

Indole carboxamide derivatives as P2X₇ receptor antagonists

The present invention relates to indole carboxamide derivatives of formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including processes
5 for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I), and especially their use as P2X₇ receptor antagonists.

The P2X₇ receptors (P2RX7) belong to the family of P2X ionotropic receptors that are activated by extracellular nucleotides, in particular adenosine triphosphate (ATP). P2RX7 is distinguished from other P2X family members by the high concentrations (mM range) of
10 ATP required to activate it and its ability to form a large pore upon prolonged or repeated stimulation (North, R. A., *Physiol. Rev.* 2002, 82(4), 1013-67; Surprenant, A., Rassendren, F. et al., *Science* 1996, 272(5262), 735-8; Virginio, C., MacKenzie, A. et al., *J. Physiol.*, 1999, 519, 335-46). P2RX7 is present on many cell types, especially ones known to be involved in inflammatory and immune processes. This is reflected within both the
15 periphery and the CNS as Lipopolysaccharide S (LPS) priming of monocytes and microglia followed by ATP stimulation has been shown to lead to the local release and processing of IL1 β and other family members including IL18 through a P2RX7 mediated mechanism. Indeed mice lacking the P2X7 receptor are unable to release IL1 β following LPS priming and ATP stimulation providing further evidence of its role in this pathway
20 (Solle, M., Labasi, J. et al., *J. Biol. Chem.*, 2001, 276(1), 125-32). In addition L-selectin shedding from monocytes, macrophages and lymphocytes, degranulation in mast cells and apoptosis in lymphocytes are all associated with P2RX7 stimulation. P2RX7 is also expressed on epithelial and endothelial cells (Ferrari, D., Chiozzi, P. et al., *Neuropharmacology* 1997, 36(9), 1295-301; Wiley, J. S., Chen, J. R. et al., *Ciba Found Symp.* 1996, 198, 149-60 and 160-5; North, R. A., *Physiol. Rev.* 2002, 82(4), 1013-67). In addition to its role in the periphery it may have an important function in neurotransmission within the CNS through its activation on postsynaptic and / or presynaptic central and peripheral neurons and glia (Deuchars, S. A., Atkinson, L. et al., *J. Neurosci.* 2001, 21(18), 7143-52; Sperlagh, B., Kofalvi, A. et al., *J. Neurochem.* 2002, 81(6), 1196-211).
30 Recent data that has emerged using *in situ* hybridization demonstrated that P2X7 receptor mRNA was widely distributed throughout the rat brain. Specifically, among the areas of high P2X7mRNA expression noted were the piriform cortex, hippocampus, pontine nuclei and the anterior horn of the spinal cord (Yu, Y., Ugawa, S. et al., *Brain. Res.* 2008, 1194, 45-55). Hence there is therapeutic rationale for the use of P2X7 ion channel blockers in

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the treatment of a variety of disease states. These include but are not limited to diseases associated with the central nervous system such as stroke or injury and diseases associated with neuro-degeneration and neuroinflammation such as Alzheimer's disease, Huntington's disease, epilepsy, Amyotrophic lateral sclerosis, acute spinal cord injury

5 additionally to meningitis, sleep disorders, mood and anxiety disorders as well as chronic and neuropathic and inflammatory pain. Furthermore, peripheral inflammatory disorders and autoimmune diseases including but not limited to rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, chronic obstructive pulmonary disease, airways hyper-responsiveness, septic shock, bronchitis, glomerulonephritis, irritable bowel

10 disease, skin injury, lung emphysema, Limb girdle dystrophy type 2B, fibrosis, Syndrome of synovitis Acne Pustulosis, atherosclerosis, burn injury, spinal cord injury, Hyperostosis Osteitis, Crohn's disease, ulcerative colitis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, trauma, meningitis, osteoporosis, burn injury, ischemic heart disease, and varicose veins and trauma, are all examples where the involvement of

15 P2X7 channels has been implicated. In addition a recent report suggests a link between P2RX7 and chronic, inflammatory and neuropathic pain (Chessell, I. P., Hatcher, J. P. et al., Pain, 2005, 114(3), 386-96). Overall, these findings indicate a role for the P2X7 receptor in the process of neuronal synaptic transmission and therefore a potential role for P2X7 antagonists as novel therapeutic tools to treat neuropathic pain.

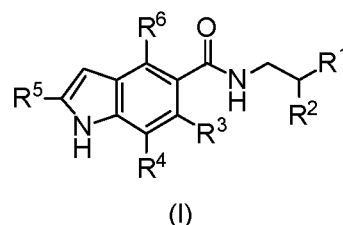
20 In view of the above observations, there is significant requirement for P2X7 antagonists that can be efficiently used in treating neuropathic pain, chronic inflammatory pain, inflammation, and neurodegenerative conditions.

Different indole carboxamide derivatives, which are also P2X₇ receptor antagonists, have been disclosed in WO 2009/023623, WO 2009/108551 and WO 2009/118175. Quinoline

25 and isoquinoline derivatives which are also P2X₇ receptor antagonists, have been disclosed in WO2009/132000.

Various embodiments of the invention are presented hereafter:

1) The present invention relates to indole carboxamide derivatives of formula (I),



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wherein

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R¹ represents a heteroaryl or an aryl group which groups are independently unsubstituted, mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₄)alkoxy, (C₁–C₃)fluoroalkyl, (C₁–C₃)fluoroalkoxy, hydroxy, halogen and phenoxy;

5 **R²** represents

- heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from (C₁–C₄)alkyl, (C₁–C₄)alkylcarbonyl, (C₁–C₄)alkoxycarbonyl, (C₁–C₄)alkylsulfonyl, and halogen;
- heterocycloxy;
- 10 • (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with halogen;
- (C₃–C₆)cycloalkyloxy;
- *N*-(C₃–C₆)cycloalkyl-amino;
- *N*-(C₃–C₆)cycloalkylmethyl-amino;
- (C₃–C₆)alkyl;
- 15 • (C₂–C₆)alkoxy;
- *N*-(C₁–C₄)alkylamino;
- *N,N*-di-[(C₁–C₄)alkyl]-amino; or
- *N*-arylmethyl-*N*-(C₁–C₄)alkyl-amino;

R³ represents hydrogen or halogen;

20 **R⁴** represents hydrogen, fluoro, chloro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy, (C₁–C₄)alkyl-carbonyl, hydroxy-(C₁–C₄)alkyl, hydroxy-(C₂–C₄)alkoxy, (C₁–C₂)alkoxy-(C₁–C₄)alkyl or (C₁–C₄)alkoxy-(C₂–C₄)alkoxy;

R⁵ represents hydrogen or (C₁–C₄)alkyl; and

R⁶ represents fluoro, chloro, methyl, ethyl or (C₁–C₂)fluoroalkyl;

25 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

The compounds of formula (I) according to embodiment 1) may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms. Substituents at a double bond may be present in the (*Z*)- or (*E*)-configuration unless indicated otherwise. The compounds of formula (I) may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

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Definitions:

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a
5 broader or narrower definition.

The term "alkyl", used alone or in combination, refers to a straight or branched chain alkyl group containing one to six carbon atoms. The term "(C_x-C_y)alkyl" (x and y each being an integer), refers to an alkyl group as defined before containing x to y carbon atoms. For example a (C₁-C₄)alkyl group contains from one to four carbon atoms. Representative
10 examples of (C₁-C₄)alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. A (C₃-C₆)alkyl group contains from three to six carbon atoms. Representative examples of (C₃-C₆)alkyl groups include *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 2-methyl-but-1-yl, 3-methyl-but-1-yl, 2-methyl-but-2-yl, 3-methyl-but-2-yl, hex-1-yl, hex-2-yl, hex-3-yl, 2-methyl-
15 pent-2-yl, 3-methyl-pent-2-yl, 4-methyl-pent-2-yl, 2-methyl-pent-3-yl, 3-methyl-pent-3-yl, 2,3-dimethyl-but-2-yl and 3,3-dimethyl-but-2-yl.

The term "alkoxy", used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined above. The term "(C_x-C_y)alkoxy" (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a
20 (C₁-C₄)alkoxy group contains from one to four carbon atoms. Representative examples of (C₁-C₄)alkoxy groups include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. A (C₂-C₆)alkoxy group contains from two to six carbon atoms. Representative examples of (C₂-C₆)alkoxy groups include ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy, *tert*-butoxy, pent-1-yloxy, pent-2-yloxy, pent-3-
25 yloxy, 2-methyl-but-1-yloxy, 3-methyl-but-1-yloxy, 2-methyl-but-2-yloxy, 3-methyl-but-2-yloxy, hex-1-yloxy, hex-2-yloxy, hex-3-yloxy, 2-methyl-pent-2-yloxy, 3-methyl-pent-2-yloxy, 4-methyl-pent-2-yloxy, 2-methyl-pent-3-yloxy, 3-methyl-pent-3-yloxy, 2,3-dimethyl-but-2-yloxy and 3,3-dimethyl-but-2-yloxy.

The term "hydroxy-(C₁-C₄)alkyl", used alone or in combination, refers to an alkyl group as
30 defined before containing from one to four carbon atoms in which one hydrogen atom has been replaced with hydroxy. Examples of said groups are hydroxy-methyl, 1-hydroxy-ethyl, 2-hydroxy-ethyl, 1-hydroxy-prop-1-yl, 2-hydroxy-prop-1-yl, 3-hydroxy-prop-1-yl, 1-hydroxy-prop-2-yl, 2-hydroxy-prop-2-yl, 1-hydroxy-but-1-yl, 2-hydroxy-but-1-yl, 3-hydroxy-but-1-yl, 4-hydroxy-but-1-yl, 1-hydroxy-but-2-yl, 2-hydroxy-but-2-yl, 3-hydroxy-but-2-yl, 4-

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hydroxy-but-2-yl, 1-hydroxy-2-methyl-prop-1-yl, 2-hydroxy-2-methyl-prop-1-yl, 3-hydroxy-2-methyl-prop-1-yl, and 2-hydroxy-1,1-dimethyl-eth-1-yl.

The term “hydroxy-(C₂-C₄)alkoxy”, used alone or in combination, refers to an alkoxy group as defined before containing from two to four carbon atoms in which one hydrogen atom
 5 has been replaced with hydroxy. Examples of said groups are 2-hydroxy-ethoxy, 2-hydroxy-prop-1-yloxy, 3-hydroxy-prop-1-yloxy, 1-hydroxy-prop-2-yloxy, 2-hydroxy-but-1-yloxy, 3-hydroxy-but-1-yloxy, 4-hydroxy-but-1-yloxy, 1-hydroxy-but-2-yloxy, 3-hydroxy-but-2-yloxy, 4-hydroxy-but-2-yloxy, 2-hydroxy-2-methyl-prop-1-yloxy, 3-hydroxy-2-methyl-prop-1-yloxy, and 2-hydroxy-1,1-dimethyl-eth-1-yloxy.

10 The term “(C₁-C₂)alkoxy-(C₁-C₄)alkyl”, used alone or in combination, refers to an alkyl group as defined before containing from one to four carbon atoms in which one hydrogen atom has been replaced with (C₁-C₂)alkoxy as defined before. Examples of said groups are methoxy-methyl, methoxy-ethyl, methoxy-propyl, methoxy-butyl, ethoxy-methyl, ethoxy-ethyl, ethoxy-propyl and ethoxy-butyl.

15 The term “(C₁-C₄)alkoxy-(C₂-C₄)alkoxy”, used alone or in combination, refers to an alkoxy group as defined before containing from two to four carbon atoms in which one hydrogen atom has been replaced with (C₁-C₄)alkoxy as defined before. A preferred example of said groups is 2-*tert*-butoxy-ethoxy.

The term “(C₁-C₄)alkylcarbonyl”, used alone or in combination, refers to a (C₁-C₄)alkyl-
 20 C(O)- group wherein the (C₁-C₄)alkyl group is as defined before, which is attached to the rest of the molecule via the carbonyl-C-atom. Representative examples of (C₁-C₄)alkylcarbonyl groups include methylcarbonyl, ethylcarbonyl, *n*-propylcarbonyl, *iso*-propylcarbonyl, *n*-butylcarbonyl, *iso*-butylcarbonyl, *sec*-butylcarbonyl and *tert*-butylcarbonyl.

25 The term “(C₁-C₄)alkoxycarbonyl”, used alone or in combination, refers to a (C₁-C₄)alkyl-O-C(O)- group wherein the (C₁-C₄)alkyl group is as defined before, which is attached to the rest of the molecule via the carboxyl-C-atom. Representative examples of (C₁-C₄)alkoxy-carbonyl groups include methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, *iso*-propoxycarbonyl, *n*-butoxycarbonyl, *iso*-butoxycarbonyl, *sec*-butoxycarbonyl and *tert*-
 30 butoxycarbonyl.

The term “(C₁-C₄)alkylsulfonyl”, used alone or in combination, refers to a (C₁-C₄)alkyl-S(O)₂- group wherein the (C₁-C₄)alkyl group is as defined before, which is attached to the rest of the molecule via the sulfonyl-S-atom. Representative examples of (C₁-C₄)alkyl-

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sulfonyl groups include methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, *iso*-propylsulfonyl, *n*-butylsulfonyl, *iso*-butylsulfonyl, *sec*-butylsulfonyl and *tert*-butylsulfonyl.

The term "*N*-(C₁-C₄)alkylamino", used alone or in combination, refers to an amino group (-NH₂) wherein one hydrogen atom has been replaced with (C₁-C₄)alkyl as defined before.

5 Representative examples of *N*-(C₁-C₄)alkylamino groups include methylamino, ethylamino, *n*-propylamino, *iso*-propylamino, *n*-butylamino, *iso*-butylamino, *sec*-butylamino and *tert*-butylamino.

The term "*N,N*-di-[(C₁-C₄)alkyl]-amino", used alone or in combination, refers to an amino group (-NH₂) wherein both hydrogen atoms have been replaced with (C₁-C₄)alkyl groups as defined before, wherein the two alkyl groups are the same or different. Representative
10 examples of *N,N*-di-[(C₁-C₄)alkyl]-amino groups include dimethylamino, methyl-ethylamino, methyl-*n*-propylamino, methyl-*iso*-propylamino, methyl-*n*-butylamino, methyl-*iso*-butylamino, methyl-*sec*-butylamino, methyl-*tert*-butylamino, diethylamino, ethyl-*n*-propylamino, ethyl-*iso*-propylamino, ethyl-*n*-butylamino, ethyl-*iso*-butylamino, ethyl-*sec*-
15 butylamino and ethyl-*tert*-butylamino.

