

100 mg (0.24 mmol) 7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-isopropyl-3-methylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **203A**), 112.06 mg (0.29 mmol) tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine-1-carboxylate and 27.7 mg (24 μmol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.24 ml (0.48 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol and 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture heated for 1h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography using dichloromethane and dichloromethane/methanol as eluent to provide 100 mg (64%) of the target compound in pure form.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 1.24 - 1.31 (m, 9H), 1.43 (s, 9H), 2.17 (s, 3H), 2.47 (s, 3H), 3.40 - 3.48 (m, 4H), 3.50 - 3.59 (m, 4H), 4.10 (q, 2H), 4.29 (d, 2H), 6.09 (s, 1H), 6.87 - 6.96 (m, 2H), 7.80 (d, 1H), 7.98 (dd, 1H), 8.53 (d, 1H), 8.69 (t, 1H), 11.47 (s, 1H).

MS (ESI): [M + H]⁺ = 644.

Step 2)

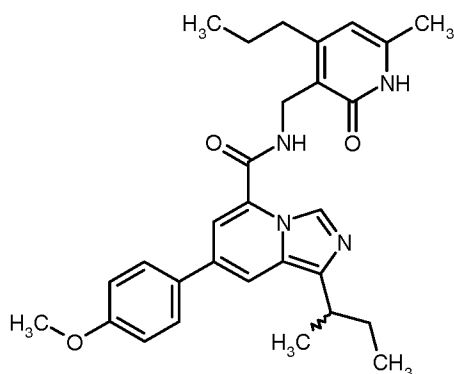
100 mg (0.155 mmol) tert-butyl 4-[5-(5-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbonyl)-1-isopropyl-3-methylimidazo[1,5-a]pyridin-7-yl)pyridin-2-yl]piperazine-1-carboxylate were dissolved in dichloromethane (2 ml)/ methanol (2 ml). 5 ml (729.2 mmol) 4 N

hydrochloric acid in dioxane were added. The reaction stirred at room temperature over night. The mixture was concentrated. The residue was extracted with water and diethyl ether. The aqueous layer was adjusted to pH 9 with aqueous sodium bicarbonate solution and extracted with ethyl acetate/ tetrahydrofurane. Organic and aqueous layer were concentrated to remove the organic solvent. The aqueous suspension was filtered, washed with water and dried *in vacuo* to give 50.9 mg (60%) of the pure compound as a solid.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.21 - 1.34 (m, 9H), 2.17 (s, 3H), 2.47 (s, 3H), 2.75 - 2.82 (m, 4H), 3.41 - 3.49 (m, 5H), 4.11 (q, 2H), 4.29 (d, 2H), 6.08 (s, 1H), 6.81 - 6.91 (m, 3H), 7.77 (s, 1H), 7.92 (dd, 1H), 8.50 (s, 1H), 8.63 - 8.70 (m, 1H), 11.42 (br. s, 1H).

MS (ESI): [M + H]⁺ = 544.

Example 94 – *rac*-1-sec-butyl-7-(4-methoxyphenyl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide



100 mg (0.241 mmol) *rac*-1-sec-butyl-7-chloro-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide (intermediate **205A**), 54.9 mg (0.36 mmol) (4-methoxyphenyl)boronic acid and 27.8 mg (24 μmol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.241 ml (0.482 mmol) aqueous sodium carbonate solution (2N), 1.0 ml ethanol und 1.5 ml toluene were added and the resulting mixture heated for 30 min to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (see box below) to provide 34.5 mg (29%) of the target compound in pure form.

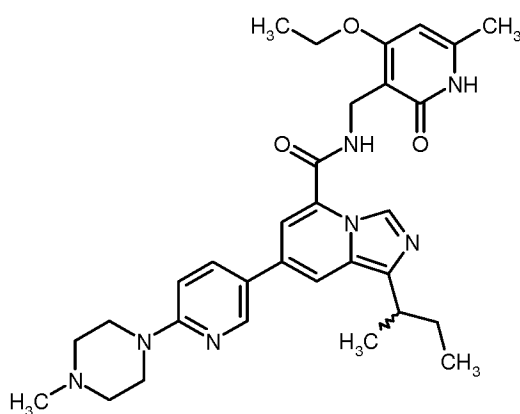
System:	Waters Autopurificationsystem: Pump 254, Sample Manager 2767, CFO, DAD 2996, SQD 3100
Column:	XBrigde C18 5μm 100x30 mm

<i>Solvent:</i>	A = H ₂ O + 0.2% NH ₃ (32%)
	B = acetonitrile
<i>Gradient:</i>	0–0.5 min 25 mL/min to 70 mL/min 45% B; 0.5–5.5 min 45–65% B
<i>Flow:</i>	70 mL/min
<i>Temperature:</i>	room temperature

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 0.76 (t, 3H), 0.89 (t, 3H), 1.11 (s, 2H), 1.28 (d, 3H), 1.52 (sxt, 2H), 1.59 - 1.78 (m, 2H), 2.13 (s, 3H), 3.19 (sxt, 1H), 3.80 (s, 3H), 4.41 (d, 2H), 5.92 (s, 1H), 7.03 (d, 2H), 7.46 (d, 1H), 7.77 (d, 2H), 7.93 (s, 1H), 8.82 (s, 1H), 8.97 (t, 1H), 11.50 - 11.58 (m, 1H).

MS (ESI): [M + H]⁺ = 487.3

10 **Example 95** – *rac*-1-sec-butyl-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



50 mg (0.12 mmol) *rac*-1-sec-butyl-7-chloro-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide (intermediate **204A**), 64.4 mg (0.216 mmol) 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine and 20.8 mg (18 μmol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.12 ml (0.24 mmol) aqueous sodium carbonate solution (2N), 0.75 ml ethanol and 0.75 ml toluene were added and the resulting mixture heated for 30 min to 130 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (Preparative HPLC conditions 1) to provide 38.2 mg (57%) of the target compound in pure form.

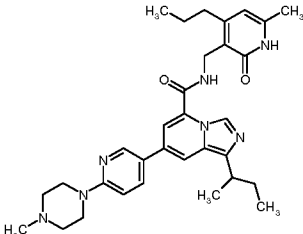
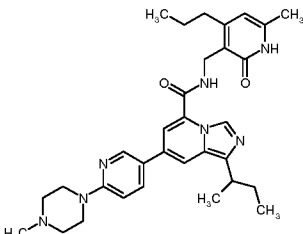
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 0.76 (t, 3H), 1.22 - 1.30 (m, 6H), 1.59 - 1.78 (m, 2H),

2.18 (s, 3H), 2.23 (s, 3H), 2.39 - 2.45 (m, 4H), 3.12 - 3.22 (m, 1H), 3.51 - 3.57 (m, 4H), 4.10 (q, 2H), 4.34 (d, 2H), 6.09 (s, 1H), 6.92 (d, 1H), 7.44 (d, 1H), 7.93 (d, 1H), 8.01 (dd, 1H), 8.59 - 8.62 (m, 1H), 8.69 (t, 1H), 8.83 (s, 1H), 11.45 (br. s, 1H).

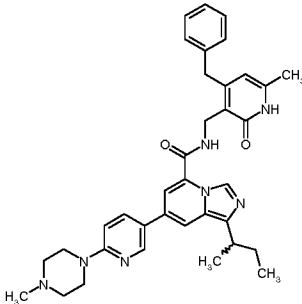
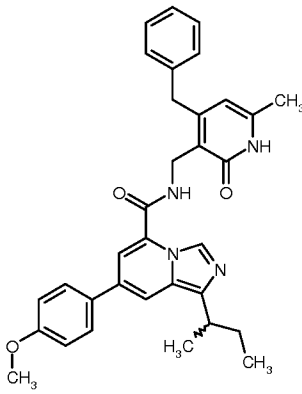
5 MS (ESI): $[M + H]^+ = 558.3$

The following example compounds were synthesized in analogy to example **95** by Suzuki coupling of intermediates **204A**, **205A**, **206A**, **207A**, **208A**, **209A**, **210A**, or **211A**, with the respective commercially available boronic acids (or their pinacolate esters) employing a palladium catalyst in the presence of a base in a suitable solvent system under microwave heating (usually 110 °C). The reaction time and temperature was individually adapted in order to achieve maximum turnover of starting material. The target compounds were in general isolated by preparative HPLC conditions, for example preparative HPLC conditions 1 or 2.

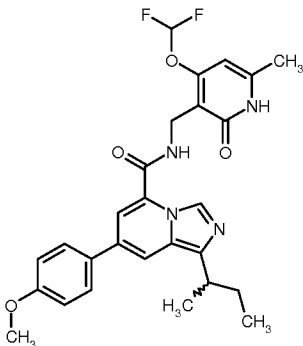
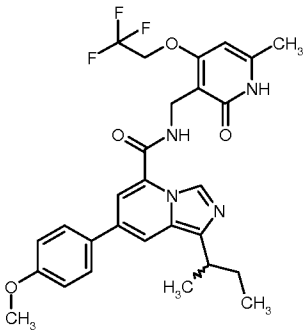
Example	Name	Structure	Analytical data
96	<i>rac</i> -1-sec-butyl-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.77 (t, 3H), 1.22 - 1.31 (m, 6H), 1.59 - 1.79 (m, 2H), 2.18 (s, 3H), 3.18 (sxt, 1H), 3.80 (s, 3H), 4.10 (q, 2H), 4.34 (d, 2H), 6.09 (s, 1H), 7.03 (d, 2H), 7.42 (d, 1H), 7.77 (d, 2H), 7.91 (d, 1H), 8.74 (t, 1H), 8.82 (s, 1H), 11.44 (s, 1H). LCMS (conditions 2.5): R_t 0.97 min MS (ESI): $[M + H]^+ = 489.35$
97	<i>rac</i> -1-sec-butyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.76 (t, 3H), 0.89 (t, 3H), 1.25 - 1.31 (m, 3H), 1.53 (sxt, 2H), 1.59 - 1.78 (m, 2H), 2.14 (s, 3H), 2.23 (s, 3H), 2.38 - 2.46 (m, 4H), 3.18 (sxt, 1H), 3.52 - 3.59 (m, 4H), 4.41 (d, 2H), 5.92 (s, 1H), 6.93 (d, 1H), 7.49 (d, 1H), 7.95 (s, 1H), 8.01 (dd, 1H), 8.61 (d,

Example	Name	Structure	Analytical data
	carboxamide		1H), 8.83 (s, 1H), 8.91 (t, 1H), 11.53 (s, 1H) (2H obscured by solvent signal). LCMS (conditions 2.5): R _t 0.77 min MS (ESI): [M + H] ⁺ = 556.3
97.1	1-[butan-2-yl]-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide (Isomer 1)	 Isomer 1 (prepared from intermediate 205.1A)	
97.2	1-[butan-2-yl]-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide (Isomer 2)	 Isomer 2 (prepared from intermediate 205.2A)	

Example	Name	Structure	Analytical data
98	<i>rac</i> -1- <i>sec</i> -butyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5- <i>a</i>]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO- <i>d</i> ₆): δ [ppm]= 0.76 (t, 3H), 1.28 (d, 3H), 1.60 - 1.77 (m, 2H), 2.20 (s, 3H), 2.23 (s, 3H), 2.41 (t, 4H), 3.18 (sxt, 1H), 3.54 (t, 4H), 3.82 (s, 3H), 4.31 (d, 2H), 6.13 (s, 1H), 6.92 (d, 1H), 7.45 (d, 1H), 7.94 (d, 1H), 8.02 (dd, 1H), 8.61 (d, 1H), 8.70 (t, 1H), 8.83 (s, 1H), 11.49 (br. s, 1H). LCMS (conditions 2.5): R _t 0.61 min MS (ESI): [M + H] ⁺ = 544
99	<i>rac</i> -1- <i>sec</i> -butyl-N-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(4-methoxyphenyl)imidazo[1,5- <i>a</i>]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO- <i>d</i> ₆): δ [ppm]= 0.77 (t, 3H), 1.29 (d, 3H), 1.60 - 1.78 (m, 2H), 2.20 (s, 3H), 3.18 (sxt, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.32 (d, 2H), 6.12 (s, 1H), 7.03 (d, 2H), 7.42 (d, 1H), 7.77 (d, 2H), 7.92 (d, 1H), 8.75 (t, 1H), 8.82 (s, 1H), 11.48 (s, 1H). LCMS (conditions 2.5): R _t 0.93 min MS (ESI): [M + H] ⁺ = 475
100	<i>rac</i> -1- <i>sec</i> -butyl-N-{[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5- <i>a</i>]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO- <i>d</i> ₆): δ [ppm]= 0.76 (t, 3H), 1.28 (d, 3H), 1.60 - 1.77 (m, 2H), 2.21 (s, 3H), 2.24 (s, 3H), 2.42 (t, 4H), 3.18 (sxt, 2H), 3.55 (t, 4H), 4.35 (d, 2H), 6.09 (s, 1H), 6.93 (d, 1H), 7.46 - 7.48 (m, 1H), 7.95 (d, 1H), 8.01 (dd, 1H), 8.60 (d, 1H), 8.81 (s, 1H), 8.86 (t, 1H),