The term "*N*-arylmethyl-*N*-(C₁-C₄)alkyl-amino", used alone or in combination, refers to an amino group (-NH₂) wherein one hydrogen atom has been replaced with (C₁-C₄)alkyl as defined before and the other hydrogen atom has been replaced with arylmethyl, wherein the term aryl refers to phenyl or naphthyl. Representative examples of *N*-arylmethyl-*N*-
20 (C₁-C₄)alkyl-amino groups include benzyl-methylamino, benzyl-ethylamino, benzyl-*n*-propylamino, benzyl-*iso*-propylamino, benzyl-*n*-butylamino, benzyl-*iso*-butylamino, benzyl-*sec*-butylamino, benzyl-*tert*-butylamino, naphthylmethyl-methylamino, naphthylmethyl-ethylamino, naphthylmethyl-*n*-propylamino, naphthylmethyl-*iso*-propylamino, naphthylmethyl-*n*-butylamino, naphthylmethyl-*iso*-butylamino, naphthylmethyl-*sec*-
25 butylamino and naphthylmethyl-*tert*-butylamino.

The term "(C_x-C_y)fluoroalkyl" (x and y each being an integer) refers to an alkyl group as defined before containing x to y carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluoro. For example a (C₁-C₃)fluoroalkyl group contains from one to three carbon atoms in which one to seven hydrogen atoms have
30 been replaced with fluoro. In analogy, a (C₁-C₂)fluoroalkyl group contains one or two carbon atoms in which one to five hydrogen atoms have been replaced with fluoro. Representative examples of said groups are difluoromethyl, trifluoromethyl, 2,2-difluoroethyl and 2,2,2-trifluoroethyl.

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The term “(C_x-C_y)fluoroalkoxy” (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluoro. For example a (C₁-C₃)fluoroalkoxy group contains from one to three carbon atoms in which one to seven hydrogen atoms have
5 been replaced with fluoro. Representative examples of said groups are difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy.

The term “(C₃-C₆)cycloalkyl”, used alone or in combination, refers to a cycloalkyl group with 3 to 6 carbon atoms. Examples of (C₃-C₆)cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

10 The term “(C₃-C₆)cycloalkyloxy”, used alone or in combination, refers to a (C₃-C₆)cycloalkyl-O- group wherein the (C₃-C₆)cycloalkyl group is as defined above. Examples of (C₃-C₆)cycloalkyloxy groups are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term “N-(C₃-C₆)cycloalkyl-amino”, used alone or in combination, refers to an amino
15 group (-NH₂) wherein one hydrogen atom has been replaced with (C₃-C₆)cycloalkyl as defined before. Representative examples of N-(C₃-C₆)cycloalkyl-amino groups include cyclopropyl-amino, cyclobutyl-amino, cyclopentyl-amino and cyclohexyl-amino.

The term “N-(C₃-C₆)cycloalkylmethyl-amino”, used alone or in combination, refers to an amino group (-NH₂) wherein one hydrogen atom has been replaced with a (C₃-
20 C₆)cycloalkylmethyl group wherein the (C₃-C₆)cycloalkyl group is as defined before. Representative examples of N-(C₃-C₆)cycloalkylmethyl-amino groups include cyclopropylmethyl-amino, cyclobutylmethyl-amino, cyclopentylmethyl-amino and cyclohexylmethyl-amino.

The term halogen means fluoro, chloro, bromo or iodo.

25 The term “aryl”, used alone or in combination, means a phenyl or a naphthyl group. The aryl group is unsubstituted or substituted as explicitly defined. Examples of unsubstituted or substituted aryl groups are 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 3,4-difluoro-phenyl, 3,5-difluoro-phenyl, 2,4,6-trifluoro-phenyl, 4-chloro-phenyl, 4-chloro-2-fluoro-phenyl, 2,4-dichloro-phenyl, 4-methyl-phenyl, 4-methoxy-phenyl,
30 4-trifluoromethyl-phenyl, 4-trifluoromethoxy-phenyl and 4-phenoxy-phenyl.

The term “heteroaryl”, used alone or in combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are

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furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzo[2,1,3]oxadiazolyl, benzo[2,1,3]thiadiazolyl, benzo[1,2,3]thiadiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl and phthalazinyl. The heteroaryl groups are unsubstituted or substituted as explicitly defined. Examples of such unsubstituted or substituted heteroaryl groups are 3,5-dimethyl-isoxazolyl (notably 3,5-dimethyl-isoxazol-4-yl), thiazolyl (notably thiazol-5-yl), isothiazolyl (notably isothiazol-5-yl), 1-methyl-pyrazolyl (notably 1-methyl-pyrazol-4-yl), pyridyl (notably pyridin-3-yl), 5-fluoro-pyridyl (notably 5-fluoro-pyridin-2-yl), 6-chloro-pyridyl (notably 6-chloro-pyridin-3-yl), 6-methyl-pyridyl (notably 6-methyl-pyridin-3-yl), 6-methoxy-pyridyl (notably 6-methoxy-pyridin-3-yl), 6-trifluoromethyl-pyridyl (notably 6-trifluoromethyl-pyridin-3-yl), 2-hydroxy-pyridyl (notably 2-hydroxy-pyridin-4-yl), pyrimidyl (notably pyrimidin-5-yl), 2-methyl-pyrimidyl (notably 2-methyl-pyrimidin-5-yl), 2-cyclopropyl-pyrimidyl (notably 2-cyclopropyl-pyrimidin-5-yl), 2-trifluoromethyl-pyrimidyl (notably 2-trifluoromethyl-pyrimidin-5-yl), pyridazinyl (notably pyridazin-3-yl) and 5-methyl-pyrazinyl (notably 5-methyl-pyrazin-2-yl).

The term "5- or 6-membered monocyclic heteroaryl", used alone or in combination, means a 5- or 6-membered monocyclic aromatic ring containing one nitrogen atom and optionally one additional heteroatom selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyridazinyl and pyrazinyl. The heteroaryl groups are unsubstituted or substituted as explicitly defined. Examples of such unsubstituted or substituted heteroaryl groups are 3,5-dimethyl-isoxazolyl (notably 3,5-dimethyl-isoxazol-4-yl), thiazolyl (notably thiazol-5-yl), isothiazolyl (notably isothiazol-5-yl), 1-methyl-pyrazolyl (notably 1-methyl-pyrazol-4-yl), pyridyl (notably pyridin-3-yl), 5-fluoro-pyridyl (notably 5-fluoro-pyridin-2-yl), 6-chloro-pyridyl (notably 6-chloro-pyridin-3-yl), 6-methyl-pyridyl (notably 6-methyl-pyridin-3-yl), 6-methoxy-pyridyl (notably 6-methoxy-pyridin-3-yl), 6-trifluoromethyl-pyridyl (notably 6-trifluoromethyl-pyridin-3-yl), 2-hydroxy-pyridyl (notably 2-hydroxy-pyridin-4-yl), pyrimidyl (notably pyrimidin-5-yl), 2-methyl-pyrimidyl (notably 2-methyl-pyrimidin-5-yl), 2-cyclopropyl-pyrimidyl (notably 2-cyclopropyl-pyrimidin-5-yl), 2-trifluoromethyl-pyrimidyl (notably 2-trifluoromethyl-pyrimidin-5-yl), pyridazinyl (notably pyridazin-3-yl) and 5-methyl-pyrazinyl (notably 5-methyl-pyrazin-2-yl).

The term "heterocyclyl", used alone or in combination, refers to a saturated mono- or bicyclic moiety of 4 to 8 ring members containing one heteroatom selected from nitrogen,

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- oxygen and sulfur and optionally one additional nitrogen atom. The sulfur atom of a heterocyclyl group may be in an oxidised form, i.e. as a sulfoxide or sulfonyl. Examples of such heterocyclyl groups are azetidiny, pyrrolidiny, piperidiny, piperaziny, tetrahydropyrany, morpholiny, thiomorpholiny, 1-oxo-thiomorpholiny, 1,1-dioxo-thiomorpholiny, azepany, 1,4-oxazepany, 6-oxa-3-azabicyclo[3.1.1]heptany and 2-oxa-5-azabicyclo[2.2.1]heptany. The heterocyclyl groups are unsubstituted or substituted as explicitly defined. Examples of such unsubstituted or substituted heterocyclyl groups are azetidin-1-yl, pyrrolidin-1-yl, 3,3-difluoro-pyrrolidin-1-yl, piperidin-1-yl, 4-fluoro-piperidin-1-yl, 3,3-difluoro-piperidin-1-yl, 4,4-difluoro-piperidin-1-yl, 2-methyl-piperidin-1-yl, 4-methyl-piperidin-1-yl, 4-(*tert*-butoxy-carbonyl)-piperidin-1-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, 1-acetyl-piperidin-4-yl, 1-(*tert*-butoxy-carbonyl)-piperidin-4-yl, 1-methylsulfonyl-piperidin-4-yl, 4-(*tert*-butoxy-carbonyl)-piperazin-1-yl, tetrahydropyran-4-yl, morpholin-4-yl, 2,6-dimethyl-morpholin-4-yl, 1,1-dioxo-thiomorpholin-4-yl, azepan-1-yl, 1,4-oxazepan-4-yl, 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl and 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl.
- 15 The term "heterocyclyloxy", used alone or in combination, refers to a heterocyclyl-O-group, wherein the heterocyclyl group is as defined above. An example of such a heterocyclyl group is tetrahydropyranoxy (notably tetrahydropyran-4-oxy).

Further embodiments of the invention are presented hereinafter:

- 1P) A further embodiment of the invention relates to compounds according to embodiment 1), wherein
- R¹** represents a heteroaryl or an aryl group which groups are independently unsubstituted, mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₄)alkoxy, (C₁-C₃)fluoroalkyl, (C₁-C₃)fluoroalkoxy, hydroxy, halogen and phenoxy;
- R²** represents
- heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from (C₁-C₄)alkyl, (C₁-C₄)alkylcarbonyl, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkylsulfonyl, and halogen;
 - heterocyclyloxy;
 - (C₃-C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with halogen;
 - (C₃-C₆)cycloalkyloxy;
 - *N*-(C₃-C₆)cycloalkyl-amino;
 - *N*-(C₃-C₆)cycloalkylmethyl-amino;
 - (C₃-C₆)alkyl;

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- (C₂–C₆)alkoxy;
- *N*-(C₁–C₄)alkylamino;
- *N,N*-di-[(C₁–C₄)alkyl]-amino; or
- *N*-arylmethyl-*N*-(C₁–C₄)alkyl-amino;

5 **R**³ represents hydrogen or halogen;

R⁴ represents hydrogen, (C₁–C₄)alkyl or (C₁–C₂)alkoxy-(C₁–C₄)alkyl;

R⁵ represents hydrogen or (C₁–C₄)alkyl; and

R⁶ represents chloro or methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

10 2) A further embodiment of the invention relates to compounds according to any one of embodiments 1) or 1P), wherein

R¹ represents a 5- or 6-membered monocyclic heteroaryl or a phenyl group which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of methyl, cyclopropyl, methoxy, trifluoromethyl, trifluoromethoxy, hydroxy, fluoro, chloro and phenoxy;

15 **R**² represents

- heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from methyl, methylcarbonyl, *tert*-butoxy-carbonyl, methylsulfonyl, and fluoro;

20 • tetrahydropyran-4-oxy;

- cyclohexyl which is unsubstituted or mono- or di-substituted with fluoro;

- cyclopentyloxy; cyclohexyloxy;

- cyclopentyl-amino;

- cyclopentylmethyl-amino;

25 • *iso*-butyl; pent-3-yl;

- ethoxy; pent-3-yloxy;

- *iso*-butylamino;

- dimethylamino; diethylamino; methyl-*iso*-butylamino; or

- *N*-benzyl-*N*-methyl-amino;

30 **R**³ represents hydrogen or chloro;

R⁴ represents hydrogen, methyl, *iso*-butyl or 3-methoxy-prop-1-yl;

R⁵ represents hydrogen or methyl; and

R⁶ represents chloro or methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

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3) A further embodiment of the invention relates to compounds according to any one of embodiments 1) or 1P), wherein

R¹ represents a heteroaryl or an aryl group which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₄)alkoxy, (C₁–C₃)fluoroalkyl and halogen;

R² represents

- heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from (C₁–C₄)alkyl and halogen;
- (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with fluoro;
- cyclopentyloxy;
- (C₃–C₆)alkyl; or
- pent-3-yloxy;

R³ represents hydrogen;

R⁴ represents hydrogen, (C₁–C₄)alkyl or (C₁–C₂)alkoxy-(C₁–C₄)alkyl;

R⁵ represents hydrogen; and

R⁶ represents chloro or methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

4) A further embodiment of the invention relates to compounds according to any one of embodiments 1) or 1P), wherein

R¹ represents a 5- or 6-membered monocyclic heteroaryl group which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₄)alkoxy, (C₁–C₃)fluoroalkyl and halogen;

R² represents

- heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from methyl and fluoro; or
- (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with fluoro;

R³ represents hydrogen;

R⁴ represents hydrogen or (C₁–C₄)alkyl;

R⁵ represents hydrogen; and

R⁶ represents chloro or methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

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- 5) A further embodiment of the invention relates to compounds according to any one of embodiments 1) or 1P), wherein
- R¹** represents a pyrimidyl or pyridyl group which is unsubstituted or mono-substituted with methyl, cyclopropyl, methoxy, trifluoromethyl or chloro;
- 5 **R²** represents heterocyclyl, wherein the heterocyclyl is selected from 3,3-difluoro-pyrrolidin-1-yl, piperidin-1-yl, 4-fluoro-piperidin-1-yl, 3,3-difluoro-piperidin-1-yl, 4,4-difluoro-piperidin-1-yl, morpholin-4-yl, azepan-1-yl, 1,4-oxazepan-4-yl and 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl;
- R³** represents hydrogen;
- 10 **R⁴** represents hydrogen or methyl;
- R⁵** represents hydrogen; and
- R⁶** represents chloro or methyl;
- and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 6) A further embodiment of the invention relates to compounds according to any one of
- 15 embodiments 1), 1P), 3) or 4), wherein the term "(C₁-C₄)alkyl" means methyl;
- and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 7) A further embodiment of the invention relates to compounds according to any one of
- embodiments 1), 1P), 3) or 6), wherein the term "(C₃-C₆)alkyl" means *iso*-butyl or pent-3-yl;
- 20 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 8) A further embodiment of the invention relates to compounds according to any one of
- embodiments 1), 1P), 3), 4), 6) or 7), wherein the term "(C₁-C₄)alkoxy" means methoxy;
- and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 9) A further embodiment of the invention relates to compounds according to any one of
- 25 embodiments 1), 1P), 3), 4) or 6) to 8), wherein the term "(C₃-C₆)cycloalkyl", if representing a substituent to a heteroaryl or an aryl group, means cyclopropyl;
- and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 10) A further embodiment of the invention relates to compounds according to any one of
- embodiments 1), 1P), 3), 4) or 6) to 9), wherein the term "(C₃-C₆)cycloalkyl", if
- 30 representing **R²**, means cyclohexyl;
- and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