Example	Name	Structure	Analytical data
	yl]imidazo[1,5-a]pyridine-5-carboxamide		11.92 (br. s, 1H). LCMS (conditions 2.5): R _t 0.66 min MS (ESI): [M + H] ⁺ = 581
101	<i>rac</i> -N-[(4-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-sec-butyl-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO-d ₆): δ [ppm]= 1.16 (s, 2H), 1.28 (d, 3H), 1.60 - 1.76 (m, 2H), 2.11 (s, 3H), 2.24 (s, 3H), 2.42 (t, 4H), 3.17 (sxt, 1H), 3.56 (t, 4H), 3.95 (s, 2H), 4.46 (d, 2H), 5.82 (s, 1H), 6.51 (s, 1H), 6.94 (d, 1H), 7.06 - 7.10 (m, 1H), 7.20 (s, 4H), 7.42 (d, 1H), 7.94 (d, 1H), 8.01 (dd, 1H), 8.61 (d, 1H), 8.80 (s, 1H), 8.94 (t, 1H), 11.62 (s, 1H). LCMS (conditions 2.5): R _t 0.77 min MS (ESI): [M + H] ⁺ = 604.35
102	<i>rac</i> -N-[(4-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-sec-butyl-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO-d ₆): δ [ppm]= 0.77 (t, 3H), 1.28 (d, 3H), 1.60 - 1.77 (m, 2H), 2.11 (s, 3H), 3.18 (sxt, 1H), 3.81 (s, 3H), 3.95 (s, 2H), 4.46 (d, 2H), 5.81 (s, 1H), 7.04 (d, 2H), 7.06 - 7.12 (m, 1H), 7.17 - 7.21 (m, 4H), 7.39 - 7.41 (m, 1H), 7.77 (d, 2H), 7.91 (d, 1H), 8.79 (s, 1H), 9.00 (t, 1H), 11.62 (s, 1H). LCMS (conditions 2.5): R _t 1.10 min MS (ESI): [M + H] ⁺ = 535.34

Example	Name	Structure	Analytical data
103	<i>rac</i> -1- <i>sec</i> -butyl-N-([4-(methoxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl)-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5- <i>a</i>]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO- <i>d</i> ₆): δ [ppm]= 0.76 (t, 3H), 1.28 (d, 3H), 1.60 - 1.78 (m, 2H), 2.17 (s, 3H), 2.22 (s, 3H), 2.41 (t, 4H), 3.18 (sxt, 1H), 3.54 (t, 4H), 4.35 (d, 2H), 4.48 (s, 2H), 6.10 (s, 1H), 6.93 (d, 1H), 7.50 (d, 1H), 7.96 (d, 1H), 8.02 (dd, 1H), 8.61 (d, 1H), 8.82 (s, 1H), 8.95 (t, 1H), 11.70 (br. s, 1H) (3 H obscured by solvent signal). LCMS (conditions 2.5): R _t 0.65 min MS (ESI): [M + H] ⁺ = 558.35
104	<i>rac</i> -1- <i>sec</i> -butyl-N-([4-(methoxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl)-7-(4-methoxyphenyl)imidazo[1,5- <i>a</i>]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO- <i>d</i> ₆): δ [ppm]= 0.76 (t, 3H), 1.28 (d, 3H), 1.59 - 1.78 (m, 2H), 2.17 (s, 3H), 3.19 (sxt, 1H), 3.80 (s, 3H), 4.36 (d, 2H), 4.48 (s, 2H), 6.10 (s, 1H), 7.03 (d, 2H), 7.47 (d, 1H), 7.77 (d, 2H), 7.94 (d, 1H), 8.81 (s, 1H), 9.01 (t, 1H), 11.70 (s, 1H) (3 H obscured by solvent signal). LCMS (conditions 2.5): R _t 0.97 min MS (ESI): [M + H] ⁺ = 489.3
105	<i>rac</i> -1- <i>sec</i> -butyl-N-([4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl)-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5- <i>a</i>]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO- <i>d</i> ₆): δ [ppm]= 0.97 (t, 3H), 1.28 (d, 3H), 1.59 - 1.78 (m, 2H), 2.16 - 2.30 (m, 8H), 2.41 (t, 4H), 3.18 (sxt, 2H), 3.54 (t, 4H), 4.41 (d, 2H), 6.11 (s, 1H), 6.94 (d, 1H), 7.44 (d, 1H), 7.96 (d, 1H), 8.00 (dd, 1H),

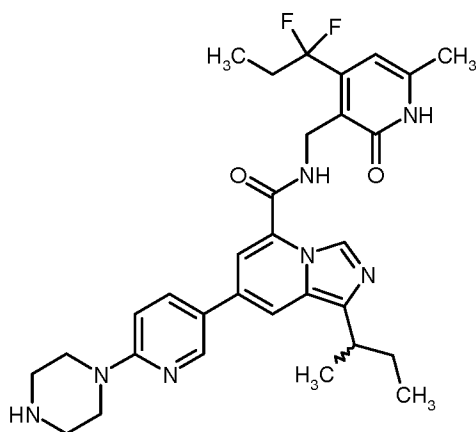
Example	Name	Structure	Analytical data
	1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		8.59 (d, 1H), 8.78 - 8.83 (m, 2H), 12.12 (br. s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R _t 0.75 min MS (ESI): [M + H] ⁺ = 592.34
106	<i>rac</i> -1-sec-butyl-N-([4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl)-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO-d ₆): δ [ppm]= 0.77 (s, 3H), 1.28 (d, 3H), 1.61 - 1.80 (m, 2H), 2.21 (s, 3H), 3.18 (sxt, 1H), 3.81 (s, 3H), 4.35 (d, 2H), 6.09 (s, 1H), 7.03 (d, 2H), 7.35 (t, 1H), 7.45 (d, 1H), 7.76 (d, 2H), 7.93 (d, 1H), 8.80 (s, 1H), 8.91 (t, 1H), 11.91 (br. s, 1H). LCMS (conditions 2.5): R _t 0.99 min MS (ESI): [M + H] ⁺ = 511.29
107	<i>rac</i> -1-sec-butyl-7-(4-methoxyphenyl)-N-([6-methyl-2-oxo-4-(2,2,2-trifluoroethoxy)-1,2-dihydropyridin-3-yl]methyl)imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, CHLOROFORM-d): δ [ppm]= 0.83 (t, 3H), 1.41 (d, 3H), 1.71 - 1.92 (m, 2H), 2.21 (s, 3H), 3.09 (sxt, 1H), 3.82 (s, 3H), 4.50 (q, 2H), 4.66 (d, 2H), 5.83 (s, 1H), 6.90 (d, 2H), 7.23 - 7.26 (m, 1H), 7.49 (d, 2H), 7.60 (d, 1H), 8.25 (br. s, 1H), 9.09 (br. s., 1H), 12.38 (br. s, 1H). LCMS (conditions 2.5): R _t 1.02 min MS (ESI): [M + H] ⁺ = 543.29

Example	Name	Structure	Analytical data
108	<i>rac</i> -1- <i>sec</i> -butyl-N-{{[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.77 (s, 3H), 0.98 (s, 3H), 1.29 (d, 3H), 1.61 - 1.80 (m, 2H), 2.15 - 2.31 (m, 5H), 3.19 (sxt, 1H), 3.80 (s, 3H), 4.42 (d, 2H), 6.10 (s, 1H), 7.04 (d, 2H), 7.41 (d, 1H), 7.75 (d, 2H), 7.93 (d, 1H), 8.78 (s, 1H), 8.86 (t, 1H), 12.10 (s, 1H). LCMS (conditions 2.5): R_t 1.08 min MS (ESI): $[M + H]^+ = 523.24$
109	<i>rac</i> -1- <i>sec</i> -butyl-7-[6-(dimethylamino)pyridin-3-yl]-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.76 (t, 3H), 1.23 - 1.30 (m, 6H), 1.59 - 1.78 (m, 2H), 2.18 (s, 3H), 3.07 (s, 6H), 3.17 (sxt, 1H), 4.10 (d, 2H), 4.34 (d, 2H), 6.10 (s, 1H), 6.72 (d, 1H), 7.44 (d, 1H), 7.90 (d, 1H), 7.98 (dd, 1H), 8.59 (d, 1H), 8.70 (t, 1H), 8.82 (s, 1H), 11.46 (br. s, 1H). LCMS (conditions 2.5): R_t 0.75 min MS (ESI): $[M + H]^+ = 503.31$
110	<i>rac</i> -1- <i>sec</i> -butyl-N-{{[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-7-[6-(dimethylamino)pyridin-3-yl]imidazo[1,5-		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.76 (t, 3H), 1.28 (d, 3H), 1.59 - 1.78 (m, 2H), 2.21 (s, 3H), 3.07 (s, 6H), 3.17 (sxt, 1H), 4.35 (d, 2H), 6.10 (s, 1H), 6.74 (d, 1H), 7.31 (t, 1H), 7.47 (d, 1H), 7.92 (d, 1H), 7.98 (dd, 1H), 8.58 (d, 1H), 8.80 (s, 1H), 8.86 (t, 1H), 11.93 (br. s, 1H).

Example	Name	Structure	Analytical data
	a]pyridine-5-carboxamide		LCMS (conditions 2.5): R _t 0.76 min MS (ESI): [M + H] ⁺ = 525.28
111	<i>rac</i> -1-sec-butyl-N-{[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-7-[6-(dimethylamino)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.76 (t, 3H), 0.97 (t, 3H), 1.28 (d, 3H), 1.59 - 1.78 (m, 2H), 2.15 - 2.31 (m, 5H), 3.07 (s, 6H), 3.17 (sxt, 1H), 4.41 (d, 2H), 6.11 (s, 1H), 6.73 (d, 1H), 7.44 (d, 1H), 7.93 (d, 1H), 7.97 (dd, 1H), 8.57 (d, 1H), 8.77 - 8.83 (m, 2H), 12.12 (s, 1H). LCMS (conditions 2.5): R _t 0.86 min MS (ESI): [M + H] ⁺ = 537.34
112	<i>rac</i> -1-sec-butyl-7-[6-(dimethylamino)pyridin-3-yl]-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.76 (t, 3H), 0.89 (t, 3H), 1.21 - 1.31 (m, 3H), 1.46 - 1.58 (m, 2H), 1.58 - 1.78 (m, 2H), 2.13 (s, 3H), 3.07 (s, 6H), 3.13 - 3.22 (m, 1H), 4.40 (d, 2H), 5.92 (s, 1H), 6.73 (d, 1H), 7.48 (d, 1H), 7.92 (s, 1H), 7.98 (dd, 1H), 8.59 (d, 1H), 8.82 (s, 1H), 8.92 (br. t, 1H), 11.55 (br. s, 1H). LCMS (conditions 2.5): R _t 0.86 min MS (ESI): [M + H] ⁺ = 501.31
113	<i>rac</i> -1-sec-butyl-N-{[6-methyl-2-oxo-4-(2,2,2-trifluoroethoxy)-1,2-dihydropyridin-3-		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 0.72 - 0.80 (m, 3H), 1.28 (d, 3H), 1.59 - 1.78 (m, 2H), 2.20 (s, 3H), 2.24 (s, 3H), 2.40 - 2.46 (m, 4H), 3.12 - 3.22 (m, 1H), 3.50 - 3.59 (m,

Example	Name	Structure	Analytical data
	yl)methyl}-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		4H), 4.35 (d, 2H), 4.82 (q, 2H), 6.20 (s, 1H), 6.93 (d, 1H), 7.45 (d, 1H), 7.94 (d, 1H), 8.01 (dd, 1H), 8.60 (d, 1H), 8.72 (t, 1H), 8.82 (s, 1H), 11.68 (s, 1H). LCMS (conditions 2.5): R _t 0.71 min MS (ESI): [M + H] ⁺ = 612.3

Example 114 – *rac*-1-sec-butyl-N-{[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-7-[6-(piperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



5

Step 1)

80 mg (0.18 mmol) *rac*-1-sec-butyl-7-chloro-N-{[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}imidazo[1,5-a]pyridine-5-carboxamide (intermediate **209A**), 90 mg (0.23 mmol) *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine-1-carboxylate and 21 mg (18 μmol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.22 ml (0.44 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture heated for 30 min to 130 °C in a Biotage Initiator® microwave oven. The reaction mixture was concentrated *in vacuo* and the residue was extracted with water and ethyl acetate. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude product (120 mg) was used directly in the following step.