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- 11) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 3), 4) or 6) to 10), wherein the terms "(C₁-C₃)fluoroalkyl" and, if present, "(C₁-C₂)fluoroalkyl" mean trifluoromethyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 5 12) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 3) or 6) to 11), wherein the term "(C₁-C₂)alkoxy-(C₁-C₄)alkyl" means 3-methoxy-prop-1-yl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 13) A further embodiment of the invention relates to compounds according to any one of
10 embodiments 1), 1P), 3), 4) or 6) to 12), wherein the term "halogen" means fluoro or chloro;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 14) A further embodiment of the invention relates to compounds according to any one of
embodiments 1), 1P), 3), 4) or 6) to 12), wherein the term "halogen" means fluoro;
15 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 15) A further embodiment of the invention relates to compounds according to any one of
embodiments 1), 1P), 3) or 6) to 14), wherein the term "heteroaryl" means "5- or 6-
membered monocyclic heteroaryl";
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 20 16) A further embodiment of the invention relates to compounds according to any one of
embodiments 1) to 4) or 6) to 14), wherein the term "heteroaryl" or the term "5- or 6-
membered monocyclic heteroaryl" means thiazolyl, isothiazolyl, pyridyl or pyrimidyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 17) A further embodiment of the invention relates to compounds according to any one of
25 embodiments 1) to 4) or 6) to 14), wherein the term "heteroaryl" or the term "5- or 6-
membered monocyclic heteroaryl" means pyridyl or pyrimidyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.
- 18) A further embodiment of the invention relates to compounds according to any one of
embodiments 1), 1P), 3) or 6) to 17), wherein the term "aryl" means phenyl;
30 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

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19) A further embodiment of the invention relates to compounds according to any one of embodiments 1) to 4) or 6) to 18), wherein the term "heterocyclyl" means pyrrolidinyl, piperidinyl, tetrahydropyranyl, morpholinyl, azepanyl, 1,4-oxazepanyl or 6-oxa-3-azabicyclo[3.1.1]heptanyl;

5 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

20) A further embodiment of the invention relates to compounds according to any one of embodiments 1) to 4) or 6) to 18), wherein the term "heterocyclyl" means piperidin-1-yl, morpholin-4-yl, azepan-1-yl, 1,4-oxazepan-4-yl or 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl; and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

10 21) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 3), 6) to 14), 16), 17), 19) or 20), wherein

R¹ represents a 5- or 6-membered monocyclic heteroaryl or a phenyl group which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₃)fluoroalkyl and halogen;

15 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

22) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 3), 4), 6) to 14), 16), 17), 19) or 20), wherein

R¹ represents a 5- or 6-membered monocyclic heteroaryl group which is unsubstituted or mono-substituted with (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₃)fluoroalkyl and halogen;

20 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

23) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 3), 6) to 14), 19) or 20), wherein

R¹ represents a phenyl group which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₁–C₄)alkoxy, (C₁–C₃)fluoroalkyl and halogen;

25 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

24) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 3), 6) or 8) to 23), wherein

30 **R²** represents

- heterocyclyl which is unsubstituted or mono- or di-substituted with fluoro; or
- (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with fluoro;

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and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25) A further embodiment of the invention relates to compounds according to any one of embodiments 1) to 4), 6), 8), 9) or 11) to 23), wherein

R² represents heterocyclyl which is unsubstituted or mono- or di-substituted with fluoro;

5 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

26) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 3), 6) to 18) or 21) to 23), wherein

R² represents (C₃–C₆)alkyl; or (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with fluoro;

10 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

27) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 6), 8) to 18) or 21) to 23), wherein

R² represents (C₃–C₆)cycloalkyloxy or (C₂–C₆)alkoxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

15 28) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 1P), 2) or 6) to 27), wherein

R³ represents hydrogen;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

29) A further embodiment of the invention relates to compounds according to any one of
20 embodiments 1), 1P), 3), 6) to 11) or 13) to 28), wherein

R⁴ represents hydrogen or (C₁–C₄)alkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

30) A further embodiment of the invention relates to compounds according to any one of
embodiments 1), 1P), 3) or 6) to 28), wherein

25 **R⁴** represents (C₁–C₂)alkoxy-(C₁–C₄)alkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

31) A further embodiment of the invention relates to compounds according to any one of
embodiments 1), 1P), 2) or 6) to 30), wherein

R⁵ represents hydrogen;

30 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

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32) A further embodiment of the invention relates to compounds according to any one of embodiments 1) to 31), wherein

R^6 represents chloro;

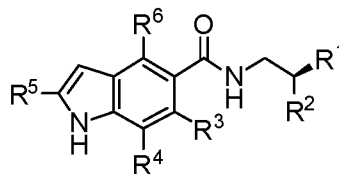
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

5 33) A further embodiment of the invention relates to compounds according to any one of embodiments 1) to 31), wherein

R^6 represents methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

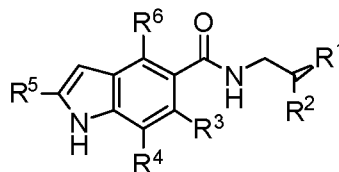
34) A further embodiment of the invention relates to compounds according to any one of
10 embodiments 1) to 33), wherein the absolute configuration of the stereogenic center is as depicted in formula (I_{St1})



(I_{St1})

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

15 35) A further embodiment of the invention relates to compounds according to any one of embodiments 1) to 33), wherein the absolute configuration of the stereogenic center is as depicted in formula (I_{St2})



(I_{St2})

20 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

36) Preferred compounds of formula (I) as defined in embodiment 1) are selected from the group consisting of:

4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide;

25 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-(4,4-difluoro-piperidin-1-yl)-ethyl]-amide;

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- 4-Chloro-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 5 4-Chloro-1H-indole-5-carboxylic acid [(R)-2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [(S)-2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-methyl-pyridin-3-yl)-2-morpholin-4-yl-ethyl]-
- 10 amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-cyclopropyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-methoxy-pyridin-3-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-dimethylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-
- 20 amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-azetidin-1-yl-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-pyrrolidin-1-yl-ethyl]-amide;
- 25 4-Chloro-1H-indole-5-carboxylic acid [2-diethylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 30 4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-difluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-{2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-pyridin-3-yl-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-4-yl-2-pyridin-3-yl-ethyl)-amide;

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- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-acetyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide;
- 5 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methanesulfonyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyridin-3-yl-ethyl)-amide;
- 10 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyrimidin-5-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyrimidin-5-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-1H-pyrazol-4-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-1H-pyrazol-4-yl)-2-piperidin-1-yl-ethyl]-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid [2-piperidin-1-yl-2-(2,4,6-trifluoro-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-difluoro-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-2-piperidin-1-yl-ethyl]-amide;
- 20 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2,4,6-trifluoro-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-difluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 25 4-Chloro-1H-indole-5-carboxylic acid [2-(2-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-chloro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 30 4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-dichloro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-chloro-2-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(*cis*-2,6-dimethyl-morpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
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- 4-Chloro-1H-indole-5-carboxylic acid [2-(*trans*-2,6-dimethyl-morpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3-fluoro-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-piperidin-1-yl-2-(4-trifluoromethyl-phenyl)-ethyl]-amide;
- 5 amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3,4-difluoro-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyridin-3-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-*p*-tolyl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-trifluoromethoxy-phenyl)-ethyl]-amide;
- 10 amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-trifluoromethyl-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3,4-difluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(tetrahydro-pyran-4-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-cyclopentyloxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-dimethyl-isoxazol-4-yl)-2-morpholin-4-yl-ethyl]-amide;
- 20 amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-dimethyl-isoxazol-4-yl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-*p*-tolyl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-piperidin-1-yl-ethyl]-amide;
- 25 amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-phenoxy-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-phenoxy-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-methoxy-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-methyl-pyrazin-2-yl)-2-piperidin-1-yl-ethyl]-amide;
- 30 amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-isothiazol-5-yl-2-piperidin-1-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-thiazol-5-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-methyl-pyrazin-2-yl)-2-morpholin-4-yl-ethyl]-amide;
- 35 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-thiazol-5-yl-ethyl)-amide;

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- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-cyclohexyl-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-4-methyl-pentyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-ethoxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(2-oxa-5-aza-
5 bicyclo[2.2.1]hept-5-yl)-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-cyclohexyloxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-
amide;
4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(tetrahydro-pyran-4-
yloxy)-ethyl]-amide;
10 4-Chloro-1H-indole-5-carboxylic acid [2-(1-ethyl-propoxy)-2-(2-methyl-pyrimidin-5-yl)-
ethyl]-amide;
4-Chloro-2-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-
yl-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyridazin-3-yl-ethyl)-amide;
15 4-Chloro-1H-indole-5-carboxylic acid [2-(2-hydroxypyridin-4-yl)-2-piperidin-1-yl-ethyl]-
amide;
1-[2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-(2-methyl-pyrimidin-5-yl)-ethyl]-piperidine-
4-carboxylic acid *tert*-butyl ester;
4-Chloro-1H-indole-5-carboxylic acid [2-(4-methyl-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-
20 yl)-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-piperidin-1-yl)-2-(2-methyl-
pyrimidin-5-yl)-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-(4-fluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-
yl)-ethyl]-amide;
25 4-Chloro-1H-indole-5-carboxylic acid [2-(3,3-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-
5-yl)-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-azepan-1-yl-2-(2-methyl-pyrimidin-5-yl)-ethyl]-
amide;
4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-[1,4]oxazepan-4-yl-
30 ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-(3,3-difluoro-pyrrolidin-1-yl)-2-(2-methyl-pyrimidin-
5-yl)-ethyl]-amide;
4-Chloro-1H-indole-5-carboxylic acid [2-cyclopentylamino-2-(2-methyl-pyrimidin-5-yl)-
ethyl]-amide;

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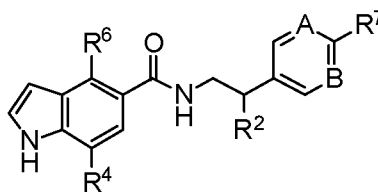
- 4-Chloro-1H-indole-5-carboxylic acid [2-(cyclopentylmethyl-amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-isobutylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 5 4-Chloro-1H-indole-5-carboxylic acid [2-(isobutyl-methyl-amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(benzyl-methyl-amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (3-ethyl-2-pyrimidin-5-yl-pentyl)-amide;
- 10 4-[2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-(2-methyl-pyrimidin-5-yl)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester;
- 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyridazin-3-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2-hydroxypyridin-4-yl)-ethyl]-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid [2-(1,1-dioxo-thiomorpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-cyclohexyl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4,6-Dichloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 20 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(6-oxa-3-aza-bicyclo[3.1.1]hept-3-yl)-ethyl]-amide;
- 4-Chloro-7-methyl-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 25 4-Chloro-7-methyl-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-isobutyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-(3-methoxy-propyl)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide; and
- 30 4-Methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- or salts (in particular pharmaceutically acceptable salts) of such compounds;
- it is to be understood for any of the above listed compounds, that a stereogenic center,
- 35 which is not specifically assigned, may be in absolute (*R*)- or absolute (*S*)-configuration;

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notably, the stereogenic center at the carbon atom attached to R^1 and R^2 may be in absolute (*R*)-configuration or absolute (*S*)-configuration. For example a compound listed as 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide may be 4-Chloro-1H-indole-5-carboxylic acid [(*S*)-2-morpholin-4-yl-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide, 4-Chloro-1H-indole-5-carboxylic acid [(*R*)-2-morpholin-4-yl-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide or any mixture thereof.

It is understood that in this specification the phrase “according to any one of embodiments 1) to X)”, wherein “X” represents an integer between 2 and 36, refers to all embodiments between 1) and X) in the alternative, including embodiment 1P) as one of the alternatives; for instance the phrase “according to any one of embodiments 1) to 4)” means “according to any one of embodiments 1) or 1P) or 2) or 3) or 4)”.

37) A further embodiment of the invention relates to compounds according to any one of embodiments 1), 34) or 35), which are also compounds of formula (I_{Af})

(I_{Af})

wherein

A represents N or CH;

B represents N or CH;

R^2 represents heterocyclyl which is unsubstituted or mono- or di-substituted with fluoro, wherein the heterocyclyl is selected from pyrrolidinyl, piperidinyl, tetrahydropyranyl, morpholinyl, azepanyl, 1,4-oxazepanyl and 6-oxa-3-azabicyclo[3.1.1]heptanyl; or

R^2 represents cyclohexyl which is unsubstituted or mono- or di-substituted with fluoro;

R^4 represents hydrogen, fluoro, chloro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy, hydroxy-(C₂–C₄)alkoxy or (C₁–C₂)alkoxy-(C₁–C₄)alkyl;

R^6 represents fluoro, chloro, methyl, ethyl or (C₁–C₂)fluoroalkyl; and

R^7 represents hydrogen, halogen, (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₄)alkoxy or (C₁–C₃)fluoroalkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

38) A further embodiment of the invention relates to compounds according to embodiment 37), wherein

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A represents N or CH;

B represents N or CH;

R² represents heterocyclyl which is unsubstituted or mono- or di-substituted with fluoro, wherein the heterocyclyl is selected from pyrrolidinyl, piperidinyl, tetrahydropyranyl, morpholinyl, azepanyl, 1,4-oxazepanyl and 6-oxa-3-azabicyclo[3.1.1]heptanyl; or

R² represents cyclohexyl which is unsubstituted or di-substituted with fluoro;

R⁴ represents hydrogen, chloro, methyl, ethyl, *n*-propyl, *iso*-butyl, methoxy, ethoxy, 2-hydroxy-ethoxy or 3-methoxy-prop-1-yl;

R⁶ represents fluoro, chloro, methyl, ethyl or trifluoromethyl; and

R⁷ represents hydrogen, fluoro, chloro, methyl, cyclopropyl, methoxy or trifluoromethyl; and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

39) A further embodiment of the invention relates to compounds according to embodiment 37), wherein

A and **B** represent N and **R**⁷ represents hydrogen, (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl or (C₁–C₃)fluoroalkyl; or

A represents N, **B** represents CH and **R**⁷ represents hydrogen, chloro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy or (C₁–C₃)fluoroalkyl; or

A and **B** represent CH and **R**⁷ represents fluoro, chloro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy or (C₁–C₃)fluoroalkyl;

R² represents pyrrolidinyl which is unsubstituted or di-substituted with fluoro; piperidinyl which is unsubstituted or mono- or di-substituted with fluoro; tetrahydropyranyl; morpholinyl; azepanyl; 1,4-oxazepanyl; 6-oxa-3-azabicyclo[3.1.1]heptanyl; or cyclohexyl which is unsubstituted or di-substituted with fluoro;

R⁴ represents hydrogen, fluoro, chloro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy, hydroxy-(C₂–C₄)alkoxy or (C₁–C₂)alkoxy-(C₁–C₄)alkyl; and

R⁶ represents fluoro, chloro, methyl, ethyl or (C₁–C₂)fluoroalkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

40) A further embodiment of the invention relates to compounds according to embodiment 37), wherein

A and **B** represent N and **R**⁷ represents hydrogen, methyl, cyclopropyl or trifluoromethyl; or

A represents N, **B** represents CH and **R**⁷ represents chloro, methyl, methoxy or trifluoromethyl; or

A and **B** represent CH and **R**⁷ represents fluoro or chloro;

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R² represents 3,3-difluoro-pyrrolidin-1-yl, piperidin-1-yl, 4-fluoro-piperidin-1-yl, 3,3-difluoro-piperidin-1-yl, 4,4-difluoro-piperidin-1-yl, tetrahydropyran-4-yl, morpholin-4-yl, azepan-1-yl, 1,4-oxazepan-4-yl, or 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl;

R⁴ represents hydrogen, chloro, methyl, ethyl, *n*-propyl, *iso*-butyl, methoxy, ethoxy, 2-hydroxy-ethoxy or 3-methoxy-prop-1-yl;

R⁶ represents fluoro, chloro, methyl, ethyl or trifluoromethyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

41) A further embodiment of the invention relates to compounds according to any one of embodiments 37) to 40), wherein

10 **A** and **B** represent N;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

42) A further embodiment of the invention relates to compounds according to any one of embodiments 37) to 41), wherein

15 **R²** represents piperidin-1-yl, 4-fluoro-piperidin-1-yl, 3,3-difluoro-piperidin-1-yl or 4,4-difluoro-piperidin-1-yl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

43) A further embodiment of the invention relates to compounds according to any one of embodiments 37) to 41), wherein

R² represents morpholin-4-yl;

20 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

44) A further embodiment of the invention relates to compounds according to any one of embodiments 37) to 39) or 41), wherein

R² represents 4,4-difluoro-cyclohexyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25 45) Further preferred compounds of formula (I) as defined in embodiment 1) are selected from the group consisting of:

4-Ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

30 7-Acetyl-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

7-Methyl-4-trifluoromethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

4,7-Dimethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

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- 4-Methyl-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Methyl-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 5 4-Chloro-7-ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 7-Chloro-4-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 7-Methoxy-4-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 10 4-Chloro-7-ethoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-propyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 15 7-(2-tert-Butoxy-ethoxy)-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-(2-hydroxy-ethoxy)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-methoxy-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 20 4-Chloro-7-methoxy-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-(1-hydroxy-1-methyl-ethyl)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 25 4,7-Difluoro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide; and
- 4-Fluoro-7-methoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- or salts (in particular pharmaceutically acceptable salts) of such compounds;
- 30 it is to be understood for any of the above listed compounds, that a stereogenic center, which is not specifically assigned, may be in absolute (*R*)- or absolute (*S*)-configuration; notably, the stereogenic center at the carbon atom attached to R¹ and R² may be in absolute (*R*)-configuration or absolute (*S*)-configuration. For example a compound listed as 4-Chloro-7-ethoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide may be 4-Chloro-7-ethoxy-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-
- 35

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pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide, 4-Chloro-7-ethoxy-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide or any mixture thereof.

It is well understood that the invention relates to compounds according to embodiment 1); or according to embodiment 1) limited by the features of an embodiment dependent on
 5 embodiment 1; or according to embodiment 1) limited by the features of a cascade of dependent embodiments in the form of “embodiment 3) depending on embodiment 2) depending on embodiment 1)”. In case of an embodiment depending on more than one other embodiment, it is understood that each combination is specifically disclosed. Also, in case an embodiment is dependent on more than one other embodiment and one or more
 10 of said other embodiments are themselves dependent on one or more further embodiments, it is understood that each combination is specifically disclosed if obtainable with regard to the given dependencies and multiple dependencies. Notably, embodiments resulting from cascades of more than three embodiments depending on each other may be construed under observance of the given dependencies and multiple dependencies
 15 and are thus intended to be specifically disclosed. Representative examples of embodiments which are possible based on the dependencies of the embodiments 1) to 45) as disclosed hereinabove and which are therefore intended and herewith specifically disclosed in individualized form are:

1, 1P+1, 2+1P+1, 3+1P+1, 4+1P+1, 5+1P+1, 6+1P+1, Y10, Y9, Y8, Y7, 7+Y10, 7+Y9, Y6,
 20 Y5, 8+Y10, 8+Y9, 8+Y8, 8+Y7, 8+7+Y10, 8+7+Y9, Y4, Y3, 9+Y10, 9+Y9, 9+Y6, 9+Y5, 9+8+Y10, 9+8+Y9, 9+8+Y8, 9+8+Y7, 9+8+7+Y10, 9+8+7+Y9, 10+3+1P+1, 10+6+1P+1, 10+Y10, 10+Y9, 10+Y4, 10+Y3, 10+9+Y10, 10+9+Y9, 10+9+Y6, 10+9+Y5, 10+9+8+Y10, 10+9+8+Y9, 10+9+8+Y8, 10+9+8+Y7, 10+9+8+7+Y10, 10+9+8+7+Y9, 11+3+1P+1, 11+6+1P+1, 11+Y10, 11+Y9, 11+10+3+1P+1, 11+10+6+1P+1, 11+10+Y10, 11+10+Y9,
 25 Y2+3+1P+1, Y2+6+1P+1, Y2+Y10, Y2+Y9, Y2+Y6, Y2+Y5, Y2+8+Y10, Y2+8+Y9, Y2+8+Y8, Y2+8+Y7, Y2+8+7+Y10, Y2+8+7+Y9, 12+3+1P+1, 12+6+1P+1, 12+Y10, 12+Y9, 12+Y6, 12+Y5, 12+8+Y10, 12+8+Y9, 12+8+Y8, 12+8+Y7, 12+8+7+Y10, 12+8+7+Y9, 12+11+3+1P+1, 12+11+6+1P+1, 12+11+Y10, 12+11+Y9, Y1+3+1P+1, Y1+6+1P+1, Y1+Y10, Y1+Y9, Y1+Y4, Y1+Y3, Y1+9+Y10, Y1+9+Y9, Y1+9+Y6,
 30 Y1+9+Y5, Y1+9+8+Y10, Y1+9+8+Y9, Y1+9+8+Y8, Y1+9+8+Y7, Y1+9+8+7+Y10, Y1+9+8+7+Y9, 13+3+1P+1, 13+6+1P+1, 13+Y10, 13+Y9, 13+11+3+1P+1, 13+11+6+1P+1, 13+11+Y10, 13+11+Y9, 13+11+10+3+1P+1, 13+11+10+6+1P+1, 13+11+10+Y10, 13+11+10+Y9, 13+Y2+3+1P+1, 13+Y2+6+1P+1, 13+Y2+Y10, 13+Y2+Y9, 13+Y2+Y6, 13+Y2+Y5, 13+Y2+8+Y10, 13+Y2+8+Y9, 13+Y2+8+Y8,
 35 13+Y2+8+Y7, 13+Y2+8+7+Y10, 13+Y2+8+7+Y9, 13+12+3+1P+1, 13+12+6+1P+1,

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- 13+12+Y10, 13+12+Y9, 13+12+Y6, 13+12+Y5, 13+12+8+Y10, 13+12+8+Y9,
 13+12+8+Y8, 13+12+8+Y7, 13+12+8+7+Y10, 13+12+8+7+Y9, 13+12+11+3+1P+1,
 13+12+11+6+1P+1, 13+12+11+Y10, 13+12+11+Y9, 13+Y1+3+1P+1, 13+Y1+6+1P+1,
 13+Y1+Y10, 13+Y1+Y9, 13+Y1+Y4, 13+Y1+Y3, 13+Y1+9+Y10, 13+Y1+9+Y9,
 5 13+Y1+9+Y6, 13+Y1+9+Y5, 13+Y1+9+8+Y10, 13+Y1+9+8+Y9, 13+Y1+9+8+Y8,
 13+Y1+9+8+Y7, 13+Y1+9+8+7+Y10, 13+Y1+9+8+7+Y9, 14+3+1P+1, 14+6+1P+1,
 14+Y10, 14+Y9, 14+12+3+1P+1, 14+12+6+1P+1, 14+12+Y10, 14+12+Y9, 14+12+Y6,
 14+12+Y5, 14+12+8+Y10, 14+12+8+Y9, 14+12+8+Y8, 14+12+8+Y7, 14+12+8+7+Y10,
 14+12+8+7+Y9, 14+12+11+3+1P+1, 14+12+11+6+1P+1, 14+12+11+Y10, 14+12+11+Y9,
 10 14+Y1+3+1P+1, 14+Y1+6+1P+1, 14+Y1+Y10, 14+Y1+Y9, 14+Y1+Y4, 14+Y1+Y3,
 14+Y1+9+Y10, 14+Y1+9+Y9, 14+Y1+9+Y6, 14+Y1+9+Y5, 14+Y1+9+8+Y10, 14+Y1+9+
 8+Y9, 14+Y1+9+8+Y8, 14+Y1+9+8+Y7, 14+Y1+9+8+7+Y10, 14+Y1+9+8+7+Y9,
 15+13+3+1P+1, 15+13+6+1P+1, 15+13+Y10, 15+13+Y9, 15+13+11+3+1P+1, 15+13+
 11+6+1P+1, 15+13+11+Y10, 15+13+11+Y9, 15+13+11+10+3+1P+1, 15+13+11+10+
 15 6+1P+1, 15+13+11+10+Y10, 15+13+11+10+Y9, 15+13+Y2+3+1P+1, 15+13+Y2+6+
 1P+1, 15+13+Y2+Y10, 15+13+Y2+Y9, 15+13+Y2+Y6, 15+13+Y2+Y5, 15+13+Y2+8+Y10,
 15+13+Y2+8+Y9, 15+13+Y2+8+Y8, 15+13+Y2+8+Y7, 15+13+Y2+8+7+Y10,
 15+13+Y2+8+7+Y9, Z8+3+1P+1, Z8+6+1P+1, Z8+Y10, Z8+Y9, Z8+Y6, Z8+Y5,
 Z8+8+Y10, Z8+8+Y9, Z8+8+Y8, Z8+8+Y7, Z8+8+7+Y10, Z8+8+7+Y9, Z8+11+3+1P+1,
 20 Z8+11+6+1P+1, Z8+11+Y10, Z8+11+Y9, 15+13+Y1+3+1P+1, 15+13+Y1+6+1P+1,
 15+13+Y1+Y10, 15+13+Y1+Y9, 15+13+Y1+Y4, 15+13+Y1+Y3, 15+13+Y1+9+Y10,
 15+13+Y1+9+Y9, 15+13+Y1+9+Y6, 15+13+Y1+9+Y5, 15+13+Y1+9+8+Y10,
 15+13+Y1+9+8+Y9, 15+13+Y1+9+8+Y8, 15+13+Y1+9+8+Y7, 15+13+Y1+9+8+7+Y10,
 15+13+Y1+9+8+7+Y9, 16+13+3+1P+1, 16+13+6+1P+1, 16+13+Y10, 16+13+Y9,
 25 16+13+11+3+1P+1, 16+13+11+6+1P+1, 16+13+11+Y10, 16+13+11+Y9, 16+13+11+10+
 3+1P+1, 16+13+11+10+6+1P+1, 16+13+11+10+Y10, 16+13+11+10+Y9, 16+13+Y2+3+
 1P+1, 16+13+Y2+6+1P+1, 16+13+Y2+Y10, 16+13+Y2+Y9, 16+13+Y2+Y6,
 16+13+Y2+Y5, 16+13+Y2+8+Y10, 16+13+Y2+8+Y9, 16+13+Y2+8+Y8, 16+13+Y2+
 8+Y7, 16+13+Y2+8+7+Y10, 16+13+Y2+8+7+Y9, 16+13+12+3+1P+1, 16+13+12+6+
 30 1P+1, 16+13+12+Y10, 16+13+12+Y9, 16+13+12+Y6, 16+13+12+Y5, 16+13+12+8+Y10,
 16+13+12+8+Y9, 16+13+12+8+Y8, 16+13+12+8+Y7, 16+13+12+8+7+Y10, 16+13+12+
 8+7+Y9, 16+13+12+11+3+1P+1, 16+13+12+11+6+1P+1, 16+13+12+11+Y10,
 16+13+12+11+Y9, 16+13+Y1+3+1P+1, 16+13+Y1+6+1P+1, 16+13+Y1+Y10,
 16+13+Y1+Y9, 16+13+Y1+Y4, 16+13+Y1+Y3, 16+13+Y1+9+Y10, 16+13+Y1+9+Y9,
 35 16+13+Y1+9+Y6, 16+13+Y1+9+Y5, 16+13+Y1+9+8+Y10, 16+13+Y1+9+8+Y9,