15

LCMS (Methode 2.4): R_t = 1.22min

MS (ESI): $[M + H]^+ = 678.5$

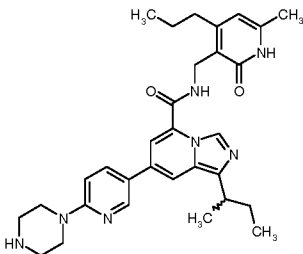
Step 2)

120 mg crude *rac*-tert-butyl 4-{5-[1-sec-butyl-5-({[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}carbamoyl)imidazo[1,5-a]pyridin-7-yl]pyridin-2-yl}piperazine-1-carboxylate (crude product from previous step) were dissolved in tetrahydrofuran (10 ml) and methanol (5 ml). Then, hydrochloric acid in dioxane (4 N, 5 ml, 729.2 mmol) was added. The reaction mixture was stirred at room temperature over night. The mixture was concentrated and purified by preparative HPLC (conditions 1) to give 3.3 mg (3%) of the pure compound as a solid.

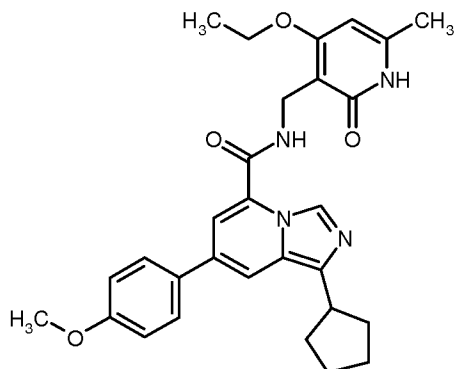
$^1\text{H-NMR}$ (500MHz, DMSO-d_6): δ [ppm]= 0.76 (t, 3H), 0.98 (t, 3H), 1.28 (d, 3H), 1.60 - 1.80 (m, 2H), 2.18 - 2.31 (m, 5H), 2.85 (t, 4H), 3.14 - 3.21 (m, 1H), 3.51 (t, 4H), 4.41 (d, 2H), 6.11 (s, 1H), 6.92 (d, 1H), 7.44 (d, 1H), 7.95 (d, 1H), 8.00 (dd, 1H), 8.18 (s, 1H), 8.60 (d, 1H), 8.78 - 8.81 (m, 1H) (2H not visible)

MS (ESI): $[M + H]^+ = 578.3$

The following example was synthesized in analogy to example 114:

Example	Name	Structure	Analytical data
115	<i>rac</i> -1-sec-butyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(piperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 0.75 (t, 3H), 0.89 (t, 3H), 1.28 (d, 3H), 1.47 - 1.58 (m, 2H), 1.59 - 1.78 (m, 2H), 2.13 (s, 3H), 2.84 (d, 4H), 3.13 - 3.23 (m, 2H), 3.46 - 3.53 (m, 4H), 4.40 (d, 2H), 5.92 (s, 1H), 6.91 (d, 1H), 7.49 (d, 1H), 7.96 (d, 1H), 8.02 (dd, 1H), 8.61 (d, 1H), 8.83 (s, 1H), 8.93 (t, 1H), 11.57 (br. s, 1H) (2 H obscured by solvent signal). LCMS (conditions 2.5): R_t 0.77 min MS (ESI): $[M + H]^+ = 542.3$

Example 116- 1-cyclopentyl-N-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide

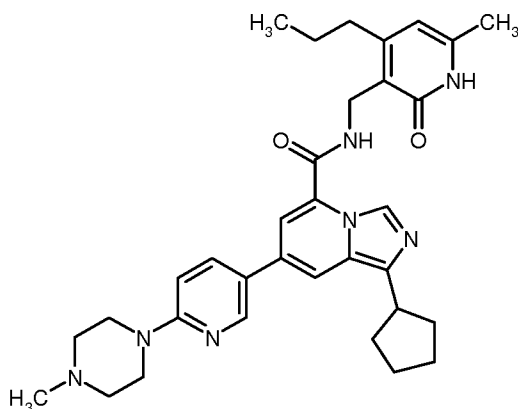


- 5 50 mg (0.117 mmol) 7-chloro-1-cyclopentyl-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide (intermediate **213A**), 31.88 mg (0.21 mmol) (4-methoxyphenyl)boronic acid and 20.2 mg (17 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.117 ml (0.233 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture heated for 30 min to 130 $^{\circ}$ C in a Biotage Initiator[®] microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (conditions 1) to provide 23.6 mg (37%) of the target compound in pure form.

- ¹H-NMR (400MHz, DMSO- d_6): δ [ppm]= 1.25 (t, 3H), 1.61 - 1.72 (m, 2H), 1.76 - 1.87 (m, 4H),
15 1.94 - 2.04 (m, 2H), 2.18 (s, 3H), 3.53 (quin, 1H), 3.80 (s, 3H), 4.09 (q, 2H), 4.34 (d, 2H), 6.09 (s, 1H), 7.02 (d, 2H), 7.43 (d, 1H), 7.77 (d, 2H), 7.93 (d, 1H), 8.74 (t, 1H), 8.82 (s, 1H), 11.45 (s, 1H).

LCMS (conditions 2.5): R_t = 1.02 min; MS (ESI): $[M + H]^+ = 501.32$

- 20 **Example 117 – 1-cyclopentyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide**

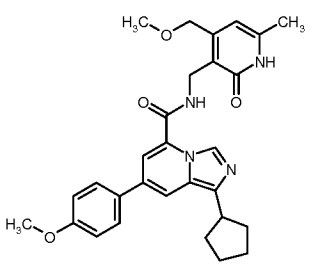


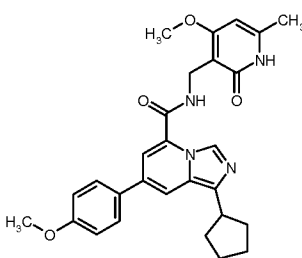
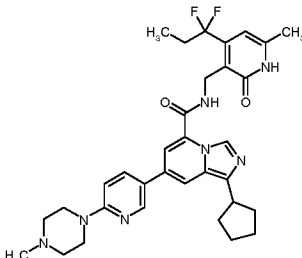
50 mg (0.117 mmol) 7-chloro-1-cyclopentyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide (intermediate **214A**), 63.9 mg (0.21 mmol) 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine and 20.3 mg (18 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. 0.117 ml (0.233 mmol) aqueous sodium carbonate solution (2N), 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture heated for 30 min to 130 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (conditions 1) to provide 28.8 mg (38%) of the target compound in pure form.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 0.89 (t, 3H), 1.52 (sxt, 2H), 1.62 - 1.71 (m, 2H), 1.75 - 1.88 (m, 4H), 1.94 - 2.04 (m, 2H), 2.14 (s, 3H), 2.23 (s, 3H), 2.42 (t, 4H), 3.49 - 3.58 (m, 5H), 4.40 (d, 2H), 5.92 (s, 1H), 6.93 (d, 1H), 7.49 (d, 1H), 7.96 (d, 1H), 8.02 (dd, 1H), 8.61 (d, 1H), 8.82 (s, 1H), 8.91 (t, 1H), 11.54 (s, 1H) (3 H obscured by solvent signal).

LCMS (conditions 2.5): R_t = 0.79 min; MS (ESI): [M + H]⁺ = 568.38

The following example compounds were synthesized in analogy to example compounds **116** and **117** by Suzuki coupling of intermediates **213A**, **214A**, **215A**, **216A**, **217A**, **218A**, **219A**, or **220A** with the respective commercially available boronic acids (or their pinacolate esters) employing a palladium catalyst in the presence of a base in a suitable solvent system under microwave heating (usually 110 °C). The reaction time and temperature was individually adapted in order to achieve maximum turnover of starting material. The target compounds were in general isolated by preparative HPLC, for example preparative HPLC conditions 1 or 2.

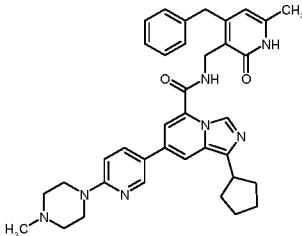
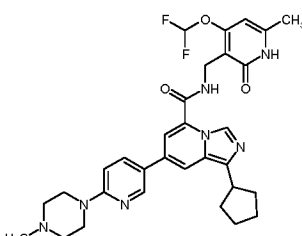
Example	Name	Structure	Analytical data
118	1-cyclopentyl-N- {[4-(methoxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.61 - 1.72 (m, 2H), 1.75 - 1.87 (m, 4H), 1.94 - 2.04 (m, 2H), 2.17 (s, 3H), 3.48 - 3.58 (m, 1H), 3.80 (s, 3H), 4.36 (d, 2H), 4.47 (s, 2H), 6.10 (s, 1H), 7.03 (d, 2H), 7.48 (d, 1H), 7.77 (d, 2H), 7.95 (d, 1H), 8.80 (s, 1H), 8.99 (t, 1H), 11.69 (s, 1H) (3 H obscured by

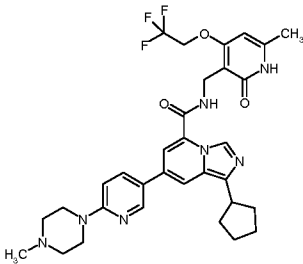
Example	Name	Structure	Analytical data
	carboxamide		solvent signal). LCMS (conditions 2.5): R_t 1.01 min MS (ESI): $[M + H]^+ = 501.32$
119	1-cyclopentyl-N- [(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 1.61 - 1.72 (m, 2H), 1.76 - 1.87 (m, 4H), 1.95 - 2.04 (m, 2H), 2.20 (s, 3H), 3.53 (quin, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.31 (d, 2H), 6.12 (s, 1H), 7.03 (d, 2H), 7.43 (d, 1H), 7.77 (d, 2H), 7.93 (d, 1H), 8.74 (t, 1H), 8.81 (s, 1H), 11.48 (s, 1H). LCMS (conditions 2.5): R_t 0.97 min MS (ESI): $[M + H]^+ = 487.3$
120	1-cyclopentyl-N- {[4-(1,1-difluoropropyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.97 (s, 3H), 1.62 - 1.71 (m, 2H), 1.76 - 1.87 (m, 4H), 1.94 - 2.03 (m, 2H), 2.16 - 2.31 (m, 8H), 3.48 - 3.60 (m, 5H), 4.41 (d, 2H), 6.11 (s, 1H), 6.51 (s, 1H), 6.94 (d, 1H), 7.44 (d, 1H), 7.97 (d, 1H), 8.01 (dd, 1H), 8.60 (d, 1H), 8.77 - 8.82 (m, 1H), 12.11 (br. s, 1H). (4 H obscured by solvent signal). LCMS (conditions 2.5): R_t 0.79 min MS (ESI): $[M + H]^+ = 604.35$