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- 16+13+Y1+9+8+Y8, 16+13+Y1+9+8+Y7, 16+13+Y1+9+8+7+Y10, 16+13+Y1+9+8+7+Y9,
 17+13+3+1P+1, 17+13+6+1P+1, 17+13+Y10, 17+13+Y9, Z7+3+1P+1, Z7+6+1P+1,
 Z7+Y10, Z7+Y9, Z7+10+3+1P+1, Z7+10+6+1P+1, Z7+10+Y10, Z7+10+Y9,
 17+13+Y2+3+1P+1, 17+13+Y2+6+1P+1, 17+13+Y2+Y10, 17+13+Y2+Y9, 17+13+Y2+Y6,
 5 17+13+Y2+Y5, 17+13+Y2+8+Y10, 17+13+Y2+8+Y9, 17+13+Y2+8+Y8, 17+13+Y2+8+Y7,
 17+13+Y2+8+7+Y10, 17+13+Y2+8+7+Y9, Z6+3+1P+1, Z6+6+1P+1, Z6+Y10, Z6+Y9,
 Z6+Y6, Z6+Y5, Z6+8+Y10, Z6+8+Y9, Z6+8+Y8, Z6+8+Y7, Z6+8+7+Y10, Z6+8+7+Y9,
 Z6+11+3+1P+1, Z6+11+6+1P+1, Z6+11+Y10, Z6+11+Y9, 17+13+Y1+3+1P+1,
 17+13+Y1+6+1P+1, 17+13+Y1+Y10, 17+13+Y1+Y9, 17+13+Y1+Y4, 17+13+Y1+Y3,
 10 17+13+Y1+9+Y10, 17+13+Y1+9+Y9, 17+13+Y1+9+Y6, 17+13+Y1+9+Y5,
 17+13+Y1+9+8+Y10, 17+13+Y1+9+8+Y9, 17+13+Y1+9+8+Y8, 17+13+Y1+9+8+Y7,
 17+13+Y1+9+8+7+Y10, 17+13+Y1+9+8+7+Y9, Z5+3+1P+1, Z5+6+1P+1, Z5+Y10,
 Z5+Y9, Z5+11+3+1P+1, Z5+11+6+1P+1, Z5+11+Y10, Z5+11+Y9, Z5+11+10+3+1P+1,
 Z5+11+10+6+1P+1, Z5+11+10+Y10, Z5+11+10+Y9, Z5+Y2+3+1P+1, Z5+Y2+6+1P+1,
 15 Z5+Y2+Y10, Z5+Y2+Y9, Z5+Y2+Y6, Z5+Y2+Y5, Z5+Y2+8+Y10, Z5+Y2+8+Y9,
 Z5+Y2+8+Y8, Z5+Y2+8+Y7, Z5+Y2+8+7+Y10, Z5+Y2+8+7+Y9, Z5+12+3+1P+1,
 Z5+12+6+1P+1, Z5+12+Y10, Z5+12+Y9, Z5+12+Y6, Z5+12+Y5, Z5+12+8+Y10,
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 Z5+12+11+3+1P+1, Z5+12+11+6+1P+1, Z5+12+11+Y10, Z5+12+11+Y9,
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 18+17+13+Y9, 18+Z7+3+1P+1, 18+Z7+6+1P+1, 18+Z7+Y10, 18+Z7+Y9,
 25 18+Z7+10+3+1P+1, 18+Z7+10+6+1P+1, 18+Z7+10+Y10, 18+Z7+10+Y9,
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 18+17+13+Y2+Y6, 18+17+13+Y2+Y5, 18+17+13+Y2+8+Y10, 18+17+13+Y2+8+Y9,
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 30 18+Z6+8+Y10, 18+Z6+8+Y9, 18+Z6+8+Y8, 18+Z6+8+Y7, 18+Z6+8+7+Y10, 18+Z6+
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 18+17+13+Y1+9+Y6, 18+17+13+Y1+9+Y5, 18+17+13+Y1+9+8+Y10, 18+17+13+Y1+
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18+17+13+Y1+9+8+7+Y9, Z4+3+1P+1, Z4+6+1P+1, Z4+Y10, Z4+Y9, Z4+11+3+1P+1,
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 Z3+Y10, Z3+Y9, Z3+11+3+1P+1, Z3+11+6+1P+1, Z3+11+Y10, Z3+11+Y9,
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 Z1+Y10, Z1+Y9, Z1+11+3+1P+1, Z1+11+6+1P+1, Z1+11+Y10, Z1+11+Y9,
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 35 Z1+Y2+3+1P+1, Z1+Y2+6+1P+1, Z1+Y2+Y10, Z1+Y2+Y9, Z1+Y2+Y6, Z1+Y2+Y5,

- 30 -

- $Z1+Y2+8+Y10$, $Z1+Y2+8+Y9$, $Z1+Y2+8+Y8$, $Z1+Y2+8+Y7$, $Z1+Y2+8+7+Y10$,
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35 $20+18+17+13+3+1P+1$, $20+18+17+13+6+1P+1$, $20+18+17+13+Y10$, $20+18+17+13+Y9$,

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- 20+18+Z7+3+1P+1, 20+18+Z7+6+1P+1, 20+18+Z7+Y10, 20+18+Z7+Y9,
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 5 20+18+17+13+Y2+8+Y9, 20+18+17+13+Y2+8+Y8, 20+18+17+13+Y2+8+Y7, 20+18+17+
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 20 22+13+Y2+8+7+Y10, 22+13+Y2+8+7+Y9, 22+13+12+3+1P+1, 22+13+12+6+1P+1,
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 22+13+12+8+Y9, 22+13+12+8+Y8, 22+13+12+8+Y7, 22+13+12+8+7+Y10,
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 22+13+Y1+9+8+Y8, 22+13+Y1+9+8+Y7, 22+13+Y1+9+8+7+Y10, 22+13+Y1+9+8+7+Y9,
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 23+13+Y1+9+Y6, 23+13+Y1+9+Y5, 23+13+Y1+9+8+Y10, 23+13+Y1+9+8+Y9,
 5 23+13+Y1+9+8+Y8, 23+13+Y1+9+8+Y7, 23+13+Y1+9+8+7+Y10, 23+13+Y1+9+8+7+Y9,
 24+13+3+1P+1, 24+13+6+1P+1, 24+13+Y10, 24+13+Y9, 24+13+11+3+1P+1,
 24+13+11+6+1P+1, 24+13+11+Y10, 24+13+11+Y9, 24+13+11+10+3+1P+1,
 24+13+11+10+6+1P+1, 24+13+11+10+Y10, 24+13+11+10+Y9, 24+13+Y2+3+1P+1,
 24+13+Y2+6+1P+1, 24+13+Y2+Y10, 24+13+Y2+Y9, 24+13+Y2+Y6, 24+13+Y2+Y5,
 10 24+13+Y2+8+Y10, 24+13+Y2+8+Y9, 24+13+Y2+8+Y8, 24+13+Y2+8+Y7,
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 35 32+24+13+Y2+8+7+Y10, 32+24+13+Y2+8+7+Y9, 32+24+13+12+3+1P+1,

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 32+25+Z3+Y1+Y10, 32+25+Z3+Y1+Y9, 32+25+Z3+Y1+Y4, 32+25+Z3+Y1+Y3,
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wherein the following abbreviations are used: Y1 means 12+11+10; Y2 means 11+10+9;

Y3 means 9+6+1P+1; Y4 means 9+3+1P+1; Y5 means 8+6+1P+1; Y6 means 8+3+1P+1; Y7 means 7+6+1P+1; Y8 means 7+3+1P+1; Y9 means 6+4+1P+1; Y10 means 6+3+1P+1; Z1 means 19+18+17+13; Z2 means 19+18+15+13; Z3 means 19+17+13; Z4 means 19+15+13; Z5 means 18+15+13; Z6 means 17+13+12; Z7 means 17+13+11; Z8 means 15+13+12; and

wherein the list above is not to be construed as limiting with respect to further embodiments which are also possible based on the dependencies of the embodiments 1) to 45) as disclosed hereinabove and which are also intended. In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the dependency from another embodiment. The different individualized embodiments are separated by commas. In other words, "6+3+1P+1" for example refers to embodiment 6) depending on embodiment 3) depending on embodiment 1P) depending on embodiment 1), i.e. embodiment "6+3+1P+1" corresponds to embodiment 1) further limited by the features of embodiments 1P), 3) and 6).

The present invention also includes isotopically labelled, especially ^2H (deuterium) labelled compounds of formula (I), which compounds are identical to the compounds of

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formula (I) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ^2H (deuterium) labelled compounds of formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen
5 with the heavier isotope ^2H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formula (I) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the
10 compounds of formula (I) are not isotopically labelled at all. Isotopically labelled compounds of formula (I) may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

The term "pharmaceutically acceptable salts" refers to non-toxic, inorganic or organic acid
15 and/or base addition salts, Lit. e.g. "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

The compounds of formula (I) according to any one of embodiments 1) to 45), or
20 pharmaceutically acceptable salts thereof, are suitable for use as medicaments. In particular, compounds of formula (I) modulate the P2X_7 receptor, i.e. they act as P2X_7 receptor antagonists, and are useful for the prevention or treatment of diseases which are associated with the activation of the P2X_7 receptor such as pain; neurodegenerative and neuroinflammatory diseases; bone and joint diseases; obstructive diseases of the airways;
25 cardiovascular diseases; eye diseases; skin diseases; abdominal and gastrointestinal tract diseases; genitourinary diseases; cancer; other auto-immune and allergic disorders; and other disorders with an inflammatory or immunological component.

In particular, the compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment
30 of pain. Pain refers to acute pain; chronic pain; pain associated with sprains and strains; chronic articular pain; pain associated with rheumatic fever; musculoskeletal pain; lower back and neck pain; inflammatory pain; neuropathic pain; visceral pain; pain associated with influenza or other viral infections; pain associated with cancer and tumor invasion; joint and bone pain; atypical facial pain; pain associated with migraine, toothache and

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dysmenorrhea; headache including tension headache and cluster headaches; pain associated with myocardial ischemia; pain associated with functional bowel disorders; sympathetically maintained pain; myositis; pain associated with cancer chemotherapy; and post operative pain.

- 5 Neuropathic pain includes especially diabetic neuropathy, sciatica, non-specific lower back pain, trigeminal neuralgia, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, and pain resulting from physical trauma, amputation, phantom limb syndrome, spinal surgery, cancer, toxins or chronic inflammatory conditions. In addition, neuropathic pain conditions include pain associated with normally non-painful
10 sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static, thermal or cold allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways
15 (hypoalgesia).

Chronic articular pain conditions include especially rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

Pain associated with functional bowel disorders includes especially non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome.

- 20 Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of neurodegenerative and neuroinflammatory diseases. Neurodegenerative and neuro-inflammatory diseases include Alzheimer's disease and other dementing disorders including, but not limited to, Creutzfeldt–Jakob disease (CJD) and new variant
25 Creutzfeldt–Jakob disease (nvCJD); Amyotrophic lateral sclerosis, amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; Huntington's disease; Lewy Body dementia; and Parkinson's disease.

- Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
30 pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of bone and joint diseases. Bone and joint diseases include arthritides such as rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy; intervertebral disc degeneration; temporomandibular joint degeneration; bone remodelling disease such as osteoporosis, Paget's disease or osteonecrosis; polychondritis; scleroderma; mixed connective tissue
35 disorder; spondyloarthropathies; periodontal disease such as periodontitis; arthritides

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associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis; Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondyloarthropathy; septic arthritis and other

5 infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus

10 erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis,

15 Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; and drug-induced arthralgias, tendonitis, and myopathies including dystrophies and other inflammatory myopathies.

20 Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of obstructive diseases of the airways. Obstructive diseases of the airways include asthma, including bronchial, allergic, intrinsic, and extrinsic asthma, exercise-induced, drug-

25 induced (including aspirin and NSAID-induced) and dust- induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias,

30 fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis

35 including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic

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rhinitis including rhinitis nervosa (hay fever); nasal polyposis; and acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
5 pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of cardiovascular diseases. Cardiovascular diseases include atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis; inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides;
10 and disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of
eye diseases. Eye diseases include blepharitis; conjunctivitis, including perennial and
15 vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; and infections of the eyes including viral, fungal, and bacterial infections.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
20 pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of skin diseases. Skin diseases include psoriasis, skin burn, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus
25 erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; and drug-induced disorders including fixed drug
30 eruptions.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of
abdominal and gastrointestinal tract diseases. Abdominal and gastrointestinal tract
diseases include hepatitis, including autoimmune, alcoholic and viral hepatitis; fibrosis and

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cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic; non-inflammatory diarrhea; glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; Coeliac disease, irritable bowel disease/syndrome, and food-related allergies
5 which may have effects remote from the gut, for example migraine, rhinitis or eczema; allograft rejection including acute and chronic allograft rejection following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; and chronic graft versus host disease;

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
10 pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of genitourinary diseases. Genitourinary diseases include nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, hemorrhagic cystitis, prostatitis, epididymitis, oophoritis and salpingitis; vulvovaginitis; Peyronie's disease; and erectile
15 dysfunction, both male and female.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of cancer. The treatment of cancer includes the treatment of brain tumors, prostate, lung, breast, ovarian, bowel and colon, stomach, pancreatic, skin and bone marrow (including
20 leukaemias) and lymphoproliferative systems, such as non-Hodgkin's and Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumor recurrences, and paraneoplastic syndromes.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of
25 other auto-immune and allergic disorders. Other auto-immune and allergic disorders include Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, and antiphospholipid syndrome.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
30 pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of other disorders with an inflammatory or immunological component. Other disorders with an inflammatory or immunological component include acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes.

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Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of mood, depression, sleep and anxiety disorders.

Further, the compounds of formula (I) according to any one of embodiments 1) to 45), or
5 pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of injury induced trauma and spinal cord injury.

Especially, compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of diseases selected from one, several or all of the following groups of diseases and
10 disorders:

1) Pain, wherein pain refers to acute pain; chronic pain; pain associated with sprains and strains; chronic articular pain; pain associated with rheumatic fever; musculoskeletal pain; lower back and neck pain; inflammatory pain; neuropathic pain; visceral pain; pain associated with influenza or other viral infections; pain
15 associated with cancer and tumor invasion; joint and bone pain; atypical facial pain; pain associated with migraine, toothache and dysmenorrhea; headache including tension headache and cluster headaches; pain associated with myocardial ischemia; pain associated with functional bowel disorders; sympathetically maintained pain; myositis; pain associated with cancer
20 chemotherapy; and post operative pain;

Neuropathic pain includes especially diabetic neuropathy, sciatica, non-specific lower back pain, trigeminal neuralgia, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and pain resulting from physical trauma, amputation, phantom limb syndrome, spinal
25 surgery, cancer, toxins or chronic inflammatory conditions. In addition, neuropathic pain conditions include pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static, thermal or cold allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the
30 stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia);

Chronic articular pain conditions include especially rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis;

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Pain associated with functional bowel disorders includes especially non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome;

- 2) Neurodegenerative and neuro-inflammatory diseases such as Alzheimer's disease and other dementing disorders including, but not limited to, Creutzfeldt–Jakob disease (CJD) and new variant Creutzfeldt–Jakob disease (nvCJD); amyloidosis; Amyotrophic lateral sclerosis, multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; Huntington's disease; Lewy Body dementia; and Parkinson's disease;
- 3) Bone and joint diseases such as arthritides such as rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy; intervertebral disc degeneration; temporomandibular joint degeneration; bone remodelling disease such as osteoporosis, Paget's disease or osteonecrosis; polychondritis; scleroderma; mixed connective tissue disorder; spondyloarthropathies; periodontal disease such as periodontitis; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; and drug-induced arthralgias, tendonitis, and myopathies;
- 4) Obstructive diseases of the airways such as chronic obstructive pulmonary disease (COPD); cystic fibrosis; lung emphysema; sarcoidosis; farmer's lung and related diseases; lung fibrosis, including fibrosis complicating tuberculosis; and chronic cough associated with inflammatory and secretory conditions of the airways;
- 5) Cardiovascular diseases such as inflammatory and auto-immune cardio-myopathies;
- 6) Eye diseases such as degenerative or inflammatory disorders affecting the retina;
- 7) Skin diseases such as psoriasis, skin burn, atopic dermatitis, contact dermatitis or other eczematous dermatoses; and discoid lupus erythematosus;

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- 8) Abdominal and gastrointestinal tract diseases such as fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic; Crohn's disease; colitis including ulcerative colitis; and irritable bowel disease/syndrome;
- 9) Genitourinary diseases such as nephritis including interstitial and glomerulonephritis; nephrotic syndrome; and cystitis including acute and chronic (interstitial) cystitis; and
- 10) Other auto-immune and allergic disorders such as Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, and antiphospholipid syndrome.

Most preferably, compounds of formula (I) according to any one of embodiments 1) to 45), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of diseases selected from one, several or all of the following groups of diseases and disorders:

- 1) Pain, wherein pain refers to acute pain; chronic pain; pain associated with sprains and strains; chronic articular pain; pain associated with rheumatic fever; musculoskeletal pain (preferred); lower back and neck pain; inflammatory pain; neuropathic pain (preferred); visceral pain; pain associated with influenza or other viral infections; pain associated with cancer and tumor invasion; joint and bone pain; atypical facial pain; pain associated with migraine, toothache and dysmenorrhea; headache including tension headache and cluster headaches; pain associated with myocardial ischemia; pain associated with functional bowel disorders; sympathetically maintained pain; myositis; pain associated with cancer chemotherapy; and post operative pain;
- Neuropathic pain includes especially diabetic neuropathy, sciatica, non-specific lower back pain, trigeminal neuralgia, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and pain resulting from physical trauma, amputation, phantom limb syndrome, spinal surgery, cancer, toxins or chronic inflammatory conditions. In addition, neuropathic pain conditions include pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static, thermal or cold allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the

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stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia);

Chronic articular pain conditions include especially rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis;

5 Pain associated with functional bowel disorders includes especially non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome;

2) Rheumatoid arthritis and osteoarthritis;

3) Chronic obstructive pulmonary disease (COPD); and

4) Crohn's disease.

10 The invention also relates to the use of a compound of formula (I) according to any one of embodiments 1) to 45) for the preparation of pharmaceutical compositions for the treatment and/or prophylaxis of the above-mentioned diseases.

The present invention also relates to pharmaceutically acceptable salts and to pharmaceutical compositions and formulations of compounds of formula (I) according to
15 any one of embodiments 1) to 45).

A pharmaceutical composition according to the present invention contains at least one compound of formula (I) according to any one of embodiments 1) to 45) (or a pharmaceutically acceptable salt thereof) as the active agent and optionally carriers and/or diluents and/or adjuvants.

20 The compounds of formula (I) according to any one of embodiments 1) to 45) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such as especially oral) or parenteral administration (including topical application or inhalation).

The production of the pharmaceutical compositions can be effected in a manner which will
25 be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula (I) or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with
30 suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of formula (I) according to any one of
35 embodiments 1) to 45), or a pharmaceutically acceptable salt thereof.

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Any reference to a compound of formula (I), (I_{Ar}), (I_{St1}) or (I_{St2}) in this text is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient. The preferences indicated for the compounds of formula (I) of course apply *mutatis mutandis* to the compounds of formula (I_{Ar}), of formula (I_{St1}) and of formula (I_{St2}) as well as to the salts and pharmaceutically acceptable salts of the compounds of formula (I), of formula (I_{Ar}), of formula (I_{St1}) and of formula (I_{St2}). The same applies to these compounds as medicaments, to pharmaceutical compositions containing these compounds as active principles or to the uses of these compounds for the manufacture of a medicament for the treatment of the diseases according to this invention.

Unless used regarding temperatures, the term "about" (or alternatively "around") placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" (or alternatively "around") placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C. Besides, the term "room temperature" (RT) as used herein refers to a temperature of about 25°C.

Whenever the word "between" is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a temperature range is described to be between 40 °C and 80 °C, this means that the end points 40 °C and 80 °C are included in the range; or if a variable is defined as being an integer between 1 and 4, this means that the variable is the integer 1, 2, 3, or 4.

The compounds of Formula (I) can be manufactured by the methods given below, by the methods given in the Examples or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures.

If not indicated otherwise, the generic groups **R¹**, **R²**, **R³**, **R⁴**, **R⁵** and **R⁶** are as defined for formula (I). Other abbreviations used are defined in the experimental section.

In some instances the generic groups **R¹**, **R²**, **R³**, **R⁴**, **R⁵** and **R⁶** might be incompatible with the assembly illustrated in the schemes below and will therefore require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-

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Interscience, 1999). For the purposes of this discussion, it will be assumed that such protecting groups are as necessary in place.

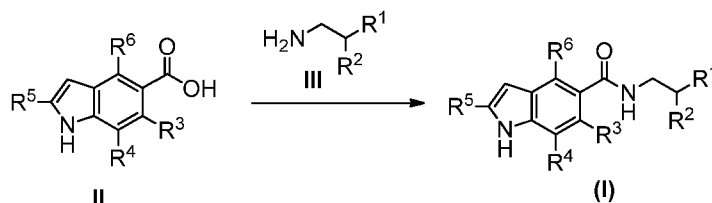
PREPARATION OF COMPOUNDS OF FORMULA (I)

Compounds of formula (I) can be prepared (Scheme 1) by reaction of carboxylic acids of formula II with amines of formula III using standard amide coupling reagents such as TBTU, EDC.HCl/HOBt, HATU or PyBOP in the presence of a suitable base such as DIPEA or Et₃N and in a suitable solvent such as DCM, THF or DMF preferably at temperatures between RT and 45°C.

Compounds of formula (I) wherein R⁴ represents –CH(OH)Me can be prepared by reduction of compounds of formula (I) wherein R⁴ represents acetyl using a suitable reducing reagent such as NaBH₄ in a suitable solvent such as MeOH at temperatures around RT. Other primary or secondary alcohols may be prepared in analogy.

Compounds of formula (I) wherein R⁴ represents –C(OH)Me₂ can be prepared from compounds of formula (I) wherein R⁴ represents acetyl by addition of a methylmagnesium halide solution in the presence of a suitable solvent such as THF at temperatures between -10°C and RT. Other tertiary alcohols may be prepared in analogy.

Compounds of formula (I) wherein R⁴ represents hydroxy-(C₂-C₄)alkoxy can be prepared from compounds of formula (I) wherein R⁴ represents *tert*-butoxy-(C₂-C₄)alkoxy by treatment with a suitable acid such as TFA in a suitable solvent such as DCM at temperatures around RT.



Scheme 1: General synthesis of compounds of formula (I)

Compounds of formula Ia wherein Y represents N or CH (Scheme 2) can be prepared as previously described in Scheme 1.

Compounds of formula Ib wherein Y represents N or CH (Scheme 2) can be prepared by cleavage of the Boc protecting group in compounds of formula Ia by treatment with a suitable acid such as HCl or TFA in the presence of a suitable solvent such as dioxane, EtOAc or DCM at temperatures around RT.

Compounds of formula Ic wherein Y represents N or CH and wherein R¹⁰ represents (C₁-C₄)alkyl (Scheme 2) can be prepared by reductive alkylation of amines of formula Ib with a

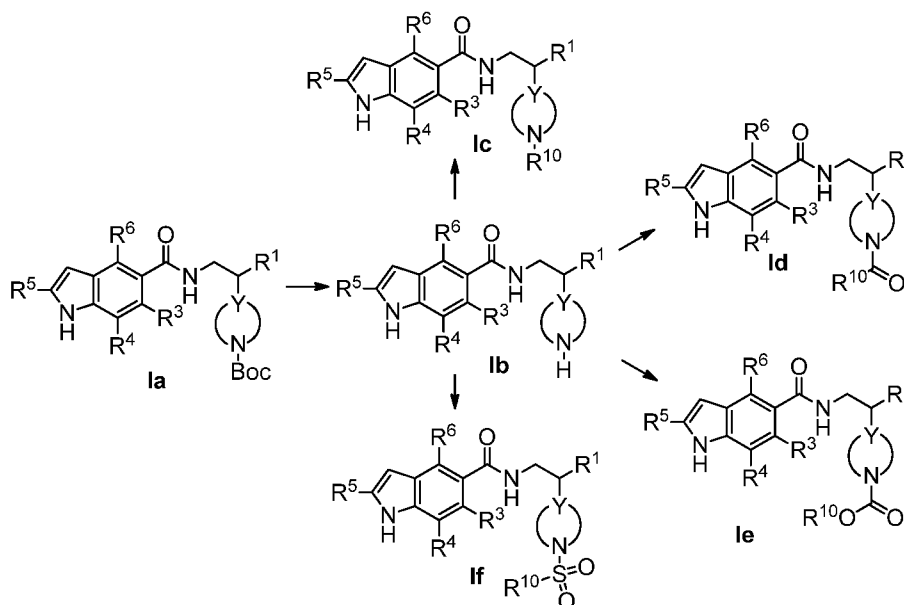
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suitable aldehyde or ketone in the presence of a suitable reducing agent such as $\text{NaBH}(\text{OAc})_3$, NaBH_3CN or NaBH_4 in a suitable solvent such as dichloroethane or mixture of solvents such as $\text{DCM}/\text{MeOH}/\text{AcOH}$ at temperatures around RT.

Compounds of formula Id wherein Y represents N or CH and wherein R^{10} represents (C₁-C₄)alkyl (Scheme 2) can be prepared by acylation of amines of formula Ib by treatment with a suitable acid chloride or acid anhydride in the presence of a suitable base such as Et_3N or DIPEA and in a suitable solvent such as DCM or THF at temperatures between 0°C and 50°C.

Compounds of formula Ie wherein Y represents N or CH and wherein R^{10} represents (C₁-C₄)alkyl (Scheme 2) can be prepared by alkoxycarbonylation of amines of formula Ib by treatment with a suitable alkyl chloroformate in the presence of a suitable base such as Et_3N or DIPEA and in a suitable solvent such as DCM or THF at temperatures between 0°C and 50°C.

Compounds of formula If wherein Y represents N or CH and wherein R^{10} represents (C₁-C₄)alkyl (Scheme 2) can be prepared by sulfonation of amines of formula Ib by treatment with a suitable alkyl sulfonyl chloride in the presence of a suitable base such as Et_3N or DIPEA and in a suitable solvent such as DCM or THF at temperatures between 0°C and 50°C.



20 Scheme 2: Synthesis of compounds of formula I wherein R^2 represents heterocyclyl (Y represents N or CH and R^{10} represents (C₁-C₄)alkyl)

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Indole carboxylic acids of formula IIa can be prepared according to the synthetic routes given in scheme 3.

Regioisomers of formula XII wherein Y represents methoxycarbonyl or cyano, together with various amounts of regioisomer XI, (Scheme 3) can be prepared by iodination of anilines of formula XIV, wherein Y represents methoxycarbonyl or cyano, using about 1.05 equivalents of a suitable iodinating reagent such as iodine in the presence of a catalyst such as silver sulfate and in a suitable solvent such as EtOH at temperatures around RT. The separation of both regioisomers can be achieved by standard CC.

Compounds of formula IX wherein R⁴ represents hydrogen and wherein Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by Sonogashira type cross-coupling of iodides of formula XI wherein Y represents methoxycarbonyl or cyano with trimethylsilylacetylene in the presence of a suitable palladium catalyst such as bis(triphenylphosphine)palladium(II) dichloride, in the presence of a suitable copper catalyst such as copper iodide, in the presence of a ligand such as triphenylphosphine, in the presence of a suitable base such as Et₃N and heating in a suitable solvent such as toluene at temperatures between 50°C and 100°C.

Alternatively, compounds of formula IX wherein R⁴ represents (C₁-C₄)alkyl or (C₁-C₂)alkoxy-(C₁-C₄)alkyl and wherein Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared from iodides of formula VII wherein R⁴ represents (C₁-C₄)alkyl or (C₁-C₂)alkoxy-(C₁-C₄)alkyl and wherein Y represents methoxycarbonyl or cyano using Sonogashira cross-coupling conditions such as those described above. Compounds of formula VII wherein R⁴ represents (C₁-C₄)alkyl or (C₁-C₂)alkoxy-(C₁-C₄)alkyl and wherein Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by iodination of anilines of formula VIII wherein R⁴ represents (C₁-C₄)alkyl or (C₁-C₂)alkoxy-(C₁-C₄)alkyl and wherein Y represents methoxycarbonyl or cyano following standard iodination conditions such as those previously described for the synthesis of compounds of formula XI and XII. Compounds of formula VIII wherein R⁴ represents (C₁-C₄)alkyl or (C₁-C₂)alkoxy-(C₁-C₄)alkyl and Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by Negishi (or Suzuki, respectively) type cross-coupling of iodides of formula XII wherein Y represents methoxycarbonyl or cyano with organozinc reagents of type R⁴ZnX (or boronic acid of type R⁴B(OH)₂, respectively) wherein R⁴ represents (C₁-C₄)alkyl or (C₁-C₂)alkoxy-(C₁-C₄)alkyl and X represents chloro, bromo or (C₁-C₄)alkyl, in the presence of a suitable palladium catalyst such as Pd(dppf)Cl₂.DCM (or bis(triphenylphosphine)palladium(II) dichloride and in the additional presence of a base such as K₃PO₄, respectively) and heating in a suitable solvent such as dioxane (or a

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mixture of toluene/water 20/1, respectively) at temperatures between 50°C and 100°C (or around 110°C, respectively).

Alternatively, compounds of formula VIII (Scheme 3) wherein R⁴ represents (C₃-C₄)alkyl or (C₁-C₂)alkoxy-(C₃-C₄)alkyl and Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by Sonogashira type cross-coupling of iodides of formula XII wherein Y represents methoxycarbonyl or cyano with (C₁-C₂)alkylacetylene or (C₁-C₂)alkoxy-(C₁-C₂)alkylacetylene in the presence of a suitable palladium catalyst such as bis(triphenylphosphine)palladium(II) dichloride, in the presence of a suitable copper catalyst such as copper iodide, in the presence of a suitable base such as Et₃N and heating in a suitable solvent such as THF at temperatures between RT and 80°C. The subsequent reduction of the triple bond can be carried out under hydrogenation conditions in the presence of a suitable catalyst such as PtO₂ and a suitable solvent such as EtOH at temperatures around RT. Alternatively, when using (C₁-C₂)alkylacetylene as reagent, the subsequent hydration of the triple bond can be carried out by treatment with an acid such as *p*-toluenesulfonic acid in the presence of a suitable solvent such as toluene at temperatures around 80°C and leads to compounds of formula VIII wherein R⁴ represents (C₂-C₄)alkyl-carbonyl and Y represents methoxycarbonyl or cyano.