Example	Name	Structure	Analytical data
121	1-cyclopentyl-7-(4-methoxyphenyl)-N-{{[6-methyl-2-oxo-4-(2,2,2-trifluoroethoxy)-1,2-dihydropyridin-3-yl]methyl}imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.61 - 1.72 (m, 2H), 1.75 - 1.87 (m, 4H), 1.94 - 2.05 (m, 2H), 2.20 (s, 3H), 3.53 (quin, 1H), 3.80 (s, 3H), 4.35 (d, 2H), 4.82 (q, 2H), 6.19 (s, 1H), 7.02 (d, 2H), 7.44 (d, 1H), 7.77 (d, 2H), 7.94 (d, 1H), 8.77 (t, 1H), 8.81 (s, 1H), 11.68 (s, 1H). LCMS (conditions 2.5): R _t 1.06 min MS (ESI): [M + H] ⁺ = 555.29
122	1-cyclopentyl-N-[(4-ethoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.25 (t, 3H), 1.61 - 1.71 (m, 2H), 1.75 - 1.87 (m, 4H), 1.94 - 2.03 (m, 2H), 2.18 (s, 3H), 2.23 - 2.31 (m, 4H), 3.47 - 3.62 (m, 5H), 4.09 (q, 2H), 4.33 (d, 2H), 6.09 (s, 1H), 6.94 (d, 1H), 7.45 (d, 1H), 7.96 (d, 1H), 8.03 (dd, 1H), 8.61 (d, 1H), 8.70 (t, 1H), 8.84 (s, 1H), 11.46 (s, 1H)) (3 H obscured by solvent signal). LCMS (conditions 2.3): R _t 0.75 min MS (ESI): [M + H] ⁺ = 571
123	1-cyclopentyl-N-{{[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-7-(4-methoxyphenyl)imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO-d ₆): δ [ppm]= 1.62 - 1.71 (m, 2H), 1.81 (br. s., 4H), 1.95 - 2.03 (m, 2H), 2.21 (s, 3H), 3.53 (quin, 1H), 3.81 (s, 3H), 4.35 (d, 2H), 6.08 - 6.10 (m, 1H), 7.03 (d, 2H), 7.30 (t, 1H), 7.45 (d, 1H), 7.77 (d, 2H),

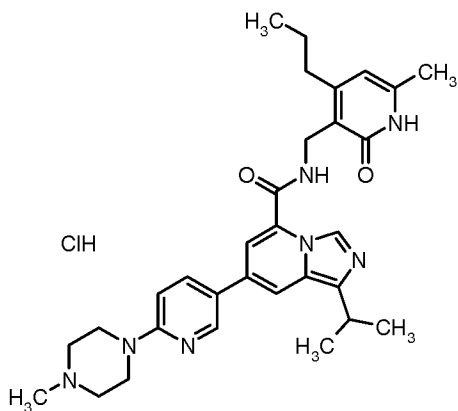
Example	Name	Structure	Analytical data
	midazo[1,5-a]pyridine-5-carboxamide		7.95 (d, 1H), 8.80 (s, 1H), 8.90 (t, 1H), 11.91 (s, 1H). LCMS (conditions 2.5): R _t 1.03 min MS (ESI): [M + H] ⁺ = 523.3
124	1-cyclopentyl-7-(4-methoxyphenyl)-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (500MHz, DMSO-d ₆): δ [ppm]= 0.89 (t, 3H), 1.52 (sxt, 2H), 1.62 - 1.71 (m, 2H), 1.76 - 1.86 (m, 4H), 1.93 - 2.03 (m, 2H), 2.13 (s, 3H), 2.51 - 2.53 (m, 2H), 3.49 - 3.57 (m, 1H), 3.80 (s, 3H), 4.41 (d, 2H), 5.91 (s, 1H), 7.03 (d, 2H), 7.47 (d, 1H), 7.77 (d, 2H), 7.94 (d, 1H), 8.81 (s, 1H), 8.96 (t, 1H), 11.53 (s, 1H). LCMS (conditions 2.5): R _t 1.11 min MS (ESI): [M + H] ⁺ = 499.39
125	1-cyclopentyl-N-{[4-(methoxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.61 - 1.71 (m, 2H), 1.75 - 1.86 (m, 4H), 1.94 - 2.03 (m, 2H), 2.17 (s, 3H), 2.23 (s, 3H), 2.42 (d, 4H), 3.48 - 3.58 (m, 5H), 4.35 (s, 2H), 4.47 (s, 2H), 6.10 (s, 1H), 6.93 (d, 1H), 7.51 (d, 1H), 7.97 (d, 1H), 8.02 (dd, 1H), 8.61 (d, 1H), 8.81 (s, 1H), 8.94 (t, 1H), 11.69 (br. s, 1H) (3 H obscured by solvent signal). LCMS (conditions 2.5): R _t 0.68 min MS (ESI): [M + H] ⁺ = 570.36

Example	Name	Structure	Analytical data
126	1-cyclopentyl-N- {[4-(1,1- difluoropropyl)-6- methyl-2-oxo-1,2- dihydropyridin-3- yl]methyl}-7-(4- methoxyphenyl)i midazo[1,5- a]pyridine-5- carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 0.98 (t, 3H), 1.61 - 1.74 (m, 2H), 1.75 - 1.88 (m, 4H), 1.94 - 2.07 (m, 2H), 2.14 - 2.32 (m, 5H), 3.48 - 3.60 (m, 1H), 3.80 (s, 3H), 4.41 (d, 2H), 6.10 (s, 1H), 7.03 (d, 2H), 7.42 (d, 1H), 7.76 (d, 2H), 7.95 (d, 1H), 8.77 (s, 1H), 8.85 (t, 1H), 12.10 (s, 1H). LCMS (conditions 2.5): R_t 1.14 min MS (ESI): $[\text{M} + \text{H}]^+ = 535.33$
127	N-[(4-benzyl-6- methyl-2-oxo-1,2- dihydropyridin-3- yl)methyl]-1- cyclopentyl-7-(4- methoxyphenyl)i midazo[1,5- a]pyridine-5- carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 1.61 - 1.72 (m, 2H), 1.75 - 1.86 (m, 4H), 1.93 - 2.05 (m, 2H), 2.10 (s, 3H), 3.48 - 3.58 (m, 1H), 3.81 (s, 3H), 3.95 (s, 2H), 4.46 (d, 2H), 5.82 (s, 1H), 7.04 (d, 2H), 7.07 - 7.14 (m, 1H), 7.20 (d, 4H), 7.40 (d, 1H), 7.77 (d, 2H), 7.93 (d, 1H), 8.78 (s, 1H), 9.00 (t, 1H), 11.62 (s, 1H). LCMS (conditions 2.5): R_t 1.14 min MS (ESI): $[\text{M} + \text{H}]^+ = 547.33$
128	1-cyclopentyl-N- [(4-methoxy-6- methyl-2-oxo-1,2- dihydropyridin-3- yl)methyl]-7-[6- (4- methylpiperazin- 1-yl)pyridin-3- yl]imidazo[1,5-		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 1.61 - 1.72 (m, 2H), 1.75 - 1.87 (m, 4H), 1.94 - 2.04 (m, 2H), 2.20 (s, 3H), 2.22 (s, 3H), 2.41 (t, 4H), 3.47 - 3.58 (m, 5H), 3.81 (s, 3H), 4.31 (d, 2H), 6.13 (s, 1H), 6.92 (d, 1H), 7.45 (d, 1H), 7.95 (d, 1H), 8.02 (dd, 1H), 8.61 (d,

Example	Name	Structure	Analytical data
	a]pyridine-5-carboxamide		1H), 8.69 (t, 1H), 8.83 (s, 1H), 11.49 (br. s, 1H). LCMS (conditions 2.5): R _t 0.64 min MS (ESI): [M + H] ⁺ = 556.35
129	N-[(4-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-cyclopentyl-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.63 - 1.72 (m, 2H), 1.75 - 1.86 (m, 4H), 1.94 - 2.03 (m, 2H), 2.11 (s, 3H), 2.23 (s, 3H), 2.41 (t, 4H), 3.49 - 3.58 (m, 5H), 3.95 (s, 2H), 4.46 (d, 2H), 5.82 (s, 1H), 6.94 (d, 1H), 7.09 (sxt, 1H), 7.20 (d, 4H), 7.43 (d, 1H), 7.95 (d, 1H), 8.01 (dd, 1H), 8.61 (d, 1H), 8.79 (s, 1H), 8.94 (t, 1H), 11.62 (br. s, 1H). LCMS (conditions 2.5): R _t 0.80 min MS (ESI): [M + H] ⁺ = 618
130	1-cyclopentyl-N-{{[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}}-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide		¹ H-NMR (400MHz, DMSO-d ₆): δ [ppm]= 1.61 - 1.72 (m, 2H), 1.76 - 1.86 (m, 4H), 1.94 - 2.04 (m, 2H), 2.22 (d, 6H), 2.37 - 2.43 (m, 4H), 3.47 - 3.59 (m, 5H), 4.35 (d, 2H), 6.09 (s, 1H), 6.93 (d, 1H), 7.31 (t, 1H), 7.47 (d, 1H), 7.97 (s, 1H), 8.01 (dd, 1H), 8.61 (d, 1H), 8.80 (s, 1H), 8.85 (t, 1H), 11.91 (br. s, 1H). LCMS (conditions 2.5): R _t 0.70 min MS (ESI): [M + H] ⁺ = 592.41

Example	Name	Structure	Analytical data
131	1-cyclopentyl-N- {[6-methyl-2- oxo-4-(2,2,2- trifluoroethoxy)- 1,2- dihydropyridin-3- yl]methyl}-7-[6- (4- methylpiperazin- 1-yl)pyridin-3- yl]imidazo[1,5- a]pyridine-5- carboxamide		$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 1.61 - 1.72 (m, 2H), 1.75 - 1.86 (m, 4H), 1.94 - 2.04 (m, 2H), 2.20 (s, 3H), 2.27 (s, 3H), 3.47 - 3.60 (m, 5H), 4.35 (d, 2H), 4.82 (q, 2H), 6.19 (s, 1H), 6.93 (d, 1H), 7.45 (d, 1H), 7.95 (d, 1H), 8.02 (dd, 1H), 8.60 (d, 1H), 8.71 (t, 1H), 8.82 (s, 1H), 11.67 (s, 1H) (4 H obscured by solvent signal). LCMS (conditions 2.5): R_t 0.77 min MS (ESI): $[\text{M} + \text{H}]^+ = 622.3$

Example 132 – 1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide hydrochloride



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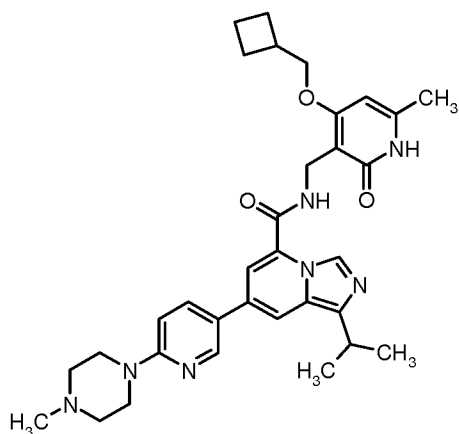
1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]imidazo[1,5-a]pyridine-5-carboxamide (example 71, 2.1 g, 4.1 mmol) was dissolved in dichloromethane (50 ml) and hydrogen chloride (4 N in dioxane, 10 ml, 40 mmol) was added. The solution was concentrated *in vacuo*, and to the residue was sequentially added dichloromethane, followed by concentration *in vacuo*; this procedure was performed three times. The residue was then dried under high vacuum to give the desired product, 1-isopropyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide hydrochloride (2.4 g).

10

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 0.89 (t, 3H), 1.40 (d, 6H), 1.53 (dq, 2H), 2.15 (s, 3H), 2.52 - 2.56 (m, 2H, obscured by solvent signal), 2.79 (d, 3H), 2.99 - 3.19 (m, 2H), 3.35 - 3.43 (m, 2H), 3.51 (m, 2H), 3.75 (m, 1H), 4.40 - 4.44 (m, 2H, obscured by water signal), 4.49 - 4.57 (m, 2H, obscured by water signal), 5.95 (s, 1H), 7.19 (d, 1H), 7.97 - 8.11 (m, 1H), 8.28 (dd, 1H), 8.44 (s, 1H), 8.77 (d, 1H), 9.28 (t, 1H), 9.96 (s, 1H), 11.32 (br. s., 1H), 11.61 (br. s., 1H).

MS (ESI): [M + H]⁺ = 541.3 (parent compound)

Example 133 – N-[[4-(cyclobutylmethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl]-1-isopropyl-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide

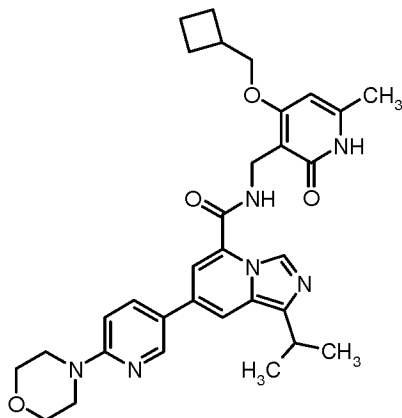


80 mg (0.181 mmol) 7-chloro-N-[[4-(cyclobutylmethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl]-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **222A**), 71.2 mg (0.24 mmol) 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine and 20.8 mg (18 μmol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. Aqueous sodium carbonate solution (2N; 0.226 ml; 0.452 mmol), 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture was heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (conditions 2) to provide 32 mg (31%) of the target compound in pure form.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.30 (d, 6H), 1.72 - 1.86 (m, 4H), 1.88 - 2.00 (m, 2H), 2.18 (s, 3H), 2.22 (s, 3H), 2.40 (t, 4H), 2.57 - 2.66 (m, 1H), 3.44 (dt, 1H), 3.49 - 3.58 (m, 4H), 4.00 (d, 2H), 4.34 (d, 2H), 6.11 (s, 1H), 6.92 (d, 1H), 7.46 (d, 1H), 7.96 (d, 1H), 8.01 (dd, 1H), 8.60 (d, 1H), 8.68 (t, 1H), 8.84 (s, 1H), 11.48 (s, 1H).

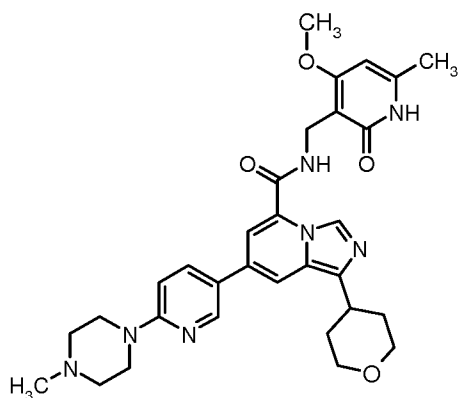
MS (ESI): [M + H]⁺ = 584.5

Example 134 – N-{{[4-(cyclobutylmethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-1-isopropyl-7-[6-(morpholin-4-yl)pyridin-3-yl]imidazo[1,5-a]pyridine-5-carboxamide



- 5 80 mg (0.181 mmol) 7-chloro-N-{{[4-(cyclobutylmethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl}-1-isopropylimidazo[1,5-a]pyridine-5-carboxamide (intermediate **222A**), 68.1 mg (0.24 mmol) 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine and 20.8 mg (18 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. Aqueous sodium carbonate solution (2N; 0.226 ml; 0.452 mmol), 1.5 ml
- 10 ethanol and 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture was heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (conditions 2) to provide 33 mg (32%) of the target compound in pure form.
- 15 ¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.30 (d, 6H), 1.69 - 1.85 (m, 4H), 1.88 - 2.00 (m, 2H), 2.18 (s, 3H), 2.56 - 2.66 (m, 1H), 3.40 - 3.47 (m, 1H), 3.48 - 3.54 (m, 4H), 3.66 - 3.76 (m, 4H), 4.00 (d, 2H), 4.34 (d, 2H), 6.11 (s, 1H), 6.93 (d, 1H), 7.47 (d, 1H), 7.98 (d, 1H), 8.05 (dd, 1H), 8.64 (d, 1H), 8.68 (t, 1H), 8.85 (s, 1H), 11.48 (s, 1H).
- 20 MS (ESI): [M + H]⁺ = 571.3

Example 135 – N-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxamide



5

90 mg (0.21 mmol) 7-chloro-N-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxamide (intermediate **225A**), 76.0 mg (0.25 mmol) 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine and 24 mg (21 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. Aqueous sodium carbonate solution (2N; 0.26 ml; 0.52 mmol), 1.5 ml ethanol und 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture was heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (conditions 2) to provide 38 mg (31%) of the target compound in pure form.

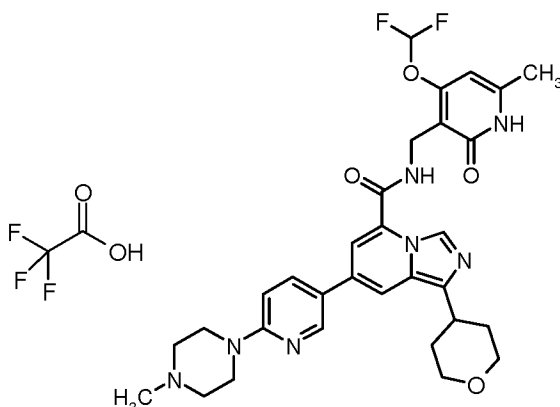
15

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.70 (d, 2H), 1.92 (m, 2H), 2.19 (s, 3H), 2.22 (s, 3H), 2.37 - 2.43 (m, 4H), 3.44 - 3.62 (m, 7H), 3.81 (s, 3H), 3.97 (dd, 2H), 4.31 (d, 2H), 6.13 (s, 1H), 6.93 (d, 1H), 7.47 (d, 1H), 7.97 - 8.12 (m, 2H), 8.63 (d, 1H), 8.71 (t, 1H), 8.84 (s, 1H), 11.51 (br. s., 1H).

20

MS (ESI): [M + H]⁺ = 572.3

Example 136 – N-[[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl]-7-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxamide trifluoroacetate



5

40 mg (86 μ mol) 7-chloro-N-[[4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl]methyl]-1-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-a]pyridine-5-carboxamide (intermediate **226A**), 31.2 mg (103 μ mol) 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine and 9.9 mg (9 μ mol) tetrakis(triphenylphosphine)palladium(0) were weighed into a microwave vial under an atmosphere of argon. Aqueous sodium carbonate solution (2N; 0.107 ml; 0.214 mmol), 1.5 ml ethanol and 1.5 ml 1,2-dimethoxyethane were added and the resulting mixture was heated for 1 h to 110 °C in a Biotage Initiator® microwave oven. The reaction mixture was filtered and concentrated. The crude product was purified by preparative HPLC (conditions 2) to yield 12 mg of impure product, which was further purified by preparative HPLC (conditions: see below) to provide 3 mg (6 %) of the trifluoroacetate salt of the target compound in pure form.

Conditions for final preparative HPLC:

Column: Waters XBrigde C18 5 μ m 100 x 30 mm;

Eluent: A: water + 0.2% vol. trifluoroacetic acid (99%); B: acetonitrile;

20 **Gradient:** 0.0-0.5 min 5% B, 0.51-5.5 min 5-50% B

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.71 (d, 2H), 1.87 - 2.01 (m, 2H), 2.22 (s, 3H), 2.86 (d, 3H), 3.04 - 3.22 (m, 5H), 3.40 - 3.57 (m, 6H, overlain by water signal), 3.99 (dd, 2H), 4.36 (d, 2H), 4.50 (d, 2H), 6.11 (s, 1H), 7.09 (d, 1H), 7.64 (br. s., 1H), 8.16 (dd, 1H), 8.20 (s, 1H), 8.72 (d, 1H), 8.97 (t, 1H), 9.15 (br. s., 1H), 9.73 (br. s., 1H).

MS (ESI): [M + H]⁺ = 608.2

Assays for profiling of Compounds of the present invention

A) Biochemical Assays

5 Assay 1 - EZH2 wild type SPA assay

EZH2 wild type (wt) inhibitory activities of the compounds described in the present invention were quantified using a scintillation proximity assay (SPA) which measures methylation by the enzyme of the synthetic, biotinylated peptide ARTKQTAR-[Kme3]-
10 STGGKAPRKQLATKAARKSAPATG-GVKKPHR-K(Btn)-Amin x TFA (Biosyntan) derived from Histone H3 and referred to from here on as H3(1-40)me3K9. The PRC2-EZH2 wt multiprotein complex used in the assay (composed by full length recombinant proteins Flag-EZH wt, SUZ12, EED and RbAp46/48) was purchased from Active Motif (Cat. No. 31387).

15 In a typical assay 11 different concentrations of each compound (0.1 nM, 0.33 nM, 1.1 nM, 3.8 nM, 13 nM, 44 nM, 0.15 μ M, 0.51 μ M, 1.7 μ M, 5.9 μ M and 20 μ M) were tested in duplicate within the same microtiter plate. To this end, 100-fold concentrated compound solutions (in DMSO) were previously prepared by serial dilution (1:3.4) of 2 mM stocks in a clear low volume 384-well source microtiter plate (Greiner Bio-One), from which 50 nl of compounds were
20 transferred into a white low volume test microtiter plate from the same supplier. Subsequently, 2.5 μ l EZH2wt in aqueous assay buffer [50 mM Hepes pH 7.5 (Applichem), 2.75 mM dithiothreitol (DTT, Sigma), 0.01 % (w/v) bovine serum albumin (BSA, Sigma), 0.01 % (v/v) Pluronic (Sigma)] were added to the compounds in the test plate to a final enzyme concentration of typically ~ 0.7-1.0 ng/ μ l (this parameter was adjusted depending on the activity of the enzyme lot in order to be within
25 the linear dynamic range of the assay). The samples were then incubated for 15 min at 22°C to allow pre-equilibration of the putative enzyme-inhibitor complexes before the start of the methylation reaction, which was initiated by the addition of 2.5 μ l 2-fold concentrated solution (in assay buffer) of “cold” S-Adenosyl -L- Methionine (SAM, Sigma, final concentration: 0.875 μ M), tritiated 3H-SAM (Perkin Elmer, final concentration: 0.125 μ M) and H3(1-40)me3K9 peptide
30 substrate (final concentration: 0.15 μ M). The resulting mixture (5 μ l final volume) was shortly centrifuged (2 min., 1500 rpm) and incubated at 22°C during 60 min. Thereupon the reaction was stopped by adding 3 μ l of Streptavidin PS SPA imaging beads (Perkin Elmer, final concentration of 1.562 μ g/ μ l) and “cold” SAM (AK Scientific, 250 μ M final concentration) for non-specific binding reduction. Plates containing the stopped reaction were sealed with transparent adhesive foil (Perkin
35 Elmer), centrifuged (2 min., 1500 rpm), and further incubated overnight at 4°C in order to allow the SPA signals to develop. Subsequently, the amount of product was evaluated by measuring the energy transfer from the β -particles emitted by the 3H-labeled substrate to the Europium scintillator co-polymerized in the polystyrene matrix of the PS imaging beads, using the standard settings for

this purpose of a Viewlux (Perkin-Elmer) CCD plate imaging device (emission filter 613/55 (IFP). The resulting scintillation counts were taken as indicator for the amount of methylated peptide per well. The data were normalised using two sets of control wells (typically 16 each) for high- (= enzyme reaction with DMSO instead of test compound = 0 % = minimum inhibition) and low- (= all assay components without enzyme = 100 % = maximum inhibition) EZH2 wt activity. IC₅₀ values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation.

Assay 2 - EZH2 Y641N SPA assay

EZH2 Y641N inhibitory activities of the compounds described in the present invention were quantified using a scintillation proximity assay (SPA) which measures methylation by the enzyme of the synthetic, biotinylated peptide ARTKQTARKSTGGKAPRKQLATKAAR-K(Me₂)-SAPATGGVKKPHR-K(Btn)-Amid x TFA (Biosyntan) derived from Histone H3 and referred to from here on as H3(1-40)me₂K27. The human mutant PRC2- EZH2 Y641N multiprotein complex used in the assay (composed by full length recombinant proteins His-EZH Y641N, His-SUZ12, His-AEBP2, Flag-EED and His-RbAp48) was produced in-house by co-expression in Sf9 insect cells with N-terminal FLAG-tag and purification by affinity chromatography on an Anti-FLAG M2 (Sigma) column followed by a desalting step on a DS 26/10 column (GE Healthcare).