Alternatively, compounds of formula VIII wherein R⁴ represents (C₁-C₂)alkoxy-(C₂-C₄)alkyl and Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by a two step procedure: (i) Suzuki type cross-coupling of iodides of formula XII wherein Y represents methoxycarbonyl or cyano with (C₁-C₂)alkoxy-vinyl boronic acid pinacol ester or (C₁-C₂)alkoxy-(C₁-C₂)alkyl-vinyl boronic acid pinacol ester reagents in the presence of a suitable palladium catalyst such as Pd(OAc)₂, a suitable ligand such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl and a base such as KOH and heating in a suitable solvent such as CH₃CN at temperatures around 70°C and (ii) reduction of the double bond under hydrogenation conditions such as those described above. Alternatively, compounds of formula VII wherein R⁴ represents acetyl or ethyl, and Y represents methoxycarbonyl (Scheme 3) can be regioselectively prepared by Sonogashira type cross-coupling of iodides of formula XXXI wherein Y represents methoxycarbonyl with trimethylsilylacetylene following standard conditions such as those previously described for the synthesis of compounds of formula VIII. The subsequent reduction of the triple bond under hydrogenation conditions as those previously described for the synthesis of compounds of formula VIII delivers compounds of formula VII wherein R⁴ represents ethyl and Y represents methoxycarbonyl. Alternatively, the subsequent hydration of the triple bond can be carried out by treatment with an acid such as *p*-toluenesulfonic acid in

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the presence of a suitable solvent such as toluene at temperatures around 80°C and provides compounds of formula VII wherein R⁴ represents acetyl and Y represents methoxycarbonyl. Compounds of formula XXXI wherein Y represents methoxycarbonyl or cyano can be prepared by bis-iodination of anilines of formula XIV wherein Y represents methoxycarbonyl or cyano following standard iodination conditions such as those previously described for the synthesis of compounds of formula XI and XII, but using about 2.2 equivalents of iodinating reagent.

Compounds of formula V wherein Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by protodesilylation of compounds of formula IX wherein Y represents methoxycarbonyl or cyano with a base such as potassium carbonate in the presence of a suitable solvent such as MeOH at temperatures around RT.

Compounds of formula IV wherein Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by rhodium-catalyzed cycloisomerization of anilines of formula V wherein Y represents methoxycarbonyl or cyano in the presence of a rhodium catalyst such as chloro(1,5-cyclooctadiene)rhodium(I) dimer and a ligand such as tris(4-fluorophenyl)phosphine and heating in a suitable solvent such as DMF at temperatures between 50°C and 90°C.

Alternatively, compounds of formula IV wherein Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by copper-catalyzed cycloisomerization of anilines of formula IX wherein Y represents methoxycarbonyl or cyano using a suitable copper catalyst such as copper iodide and heating in a suitable solvent such as DMF at temperatures between 50°C and 100°C.

Alternatively, compounds of formula IV wherein R⁴ represents hydrogen and Y represents methoxycarbonyl (Scheme 3) can be prepared by simultaneous deiodination and desulfurization of methylsulfanyl indoles of formula XIII by treatment with a suitable catalyst such as Raney nickel in the presence of a suitable solvent such as EtOH at temperatures around RT.

Alternatively, compounds of formula IV wherein R⁴ represents (C₁-C₄)alkyl and Y represents methoxycarbonyl (Scheme 3) can be prepared by desulfurization of methylsulfanyl indoles of formula VI wherein R⁴ represents (C₁-C₄)alkyl by treatment with a suitable catalyst such as Raney nickel in the presence of a suitable solvent such as EtOH at temperatures around RT.

Compounds of formula VI wherein R⁴ represents (C₁-C₄)alkyl (Scheme 3) can be prepared from compounds of formula XIII by Negishi type cross-coupling following standard

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conditions such as those previously described for the synthesis of compounds of formula VIII.

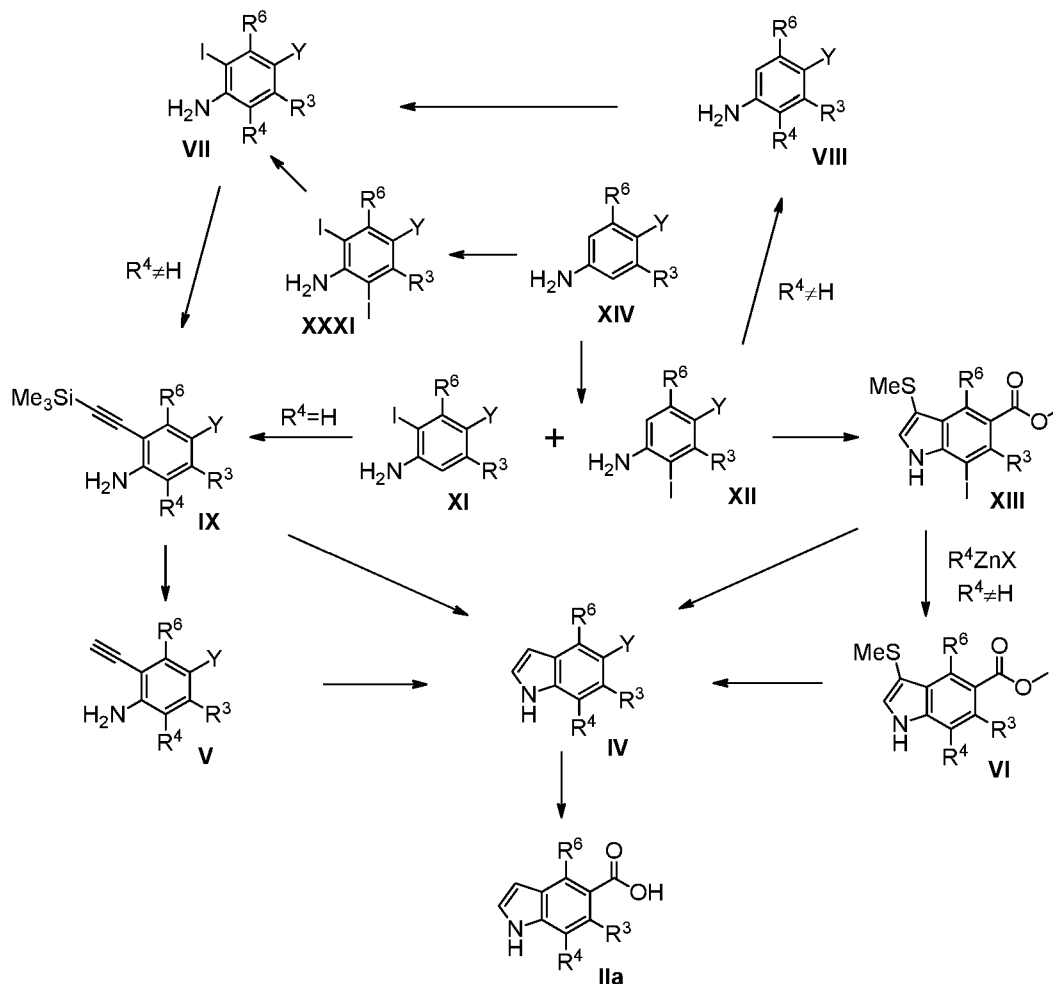
Compounds of formula XIII (Scheme 3) can be prepared by Gassman indole synthesis by consecutive treatment of anilines of formula XII wherein Y represents methoxycarbonyl with (i) a chlorinating reagent such as N-chlorosuccinimide or *tert*-butyl hypochlorite, (ii) a methyl sulfanyl protected aldehyde such as methylthioacetaldehyde dimethylacetal in the presence for both steps of a suitable solvent such as DCM at temperatures between -50°C and -78°C, (iii) a base such as Et₃N in the presence of a suitable solvent such as chlorobenzene at temperatures between 80°C and 120°C and finally with (iv) an acid such as HCl in the presence of a solvent such as dioxane or Et₂O at temperatures around RT.

Alternatively, compounds of formula IV wherein R³ represents hydrogen, R⁶ represents methyl (or ethyl, respectively) and Y represents methoxycarbonyl or cyano (Scheme 3) can be prepared by Suzuki type cross-coupling of chlorides of formula IV wherein R³ represents hydrogen, R⁶ represents chloro and Y represents methoxycarbonyl or cyano with trimethylboroxine (or vinyl boronic acid pinacol ester, respectively), in the presence of a suitable palladium catalyst such as [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride, in the presence of a suitable base such as K₂CO₃ and heating in a suitable solvent such as dioxane at temperatures around 110°C. When using vinyl boronic acid pinacol ester as reagent, the subsequent reduction of the double bond was carried out under hydrogenation conditions such as those described above.

Alternatively, compounds of formula IV (Scheme 3) wherein R⁴ represents hydroxy (or hydroxy-(C₁-C₄)alkyl respectively) and Y represents cyano can be prepared from methyl ether of formula IV wherein R⁴ represents methoxy (or methoxy-(C₁-C₄)alkyl respectively) and Y represents cyano by treatment with BBr₃ in the presence of a suitable solvent such as DCM at temperatures between -78°C and 55°C. The possible subsequent alkylation of the phenol of formula IV wherein R⁴ represents hydroxy and Y represents cyano by treatment with (C₁-C₄)alkyl halide or (C₁-C₄)alkoxy-(C₂-C₄)alkyl halide in the presence of a suitable base such as K₂CO₃ and a suitable solvent such as DMF at temperatures between 0°C and 80°C provides compounds of formula IV wherein R⁴ represents (C₁-C₄)alkoxy or (C₁-C₄)alkoxy-(C₂-C₄)alkoxy and Y represents cyano.

Carboxylic acid derivatives of formula IIa (Scheme 3) can be prepared by hydrolysis of methyl esters of formula IV wherein Y represents methoxycarbonyl by standard treatment with a suitable base such as LiOH, NaOH or KOH in the presence of water and a suitable organic solvent such as MeOH, EtOH or THF at temperatures between RT and 60°C.

Alternatively, carboxylic acid derivatives of formula IIa (Scheme 3) can be prepared by hydrolysis of nitriles of formula IV wherein Y represents cyano with a suitable base such as KOH or NaOH in the presence of water and optionally a suitable organic solvent such as 2-propanol at temperatures around 150°C.



Scheme 3: Synthesis of carboxylic acid intermediates of formula II wherein R⁵ represents hydrogen

Indole carboxylic acids of formula IIb can be prepared according to the synthetic routes given in scheme 4.

- 10 Hydrazines of formula XVII (Scheme 4) can be prepared by diazotisation of anilines of formula XII with for instance sodium nitrite in a suitable solvent such as concentrated HCl and water at temperatures around 0°C and subsequent reduction of the diazonium salt with for instance tin(II) chloride dihydrate in a suitable solvent such as HCl and water at temperatures between 0°C and RT.

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Indoles of formula XVIII (Scheme 4) can be prepared by Fisher indole reaction between hydrazine derivatives of formula XVII and ketones of formula R^5COCH_2SMe wherein R^5 represents (C₁-C₄)alkyl in the presence of a suitable acid such as HCl and a suitable solvent such as EtOH at temperatures between 50°C and 80°C.

- 5 Compounds of formula XVI wherein R^4 represents (C₁-C₄)alkyl, (C₁-C₂)alkoxy-(C₁-C₄)alkyl or (C₁-C₄)alkyl-carbonyl (Scheme 4) can be prepared from iodides of formula XVIII by Negishi, Sonogashira or Suzuki cross-coupling reactions following standard conditions such as those previously described for the synthesis of compounds of formula VIII. The possible subsequent reduction or hydration step can be carried out as previously
10 described for the synthesis of compounds VIII.

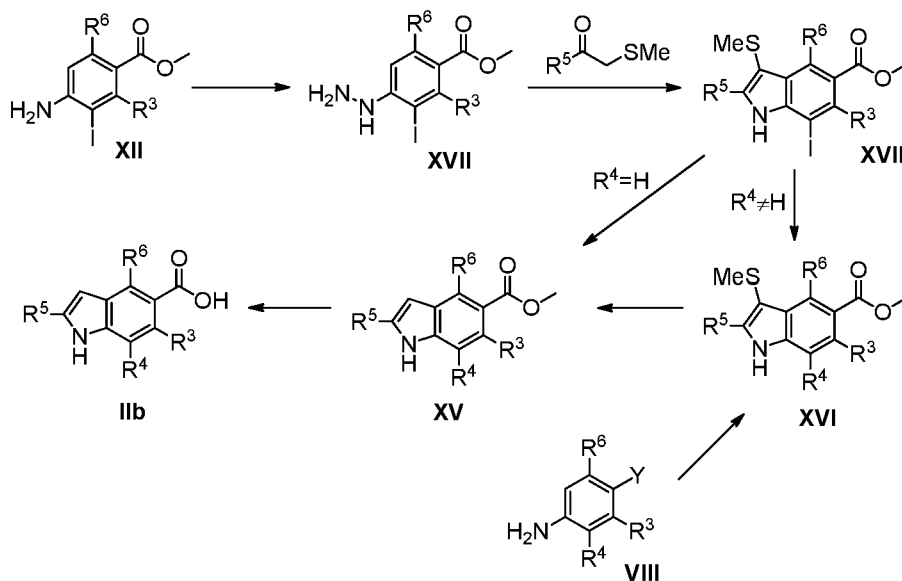
Alternatively, compounds of formula XVI (Scheme 4) can be prepared from anilines of formula VIII wherein Y represents methoxycarbonyl by a similar two-step sequence (hydrazine formation and Fisher indole synthesis) using similar conditions such as those previously described for the synthesis of compounds of formula XVIII from compounds of
15 formula XII.

Compounds of formula XV wherein R^4 represents fluoro, chloro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-carbonyl, (C₁-C₂)alkoxy-(C₁-C₄)alkyl or (C₁-C₄)alkoxy-(C₂-C₄)alkoxy (Scheme 4) can be prepared from compounds of formula XVI by desulfurization following standard conditions such as those previously described for the synthesis of compounds of
20 formula IV.

Alternatively, compounds of formula XV wherein R^4 represents hydrogen can be prepared from compounds of formula XVIII by simultaneous deiodination and desulfurization following standard conditions such as those previously described for the synthesis of compounds of formula IV from compounds of formula XIII.

- 25 Carboxylic acid derivatives of formula IIb (Scheme 4) can be prepared by hydrolysis of methyl esters of formula XV following standard conditions such as those previously described for the synthesis of compounds of formula IIa.

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Scheme 4: Synthesis of carboxylic acid intermediates of formula IIb wherein R⁵ represents (C₁-C₄)alkyl

If not commercially available, aniline intermediates of formula XIV can be prepared according to procedures known in the art. Possible synthetic routes are outlined in Scheme 5 below.

Carboxylic acid derivatives of formula XX wherein R⁴ represents hydrogen, (C₁-C₄)alkoxy, fluoro or chloro and R⁶ represents fluoro, chloro or (C₁-C₂)fluoroalkyl can be prepared by oxidation of toluene derivatives of formula XIX wherein R⁴ represents hydrogen, (C₁-C₄)alkoxy, fluoro or chloro and R⁶ represents fluoro, chloro or (C₁-C₂)fluoroalkyl with a suitable oxidizing reagent such as KMnO₄ in the presence of water and a solvent such as pyridine at temperatures around 100°C. Toluene derivatives of formula XIX wherein R⁴ represents (C₁-C₄)alkoxy can be prepared by treatment of phenols of formula XIX wherein R⁴ represents hydroxy with a suitable base such as Cs₂CO₃ or K₂CO₃ and a suitable alkylating reagent such as (C₁-C₄)alkyl iodide or bromide in the presence of a suitable solvent such as DMF at temperatures around RT.