In a typical assay 11 different concentrations of each compound (0.1 nM, 0.33 nM, 1.1 nM, 3.8 nM, 13 nM, 44 nM, 0.15 μ M, 0.51 μ M, 1.7 μ M, 5.9 μ M and 20 μ M) were tested in duplicate within the same microtiter plate. To this end, 100-fold concentrated compound solutions (in DMSO) were previously prepared by serial dilution (1:3.4) of 2 mM stocks in a clear low volume 384-well source microtiter plate (Greiner Bio-One), from which 50 nl of compounds were transferred into a white low volume test microtiter plate from the same supplier. Subsequently, 2.5 μ l EZH2 Y641N in aqueous assay buffer [50 mM Hepes pH 7.5 (Appllichem), 2.75 mM dithiothreitol (DTT, Sigma), 0.01 % (w/v) bovine serum albumin (BSA, Sigma), 0.01 % (v/v) Pluronic (Sigma)] were added to the compounds in the test plate to a final enzyme concentration of typically ~ 0.95 ng/ μ l (this parameter was adjusted depending on the activity of the enzyme lot in order to be within the linear dynamic range of the assay). The samples were then incubated for 15 min at 22°C to allow pre-equilibration of the putative enzyme-inhibitor complexes before the start of the methylation reaction, which was initiated by the addition of 2.5 μ l 2-fold concentrated solution (in assay buffer) of “cold” S-adenosyl -L- Methionine (SAM, Sigma, final concentration: 0.875 μ M), tritiated 3H-SAM (Perkin Elmer, final concentration: 0.125 μ M) and H3(1-40)me₂K27 peptide substrate (final concentration: 0.15 μ M). The resulting mixture (5 μ l final volume) was shortly centrifuged (2 min., 1500 rpm) and incubated at 22°C during 90 min. Thereupon the reaction was stopped by adding 3 μ l of streptavidin PS SPA imaging beads (Perkin Elmer, final concentration of 1.562 μ g/ μ l) and “cold” SAM (AK Scientific, 250 μ M final concentration) for

non-specific binding reduction. Plates containing the stopped reaction were sealed with transparent adhesive foil (Perkin Elmer), centrifuged (2 min., 1500 rpm), and further incubated overnight at 4°C in order to allow the SPA signals to develop. Subsequently, the amount of product was evaluated by measuring the energy transfer from the β -particles emitted by the ³H-labeled substrate to the Europium scintillator co-polymerized in the polystyrene matrix of the PS imaging beads, using the standard settings for this purpose of a Viewlux (Perkin-Elmer) CCD plate imaging device (emission filter 613/55 (IFP)). The resulting scintillation counts were taken as indicator for the amount of methylated peptide per well. The data were normalised using two sets of control wells (typically 16 each) for high- (= enzyme reaction with DMSO instead of test compound = 0 % = minimum inhibition) and low- (= all assay components without enzyme = 100 % = maximum inhibition) EZH2 Y641N activity. IC₅₀ values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation.

B) Cellular Assays

Assay 3 – H3K27me3 High Content Assay

Quantification of Histone H3 Lys27 Trimethylation (H3K27me3) after small molecule treatment of cancer cells

The H3K27me3-assay based on High-Content Analysis (HCA) enables the biological characterization of compounds inhibiting histone methyl transferase EZH2. By this assay, the substances are benchmarked on their cellular activity to modulate histone H3 modification levels on Lys 27 over broad inhibitor concentration ranges.

Cultivated cells of the human triple negative/basal-B breast adenocarcinoma tumor cell line MDA-MB-231 (ATCC HTB-26) were plated at a density of 2500 cells per well in a 384-well microtiter plate in 20 μ l RPMI 1640 supplemented with 1% (v/v) glutamine, 1% (v/v) penicillin, 1% (v/v) streptomycin and 10% (v/v) fetal calf serum. After pre-incubation at 37°C overnight, test compounds solubilized in dimethyl sulfoxide (DMSO) were added at various concentrations (0 μ M, as well as in the range of 0.005 μ M – 30 μ M; the final concentration of the solvent DMSO was 0.5% (v/v)). Cells were incubated at 37°C for 72h in the presence of test compounds. Thereafter, cells were fixed with 4% (v/v) paraformaldehyde in phosphate buffered saline (PBS) at room temperature for 12min, permeabilized using 0.5% (v/v) Triton XTM 100 in PBS and blocked with 1% (v/v) bovine serum albumin (BSA) in PBS. In the following, the cells were incubated with the histone-H3-specific H3K27me3 primary antibody (Cell Signaling #9733), followed by the species-specific fluorescent conjugated secondary antibody DyLight™488-conjugated goat anti-mouse

(Jackson Immuno Research #115-486-062) and Hoechst 33342 stain for chromatin staining and determination of total cell number. Primary antibodies were diluted in 1% (v/v) BSA/PBS containing 0.5% (v/v) Triton XTM 100 in PBS and the cells were incubated at 4°C for 16h after one hour blocking with the antibody diluent. Secondary antibodies were diluted in 0.5% (v/v) BSA/PBS containing 0.5% (v/v) Triton XTM 100 in PBS and 22µg/ml goat IgG (Jackson Immuno Research #005-000-003). After 15min blocking with secondary antibody diluent, the cells were incubated with the secondary antibodies at 37°C for 1h. For chromatin staining, the cells were incubated for 10min at room temperature using Hoechst at 4µg/ml. Antibodies and Hoechst 33342 were added at a volume of 20µl per well for 384-well microtiter plate. The cells were washed three times using PBS after each antibody or Hoechst 33342 incubation step. PBS was added and microtiter plates were stored at 4°C until analysis.

Image acquisition for cells was carried out using the confocal imaging system OPERA® (PerkinElmer). Images were captured using two channels: Hoechst 33342 stain (DNA) and DyLight™488 (H3K27me3 staining); and were analyzed using the MetaXpress® software (Molecular Devices). Exposure times were chosen for individual experiments to prevent saturation and allow for quantification in the linear range. A minimum of 1000 cells in 5 field views were analyzed per well using 10x water immersion objective with a two-fold binning.

The image analysis routine was developed in MetaXpress®. The standardized image-analysis module “Count Nuclei” and the images of the DNA-channel were used for nuclei segmentation. The segmented nuclei were filtered for size, shape and signal intensity to exclude possible apoptotic and non-viable cells along with metaphase nuclei. These phenotypes result in overestimated antibody signals, due to their strong chromatin compaction. For further processing, binary object masks were calculated from the segmented and positively selected nuclei. The binary masks served as templates to be superimposed over the images of the H3K27me3 channel. The nuclear H3K27me3 average signal intensity was quantified for every image set. The assay raw data were further analyzed by four parameter logistic regression analysis using Genedata’s Assay Analyzer and Condoseo software to determine the IC₅₀ value for each tested compound.

Activity Data for Compounds of the present invention

Example #	IC₅₀ [M] wt hEZH2 (Assay 1)	IC₅₀ [M] Y641N hEZH2 (Assay 2)	IC₅₀ [M] H3K27me3 (Assay 3)
1	5.54 E-8	3.79 E-7	1.76 E-6
2	2.51 E-8	1.46 E-7	8.97 E-7
3	8.16 E-8	3.66 E-7	7.16 E-7
4	4.51 E-8	3.77 E-7	2.54 E-6
5	1.07 E-6	4.09 E-6	5.58 E-6
6		2.12 E-7	
7	1.69 E-7	1.55 E-6	1.63 E-6
8	1.17 E-7	4.52 E-7	4.19 E-6
9	5.79 E-8	3.47 E-7	3.53 E-6
10	5.74 E-8	4.42 E-7	1.43 E-6
11	8.13 E-8	4.64 E-7	1.35 E-6
12	1.30 E-7	6.37 E-7	9.93 E-7
13		3.85 E-7	1.08 E-6
14	1.81 E-7	4.05 E-7	>5.00 E-6
15	1.90 E-7	1.28 E-6	5.39 E-6
16		3.98 E-7	4.53 E-6
17	1.15 E-7	6.96 E-7	2.62 E-6
18	9.78 E-8	6.94 E-7	6.39 E-6
19	1.64 E-7	6.15 E-7	2.01 E-6
20	9.80 E-8	5.98 E-7	1.55 E-6
21	6.20 E-8	7.28 E-7	
22	4.61 E-7	3.07 E-6	>2.00 E-5
23	1.82 E-7	1.02 E-6	
24	2.53 E-7	7.98 E-7	
25	3.52 E-7	1.92 E-6	4.94 E-6
26	1.20 E-7	7.38 E-7	
27	1.75 E-7	7.36 E-7	
28	2.39 E-7	7.18 E-7	
29	4.21 E-7	1.02 E-6	>4.30 E-5
30	7.80 E-7	1.26 E-6	~2.00 E-5
31	2.60 E-7	1.37 E-6	

Example #	IC₅₀ [M] wt hEZH2 (Assay 1)	IC₅₀ [M] Y641N hEZH2 (Assay 2)	IC₅₀ [M] H3K27me3 (Assay 3)
32	1.21 E-7	1.46 E-6	
33	5.47 E-7	3.55 E-6	5.93 E-6
34	2.33 E-7	1.76 E-6	2.00 E-5
35	1.69 E-7	1.84 E-6	
36		2.54 E-6	
37	7.40 E-7	2.75 E-6	
38	1.51 E-7	2.94 E-6	
39	8.82 E-7	3.04 E-6	
40	4.79 E-8	3.42 E-7	1.25 E-5
41	4.47 E-8	3.68 E-7	2.10 E-6
42	4.75 E-8	3.44 E-7	7.44 E-7
43	6.77 E-8	5.53 E-7	
44	6.12 E-8	5.11 E-7	
45	1.22 E-7	1.14 E-6	
46	2.18 E-8	1.38 E-7	
47	3.38 E-8	2.72 E-7	
48	2.20 E-8	3.30 E-7	7.04 E-7
49	1.95 E-8	4.07 E-7	6.81 E-8
50	3.41 E-8	5.52 E-7	1.05 E-6
51	6.42 E-8	8.52 E-7	
52	6.39 E-7	1.84 E-5	
53	1.40 E-8	1.63 E-7	1.00 E-6
54	7.44 E-8	1.65 E-6	
55	3.04 E-8	6.12 E-7	
56	7.11 E-8	1.75 E-6	
57	7.10 E-8	1.60 E-6	
58	1.65 E-7	5.40 E-6	
59	4.30 E-7	1.71 E-5	
60	5.75 E-8	1.02 E-6	
61	1.51 E-7	2.61 E-6	
62	4.51 E-8	7.18 E-7	3.58 E-6
63	9.11 E-8	1.91 E-6	1.00 E-5
64	6.49 E-8	9.64 E-7	6.65 E-6

Example #	IC₅₀ [M] wt hEZH2 (Assay 1)	IC₅₀ [M] Y641N hEZH2 (Assay 2)	IC₅₀ [M] H3K27me3 (Assay 3)
65	2.94 E-8	5.52 E-7	1.79 E-6
66	4.39 E-8	7.07 E-7	2.73 E-6
67	1.47 E-7	3.41 E-6	
68	1.98 E-7	6.01 E-6	
69	1.08 E-7	3.78 E-6	
70	3.00 E-7	>2.00 E-5	
71	1.05 E-8	1.99 E-7	4.60 E-8
72	2.04 E-8	3.98 E-7	1.29 E-6
73	3.22 E-8	3.08 E-7	2.97 E-6
74	1.86 E-8	3.81 E-7	1.79 E-6
75	5.55 E-8	9.07 E-7	5.09 E-6
76	8.27 E-8	9.61 E-7	2.15 E-6
77	3.62 E-8	3.57 E-7	3.64 E-6
78	2.55 E-8	4.84 E-7	1.84 E-7
79	1.18 E-8	1.68 E-7	1.14 E-7
80	2.46 E-8	2.70 E-7	3.34 E-7
81	3.57 E-8	6.45 E-7	
82	6.39 E-9	1.02 E-7	5.19 E-8
83	9.77 E-9	2.43 E-7	4.98 E-8
84	1.95 E-8	4.02 E-7	4.12 E-7
85	1.87 E-8	2.34 E-7	1.55 E-6
86	5.56 E-8	1.02 E-6	1.00 E-6
87	2.99 E-8	6.23 E-7	2.16 E-6
88	3.17 E-8	1.23 E-7	4.00 E-6
89	2.92 E-8	2.57 E-7	8.82 E-7
90	4.59 E-8	5.81 E-7	
91	3.02 E-7	2.29 E-6	
92	7.12 E-8	9.06 E-7	
93	2.53 E-8	2.14 E-7	5.62 E-6
94	7.48 E-8	1.09 E-6	3.35 E-6
95	3.60 E-8	3.10 E-7	1.29 E-6
96	9.71 E-8	9.04 E-7	2.91 E-6
97	1.07 E-8	1.02 E-7	6.03 E-7

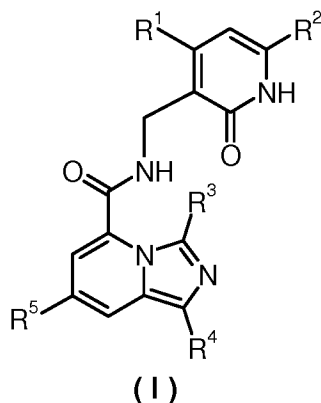
Example #	IC₅₀ [M] wt hEZH2 (Assay 1)	IC₅₀ [M] Y641N hEZH2 (Assay 2)	IC₅₀ [M] H3K27me3 (Assay 3)
97.1	8.76 E-9	9.31 E-8	3.08 E-7
97.2	1.00 E-8	1.17 E-7	3.29 E-7
98	2.17 E-8	6.81 E-8	7.41 E-6
99	7.71 E-8	3.70 E-7	3.50 E-6
100	1.70 E-8	1.08 E-7	2.87 E-6
101	3.24 E-8	7.87 E-7	1.28 E-6
102	3.14 E-7	>2.00 E-5	1.24 E-5
103	1.06 E-7	6.00 E-7	2.41 E-6
104	4.59 E-7	3.31 E-6	1.24 E-5
105	2.29 E-8	2.50 E-7	7.58 E-7
106	8.86 E-8	7.01 E-7	2.18 E-6
107	2.12 E-7	2.61 E-6	9.32 E-6
108	1.22 E-7	2.66 E-6	
109			4.09 E-7
110	3.80 E-8	3.92 E-7	1.15 E-6
111	5.08 E-8	7.45 E-7	1.33 E-6
112	4.18 E-8	5.68 E-7	7.30 E-7
113	3.83 E-8	3.66 E-7	4.07 E-6
114	1.94 E-8	2.77 E-7	1.79 E-6
115	8.13 E-9	7.61 E-8	6.64 E-7
116	1.39 E-7	1.75 E-6	6.07 E-6
117	2.17 E-8	2.10 E-7	2.05 E-6
118	5.30 E-7	5.88 E-6	>1.24 E-5
119	9.69 E-8	4.53 E-7	4.91 E-6
120	2.33 E-8	3.48 E-7	6.47 E-6
121	2.39 E-7	>2.00 E-5	>1.24 E-5
122	6.47 E-8	5.05 E-7	1.16 E-6
123	9.88 E-8	1.57 E-6	7.62 E-6
124	1.03 E-7	2.55 E-6	5.54 E-6
125	8.82 E-8	6.10 E-7	1.84 E-6
126	3.02 E-7	1.31 E-5	
127	3.48 E-7	>2.00 E-5	
128	5.36 E-8	2.21 E-7	8.54 E-7

Example #	IC₅₀ [M] wt hEZH2 (Assay 1)	IC₅₀ [M] Y641N hEZH2 (Assay 2)	IC₅₀ [M] H3K27me3 (Assay 3)
129	1.59 E-8	3.46 E-7	1.45 E-6
130	3.87 E-8	2.93 E-7	4.08 E-7
131	1.37 E-8	1.76 E-7	2.15 E-6
132	1.34 E-8	1.46 E-7	4.73 E-7
133	1.88 E-8	5.23 E-7	1.66 E-6
134	3.36 E-8	1.07 E-6	
135	7.17 E-8	4.83 E-7	
136	4.00 E-8	7.57 E-7	

An empty field means “not determined yet”

Patent Claims

1. A compound of general formula (I)



5 in which

R^1 represents a group selected from C_1 - C_6 -alkyl-, C_2 - C_6 -alkenyl-, C_3 - C_7 -cycloalkyl-, (C_3 - C_7 -cycloalkyl)-(L^1)-, 4- to 7-membered monocyclic heterocycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-(L^1)-, C_1 - C_6 -haloalkyl-, C_2 - C_6 -haloalkenyl-, C_1 - C_6 -alkoxy-, C_1 - C_6 -haloalkoxy-, (C_1 - C_3 -alkoxy)-(C1-C3-alkyl)-, $-NR^6R^7$ and phenyl-(C1-C3-alkyl)-,

10 wherein any C_3 - C_7 -cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituent, each substituent independently selected from fluorine, hydroxy-, oxo, C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl-, C_1 - C_3 -alkoxy-, C_1 - C_3 -haloalkoxy-, $-C(=O)-R^8$, $-C(=O)-OR^9$ and $-S(=O)_2-R^8$, and

15 wherein the phenyl group present in said phenyl-(C1-C3-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C_1 - C_3 -alkyl-, C_1 - C_3 -haloalkyl- and C_1 - C_3 -alkoxy- C_1 - C_3 -haloalkoxy-;

R^2 represents a C_1 - C_3 -alkyl- group;

20 R^3 represents a hydrogen atom or a C_1 - C_3 -alkyl- group;

R^4 represents a hydrogen atom or a group selected from C_1 - C_8 -alkyl-, (C_1 - C_3 -alkoxy)-(C1-C3-alkyl)-, C_3 - C_{10} -cycloalkyl-, 4- to 10-membered heterocycloalkyl- and phenyl-(C1-C3-alkyl)-,

25 wherein any C_3 - C_{10} -cycloalkyl- or 4- to 10-membered heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C_1 - C_3 -alkyl-, C_1 - C_3 -

haloalkyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

5 wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy;

10 R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, C₃-C₁₀-cycloalkyl-, 4- to 10- membered heterocycloalkyl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;

R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

15 R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₃-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

20 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently, selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂R⁸, and

25 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-, C₁-C₂-haloalkoxy-,

or

30 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a group selected from C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-, C₁-C₂-haloalkoxy-;

- 5 R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₁-C₆-haloalkyl-, C₃-C₇-cycloalkyl- and phenyl-(C₁-C₃-alkyl)-,

wherein the phenyl group present in said phenyl-(C₁-C₃-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from halogen, cyano-, hydroxy-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-, C₁-C₂-haloalkoxy-;

10

- R¹⁰ represents, independently for each occurrence, a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, wherein said groups is optionally substituted with one, two or three substituents, each substituent independently, selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-;

- 15 R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, nitro-, C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, C₁-C₆-haloalkyl-, C₁-C₆-haloalkoxy-, hydroxy-(C₁-C₆-alkyl)-, (C₁-C₃-alkoxy)-(C₁-C₃-alkyl)-, (C₁-C₃-haloalkoxy)-(C₁-C₃-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, C₃-C₇-cycloalkyl-(L³)-, 4- to 7-membered monocyclic heterocycloalkyl-(L³)-, phenyl-(L³)-, 5- to 6-membered monocyclic heteroaryl-(L³)-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -O-C(=O)-R⁸, -N(R⁶)-C(=O)-R⁷, -N(R⁶)-C(=O)-NR⁶R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -SR⁸, -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)-R⁸, -S(=O)-NR⁶R⁷, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷, -S(=O)(=NR¹²)-R⁸ and -N=S(=O)(R⁶)-R⁸;
- 20

25 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently, selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-haloalkyl-, C₃-C₆-cycloalkyl-, cyclopropylmethyl-, C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

30 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituents, each substituent independently, selected from halogen, cyano-, hydroxy-, C₁-C₃-alkyl-, C₁-C₃-haloalkyl- and C₁-C₃-alkoxy-, C₁-C₃-haloalkoxy,

or

two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-CH₂-, -CH₂-CH₂-O-, -O-CH₂-O-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-O- and -O-CH₂-CH₂-O-;

5 R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, phenyl-(C₁-C₃-alkyl)- and -C(=O)-OR⁹;

L¹ represents a group selected from -CH₂-, -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C-, -CH₂- and -CH₂CH₂-;

L³ represents, independently for each occurrence, a group selected from -CH₂- and -CH₂CH₂-;

10 or an N-oxide, salt, tautomer, or stereoisomer of said compound, or a salt of said N-oxide tautomer, or stereoisomer.

2. The compound of general formula (I) according to claim 1,

in which

15 R¹ represents a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl-, (C₃-C₆-cycloalkyl)-(L¹)-, 4- to 6-membered monocyclic heterocycloalkyl-, 4- to 6-membered monocyclic heterocycloalkyl-(L¹)-, C₁-C₄-fluoroalkyl-, C₂-C₄-fluoroalkenyl-, C₁-C₄-alkoxy-, C₁-C₄-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and phenyl-(C₁-C₂-alkyl)-,

20 wherein any C₃-C₆-cycloalkyl- or 4- to 6-membered monocyclic heterocycloalkyl- group is optionally substituted once with a C₁-C₃-alkyl-, and

wherein the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

25 R² represents a C₁-C₃-alkyl- group;

R³ represents a hydrogen atom or a methyl- group;

R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl- and 4- to 7-membered monocyclic heterocycloalkyl-,

30 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted once with a C₁-C₃-alkyl-, and

- R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, -NR⁶R¹⁰, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;
- R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;
- 5 R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,
- 10 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, -C(=O)-R⁸ and -C(=O)-OR⁹, and
- 15 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, including the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,
- or
- 20 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group-;
- R⁸ represents a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl-,
- 25 wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently, selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;
- R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₃-C₆-cycloalkyl- and benzyl-,
- 30 wherein the phenyl group present in said benzyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;

- R¹⁰ represents, independently for each occurrence, a phenyl group which is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-;
- 5 R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from hydroxy-, cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, (C₁-C₂-fluoroalkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, -OR⁷, -C(=O)-R⁸, -C(=O)-OR⁹, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷,
 10 -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₃-alkyl-, C₁-C₃-alkoxy-, -C(=O)-R⁸, -C(=O)-OR⁹ and -S(=O)₂-R⁸, and

- 15 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is optionally substituted with one, two or three substituent, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

- 20 two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-;

R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano-, C₁-C₄-alkyl- and -C(=O)-OR⁹;

- 25 L¹ represents a group selected from -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C- and -CH₂-;

or an N-oxide, salt, tautomer, or stereoisomer of said compound, or a salt of said N-oxide, tautomer, or stereoisomer.

- 30 3. The compound of general formula (I) according to claim 1,
 in which

R¹ represents a group selected from C₁-C₃-alkyl-, C₃-C₆-cycloalkyl-, (C₃-C₆-cycloalkyl)-(L¹)-,

C₁-C₃-fluoroalkyl-, C₂-C₃-fluoroalkenyl-, C₁-C₃-alkoxy-, C₁-C₃-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and benzyl-;

R² represents a C₁-C₃-alkyl- group;

R³ represents a hydrogen atom or a methyl- group;

5 R⁴ represents a hydrogen atom or a group selected from C₁-C₆-alkyl-, C₃-C₆-cycloalkyl- and 4- to 6-membered monocyclic heterocycloalkyl-;

R⁵ represents a group selected from phenyl-, naphthyl-, heteroaryl-, phenyl-(L²)- and heteroaryl-(L²)-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;

10 R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,

15 wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C₁-C₃-alkyl-, acetyl- and *tert*-butoxycarbonyl and

20 wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, and the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group is optionally substituted with one or two substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,

or

25 R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;

R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-;

30 R⁹ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl- and benzyl-;

R¹¹ represents, independently for each occurrence, a halogen atom or a group selected from

hydroxy-, cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-,
 hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-,
 (C₁-C₂-fluoroalkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic
 heterocycloalkyl-, phenyl-, 5- to 6-membered monocyclic heteroaryl-, -OR⁷, -C(=O)-
 5 R⁸, -C(=O)-OR⁹, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷,
 -S(=O)-R⁸, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-
 group is optionally substituted with one, two or three substituents, each substituent
 independently selected from fluorine, hydroxy-, oxo, C₁-C₂-alkyl-, -C(=O)-R⁸ and -
 10 C(=O)-OR⁹, and

wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group is
 optionally substituted with one, two or three substituents, each substituent
 independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-,
 trifluoromethyl- and C₁-C₂-alkoxy-,

15 or
 two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered
 monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-,
 -O-CH₂-O- and -O-CH₂-CH₂-O-.

20 R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from
 cyano-, C₁-C₄-alkyl- and -C(=O)-OR⁹;

L¹ represents a group selected from -CH₂-O- and -O-;

L² represents a group selected from -CH=CH-, -C≡C- and -CH₂-;

or an N-oxide, salt, or tautomer or stereoisomer of said compound, or a salt of said N-oxide or
 tautomer, or stereoisomer.

25

4. The compound of general formula (I) according to claim 1,

in which

R¹ represents a group selected from C₁-C₃-alkyl-, (C₃-C₆-cycloalkyl)-(L¹)-, C₁-C₃-fluoroalkyl-,
 C₁-C₃-alkoxy-, C₁-C₃-fluoroalkoxy-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl-) and benzyl-;

30 R² represents a methyl- group;

R³ represents a hydrogen atom or a methyl- group;

- R⁴ represents a group selected from C₂-C₅-alkyl-, C₃-C₆-cycloalkyl- and 5- to 6-membered monocyclic heterocycloalkyl-;
- R⁵ represents a group selected from phenyl- and 5- to 6-membered monocyclic heteroaryl-, said group being optionally substituted with one, two or three substituents, each substituent independently selected from R¹¹;
- R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;
- R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, phenyl-(C₁-C₂-alkyl)-, phenyl- and 5- to 6-membered monocyclic heteroaryl-,
- wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from fluorine, oxo, C₁-C₃-alkyl-, acetyl- and *tert*-butoxycarbonyl-, and
- wherein any phenyl- or 5- to 6-membered monocyclic heteroaryl- group, including the phenyl group present in said phenyl-(C₁-C₂-alkyl)- group, is optionally substituted with one or two substituents, each substituent independently selected from fluorine, chlorine, bromine, cyano-, C₁-C₂-alkyl-, trifluoromethyl- and C₁-C₂-alkoxy-,
- or
- R⁶ and R⁷, together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;
- R⁸ represents, independently for each occurrence, a group selected from C₁-C₄-alkyl- and benzyl-;
- R⁹ represents a C₁-C₂-alkyl- group, independently for each occurrence;
- R¹¹ represents, independently for each occurrence, a fluoro atom, a chloro atom, a bromo atom, or a group selected from cyano-, C₁-C₄-alkyl-, C₁-C₄-fluoroalkyl-, C₁-C₄-fluoroalkoxy-, hydroxy-(C₁-C₄-alkyl)-, (C₁-C₂-alkoxy)-(C₁-C₂-alkyl)-, C₃-C₇-cycloalkyl-, 4- to 7-membered monocyclic heterocycloalkyl-, -OR⁷, -N(R⁶)-C(=O)-R⁷, -NR⁶R⁷, -C(=O)-NR⁶R⁷, -S(=O)₂-R⁸, -N(R⁶)-S(=O)₂-R⁸, -S(=O)₂-NR⁶R⁷ and -S(=O)(=NR¹²)-R⁸,

wherein any C₃-C₇-cycloalkyl- or 4- to 7-membered monocyclic heterocycloalkyl-

group is optionally substituted with one or two substituents, each substituent independently selected from fluorine, hydroxy-, oxo, C₁-C₂-alkyl-, acetyl- and *tert*-butoxycarbonyl-,

or

- 5 two R¹¹ groups together, if attached to adjacent ring atoms of a phenyl- or 5- to 6-membered monocyclic heteroaryl- group, represent a group selected from -CH₂-CH₂-O-, -O-CH₂-O- and -O-CH₂-CH₂-O-;

R¹² represents, independently for each occurrence, a hydrogen atom or a group selected from cyano- and -C(=O)-OR⁹;

- 10 L¹ represents a -CH₂-O- group;

or an N-oxide, salt, tautomer, or stereoisomer of said compound, or a salt of said N-oxide tautomer, or stereoisomer.

5. The compound of general formula (I) according to claim 1,

- 15 in which

R¹ represents a group selected from *n*-propyl-, cyclobutylmethoxy-, 1,1-difluoro-*n*-propyl-, methoxy-, ethoxy-, *iso*-propoxy-, difluoromethoxy-, 2,2,2-trifluoroethoxy- and benzyl-;

R² represents a methyl- group;

R³ represents a hydrogen atom or a methyl- group;

- 20 R⁴ represents a group selected from C₃-C₄-alkyl-, cyclopentyl- and tetrahydropyran-4-yl-;

R⁵ represents a group selected from phenyl-, pyridyl-, pyrimidyl- or pyrazolyl-, said group being optionally substituted with one or two substituents, each substituent independently selected from R¹¹;

R⁶ represents, independently for each occurrence, a hydrogen atom or a C₁-C₃-alkyl- group;

- 25 R⁷ represents, independently for each occurrence, a hydrogen atom or a group selected from C₁-C₃-alkyl-, hydroxy-(C₁-C₄-alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-,

wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one, two or three substituents, each substituent independently selected from oxo and C₁-C₃-alkyl-,

- 30 or

R^6 and R^7 , together with the nitrogen atom they are attached to, represent a 4- to 7-membered monocyclic heterocycloalkyl- group, which is optionally substituted once with a methyl- group;

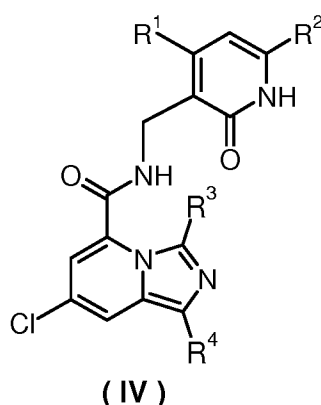
R^8 represents, independently for each occurrence, a C_1 - C_3 -alkyl- group;

- 5 R^{11} represents, independently for each occurrence, a fluoro atom, a chloro atom, or a group selected from cyano-, C_1 - C_3 -alkyl-, hydroxy-(C_1 - C_4 -alkyl)-, 4- to 7-membered monocyclic heterocycloalkyl-, $-OR^7$, $-N(R^6)-C(=O)-R^7$, $-NR^6R^7$, $-C(=O)-NR^6R^7$, $-S(=O)_2-R^8$, $-N(R^6)-S(=O)_2-R^8$, $-S(=O)_2-NR^6R^7$ and $-S(=O)(=NH)-R^8$,

10 wherein any 4- to 7-membered monocyclic heterocycloalkyl- group is optionally substituted with one or two substituents, each substituent independently selected from oxo and C_1 - C_2 -alkyl-;

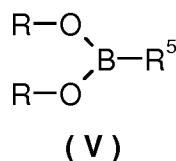
or an N-oxide, salt, tautomer, or stereoisomer of said compound, or a salt of said N-oxide tautomer, or stereoisomer.

6. A method of preparing a compound of general formula (I) according to any one of claims 1
15 to 5, in which method an intermediate compound of formula (IV),



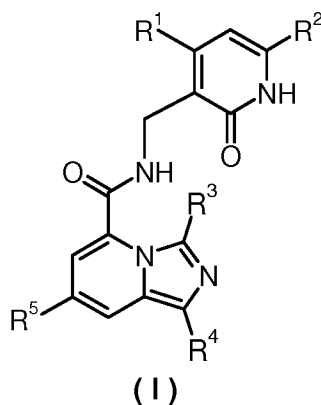
in which R^1 , R^2 , R^3 , and R^4 are as defined in any one of claims 1 to 5;

is allowed to react with a compound of formula (V) :



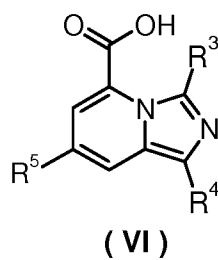
- 20 in which R^5 is as defined in any one of claims 1 to 5, and in which R represents a hydrogen atom or a C_1 - C_3 -alkyl- group, or R-R together represent a $-C_2$ - C_6 -alkylene- group,

thus providing a compound of general formula (I) :



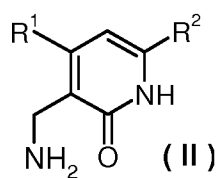
in which R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in any one of claims 1 to 5.

7. A method of preparing a compound of general formula (I) according to any one of claims 1
5 to 5, in which method an intermediate compound of formula (VI):



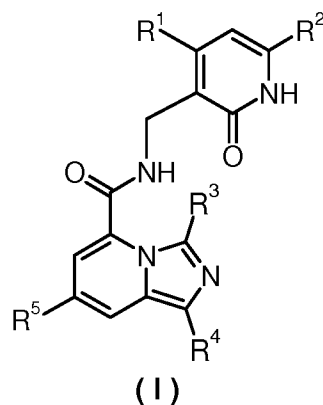
in which R^3 , R^4 , and R^5 are as defined in any one of claims 1 to 5;

is allowed to react with a compound of formula (II):



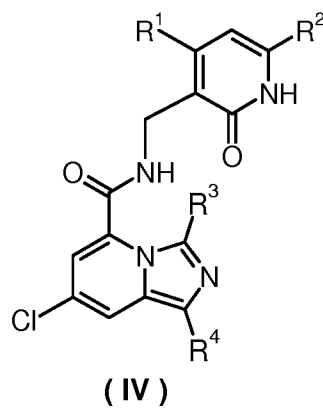
- 10 in which R^1 and R^2 are as defined in any one of claims 1 to 5;

thus providing a compound of general formula (I):



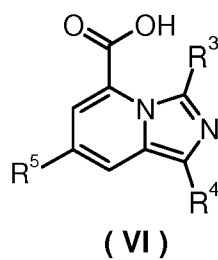
in which R¹, R², R³, R⁴, and R⁵ are as defined in any one of claims 1 to 5.

8. A compound of formula (IV):



in which R¹, R², R³, and R⁴ are as defined in any one of claims 1 to 5.

9. A compound of formula (VI):



in which R³, R⁴, and R⁵ are as defined in any one of claims 1 to 5.

10. A compound of formula (IV) according to claim 8 for use in the preparation of a compound of general formula (I) according to any one of claims 1 to 5.
11. A compound of formula (VI) according to claim 9 for use in the preparation of a compound of general formula (I) according to any one of claims 1 to 5.
- 5 12. A compound of general formula (I) according to claim 1 for use in the treatment of diseases.
13. A compound for use according to claim 12, wherein the disease is cancer.
14. A compound for use according to claim 13, wherein the cancer disease is Bladder cancer, Brain cancer, Breast cancer, Colorectal cancer, Chronic myelomonocytic leukemia, MLL-
10 rearranged leukemia, Lung adenocarcinomas, Lymphoma, Medulloblastoma, Melanoma, Multiple myeloma, Prostate cancer, Malignant rhabdoid tumors, Synovial sarcoma, Teratoid/rhabdoid tumors, T-cell acute lymphoblastic leukemia.
15. A compound for use according to claim 14, wherein the cancer disease is Breast Cancer.
- 15 16. Combination comprising one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 5, and one or more second active ingredients selected from chemotherapeutic anti-cancer agents and target-specific anti-cancer agents.
17. Pharmaceutical composition comprising a compound of general formula (I) according to claim 1 to 5 together with one or more pharmaceutically acceptable excipients.
- 20 18. Pharmaceutical composition according to claim 17 for use according to claims 12 to 15.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/080835

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/118812 A2 (EPIZYME INC [US]; KUNTZ KEVIN WAYNE [US]; OLHAVA EDWARD JAMES [US]; CH) 7 September 2012 (2012-09-07) the whole document -----	1-18
A	WO 2014/155301 A1 (PIRAMAL ENTPR LTD [IN]) 2 October 2014 (2014-10-02) the whole document -----	1-18
A	WO 2014/151142 A1 (CONSTELLATION PHARMACEUTICALS INC [US]) 25 September 2014 (2014-09-25) the whole document -----	1-18
A	WO 2013/039988 A1 (GLAXOSMITHKLINE LLC [US]; BURGESS JOELLE LORRAINE [US]; JOHNSON NEIL W) 21 March 2013 (2013-03-21) the whole document ----- -/-	1-18



Further documents are listed in the continuation of Box C.



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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

12 February 2016

Date of mailing of the international search report

25/02/2016

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/080835

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/075080 A1 (GLAXOSMITHKLINE LLC [US]; KNIGHT STEVEN DAVID [US]; MILLER WILLIAM HEN) 7 June 2012 (2012-06-07) the whole document -----	1-18
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INTERNATIONAL SEARCH REPORT

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International application No

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