Alternatively, carboxylic acids derivatives of formula XX wherein R⁴ represents hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro (Scheme 5) can be prepared by hydrolysis of nitriles of formula XXIII wherein R⁴ represents hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro by treatment with a suitable base such as KOH or NaOH in the presence of water and a suitable organic solvent such as 2-propanol. An additional treatment with sodium nitrite in the presence of water and an acid such as sulphuric acid at temperatures

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around 80°C may be required for the hydrolysis of the primary amide intermediates. Nitriles of formula XXIII wherein R⁴ represents hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro (Scheme 5) can be prepared by treatment of anilines of formula XXII wherein R⁴ represents hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro with a
5 suitable diazotisation reagent such as *tert*-butyl nitrite in the presence of a suitable cyanating reagent such as copper(I) cyanide in a suitable solvent such as CH₃CN at temperatures between 0°C and 80°C.

Alternatively, carboxylic acid derivatives of formula XX wherein R⁴ represents (C₁-C₄)alkoxy (Scheme 5) can be prepared by nucleophilic aromatic substitution of fluorides of
10 formula XX wherein R⁴ represents fluoro with (C₁-C₄)-alcohol in the presence of a base such as Cs₂CO₃ and a suitable solvent such as DMF at temperatures between RT and 110°C.

Methyl esters of formula XXI wherein R^N represents nitro (Scheme 5) can be prepared by treatment of carboxylic acids of formula XX with a suitable base such as Cs₂CO₃ or K₂CO₃
15 and a suitable alkylating reagent such as MeI in the presence of a suitable solvent such as DMF at temperatures around RT.

Alternatively, compounds of formula XXI wherein R^N represents acetylamino and R⁶ represents methyl or ethyl (Scheme 5) can be prepared from phenols of formula XXI wherein R^N represents acetylamino and R⁶ represents hydroxy following a two-step
20 procedure: (i) triflate formation by treatment with trifluoromethanesulfonic anhydride in the presence of a base such as Et₃N and a suitable solvent such as DCM at temperatures around RT and (ii) subsequent Suzuki type cross coupling with methyl- or ethyl-boronic acid in the presence of a suitable palladium catalyst such as Pd(dppf)Cl₂.DCM and a base such as K₃PO₄ and heating in a suitable solvent such as THF at temperatures around
25 65°C.

Anilines of formula XIV wherein Y represents methoxycarbonyl (or VIII wherein R⁴ represents (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro and Y represents methoxycarbonyl, respectively) (Scheme 5) can be prepared by reduction of nitrobenzene derivatives of
30 formula XXI wherein R^N represents nitro and R⁴ represents hydrogen (or XXI wherein R^N represents nitro and R⁴ represents (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro, respectively) with a suitable reducing reagent such as tin(II) chloride dihydrate in the presence of a suitable solvent such as DMF at temperatures around 100°C or with zinc dust and ammonium formate in the presence of a suitable solvent such as MeOH at temperatures around RT.

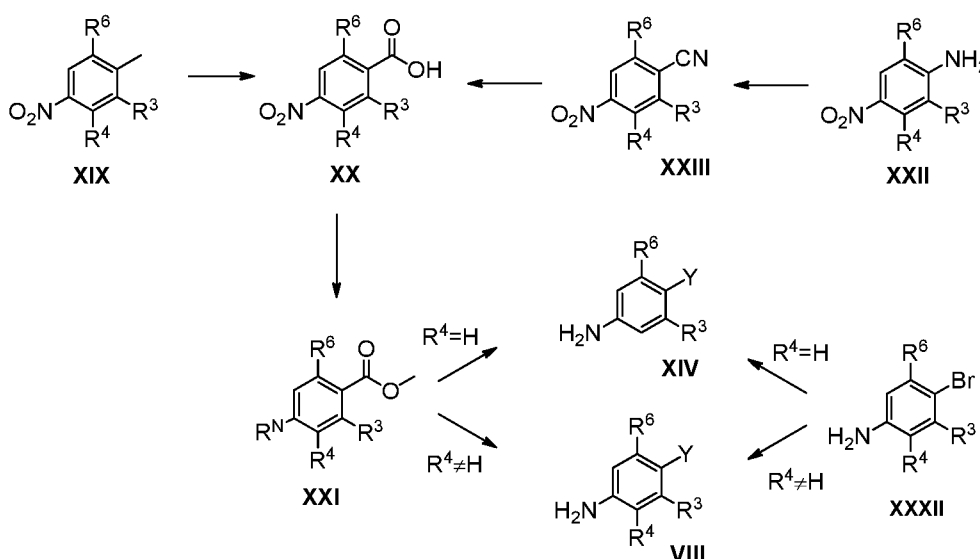
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Alternatively, anilines of formula XIV wherein Y represents methoxycarbonyl (or VIII wherein R^4 represents (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro and Y represents methoxycarbonyl, respectively) (Scheme 5) can be prepared by methanolysis of acetylated anilines of formula XXI wherein R^N represents acetylamino and R^4 represents hydrogen (or XXI wherein R^N represents acetylamino and R^4 represents (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro, respectively) with K₂CO₃ in the presence of MeOH at temperatures around RT.

Alternatively, anilines of formula XIV wherein R^3 represents hydrogen or chloro and Y represents cyano (or VIII wherein R^4 represents (C₁-C₄)alkyl, (C₁-C₄)alkoxy or chloro, R^3 represents hydrogen or chloro and Y represents cyano, respectively) (Scheme 5) can be prepared by palladium catalysed cyanation of bromides of formula XXXII wherein R^3 represents hydrogen or chloro and R^4 represents hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy or chloro with zinc cyanide in the presence of a suitable palladium catalyst such as Pd(PPh₃)₄ and heating in a suitable solvent such as DMF at temperatures around 110°C.

Alternatively, anilines of formula XIV wherein Y represents methoxycarbonyl (or VIII wherein R^4 represents (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro and Y represents methoxycarbonyl, respectively) (Scheme 5) can be prepared by esterification of anilines of formula XIV wherein Y represents hydroxycarbonyl (or VIII wherein R^4 represents (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoro or chloro and Y represents hydroxycarbonyl, respectively) by standard procedures as for example the treatment with acetylchloride in the presence of MeOH at temperatures around 65°C.

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Scheme 5: Synthesis of aniline precursors XIV and VIII

- If not commercially available, amine precursors of formula III can be prepared according to procedures described in *WO2009/132000* or outlined in Scheme 6 below.
- Amino nitriles of formula XXV wherein $\text{NR}^{11}\text{R}^{12}$ represents heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from $(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$, $(\text{C}_1\text{--}\text{C}_4)\text{alkylcarbonyl}$, $(\text{C}_1\text{--}\text{C}_4)\text{alkoxycarbonyl}$, $(\text{C}_1\text{--}\text{C}_4)\text{alkylsulfonyl}$, and halogen; cycloalkylamino; cycloalkylmethylamino; *N*-($\text{C}_1\text{--}\text{C}_4$)alkylamino; *N,N*-di-[($\text{C}_1\text{--}\text{C}_4$)alkyl]-amino or *N*-arylmethyl-*N*-($\text{C}_1\text{--}\text{C}_4$)alkyl-amino (Scheme 6) can be prepared by Strecker reaction between aldehydes of formula XXIV and amines of formula $\text{R}^{11}\text{R}^{12}\text{NH}$ in the presence of a suitable cyanating reagent such as TMSCN and a suitable Lewis acid catalyst such as ZnI_2 in a suitable mixture of solvents such as $\text{Et}_2\text{O}/\text{MeOH}$ at temperatures between 0°C and 80°C . The resulting nitriles of formula XXV can be transformed to diamines of formula IIIa (Scheme 6) by reduction under hydrogenation conditions in the presence of a suitable catalyst such as Raney nickel and a suitable solvent such as methanolic ammonia at temperatures around RT.
- Nitroalkenes of formula XXVI (Scheme 6) can be prepared by Henry reaction between aldehydes of formula XXIV and nitromethane following a two step procedure: (i) treatment with a suitable base such as KOtBu in a suitable solvent such as tBuOH/THF at temperatures around 0°C and (ii) treatment of the isolated β -nitro alcohol intermediates with a suitable dehydrating reagent such as acetyl anhydride in the presence of a base such as DMAP and in a suitable solvent such as DCM at temperatures around RT.

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Ether derivatives of formula XXVII wherein OR^{11} represents heterocycloxy; (C_3-C_6)cycloalkoxy or (C_2-C_6)alkoxy (Scheme 6) can be prepared by Michael addition of an alcohol of formula $R^{11}OH$ to a nitro alkene of formula XXVI in the presence of a suitable base such as NaH in a suitable solvent such as THF at temperatures between $0^\circ C$ and RT.

The obtained ether XXVII can be converted to amino ethers of formula IIIb (Scheme 6) by reduction of the nitro group under hydrogenation conditions in the presence of a suitable catalyst such as platinum dioxide and a suitable solvent such as EtOH at temperatures around RT.

If not commercially available, nitriles of formula XXIX (Scheme 6) can be prepared by a two step procedure: (i) arylation or heteroarylation of methylcyanoacetate by treatment with a bromoarene or bromoheteroarene of formula $Br-R^1$ in the presence of a suitable base such as KOtBu, a suitable palladium catalyst such as $Pd(OAc)_2$, a suitable ligand such as dppf in a suitable solvent such as dioxane as described in *J. Org. Chem.*, 2008, 73, 4, 1643-1645 and (ii) subsequent decarboxylation of the isolated methyl aryl- or heteroarylcianoacetate intermediates by treatment with a suitable salt such as LiCl in a suitable mixture of solvents such as DMSO/water at temperatures around $140^\circ C$.

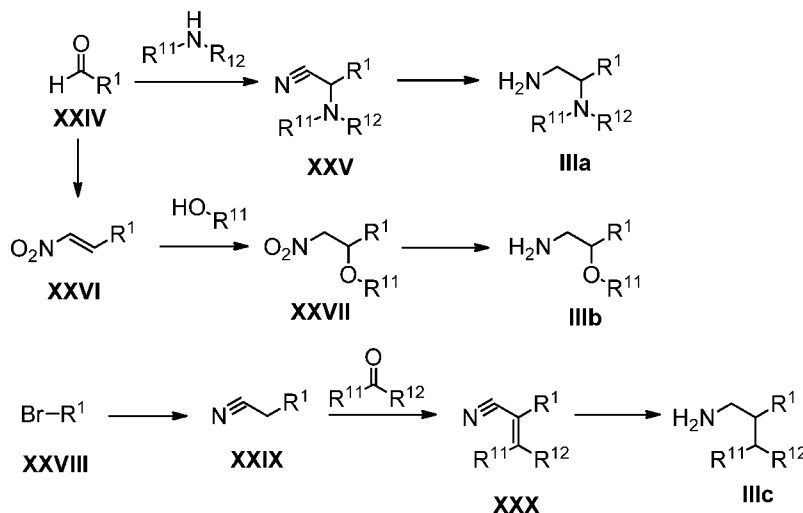
Alternatively, if not commercially available, nitriles of formula XXIX can be prepared according to *J. Am. Chem. Soc.*, 2011, 133, 6948-6951.

Cyano alkenes of formula XXX (Scheme 6) wherein R^{11} and R^{12} , together with the carbon atom to which they are attached, represent heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkylcarbonyl, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylsulfonyl, and halogen; (C_3-C_6)cycloalkyl which is unsubstituted or mono- or di-substituted with halogen or (C_3-C_6)alkyl can be prepared by Knoevenagel condensation of aryl- or heteroaryl-acetonitriles of formula XXIX with aldehydes or ketones of formula $R^{11}COR^{12}$ by treatment with a suitable base such as KOH or NaOMe in a suitable solvent such as MeOH at temperatures between $0^\circ C$ and $60^\circ C$.

The respective amines of formula IIIc (Scheme 6) can be prepared by reduction of cyano alkenes of formula XXX using a two step procedure: (i) hydrogenation in the presence of a suitable catalyst such as Pd/C followed by (ii) hydrogenation in the presence of a suitable catalyst such as Raney nickel, both steps being carried out in a suitable solvent such as methanolic ammonia at temperatures around RT.

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Alternatively, amines of formula IIIc can be prepared by reduction of cyano alkenes of formula XXX in the presence of a suitable reducing reagent such as BH_3 THF complex in a suitable solvent such as THF at temperatures around 60°C .



5

Scheme 6: Synthesis of amine intermediates of formula III

EXPERIMENTAL PART

Abbreviations (as used herein and in the description above)

Ac	acetyl
anh.	anhydrous
10 aq.	Aqueous
ATP	adenosine-5'-triphosphate
Boc	<i>tert</i> -butoxycarbonyl
tBu	<i>tert</i> -butyl
CC	column chromatography
15 cDNA	complementary deoxyribonucleic acid
CNS	central nervous system
DCM	dichloromethane
DEA	diethylamine
DIPEA	diisopropylethylamine
20 DMAP	4-(dimethylamino)pyridine
DMEM	dulbecco's modified eagle's medium
DMF	dimethylformamide
DMSO	dimethylsulfoxide

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	DNA	desoxyribonucleic acid
	dppf	1,1'-bis(diphenylphosphino)ferrocene
	EDC.HCl	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
	eq	equivalent
5	Et	ethyl
	FCS	fetal calf serum
	FLIPR	fluorescent imaging plate reader
	h	hour(s)
	HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
10		hexafluorophosphate
	Hept	heptanes
	HOBT	1-hydroxybenzotriazole hydrate
	HV	high vacuum
	LC-MS	liquid chromatography – mass spectrometry
15	M	molar(ity)
	Me	methyl
	min	minute(s)
	MS	mass spectrometry
	NCS	N-chlorosuccinimide
20	NMR	nuclear magnetic resonance
	ON	overnight
	PBS	phosphate buffered saline
	PEPPSI TM -IPr	[1,3-bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
25	PG	protecting group
	Ph	phenyl
	PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium
		hexafluorophosphate
	RNA	ribonucleic acid
30	RT	room temperature
	sat.	saturated
	TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
35	TMS	trimethylsilyl

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t_R	retention time
UV	ultra-violet
Vis	visible

A. Characterization methods used

- 5 NMR: Bruker Avance 400, 400 MHz ; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad, coupling constants are given in Hz.

LC-MS (I): Thermo Finnigan MSQ Surveyor MS with Agilent 1100 Binary Pump and DAD.

Eluents (acidic conditions): A: H₂O + 0.04% TFA; B: CH₃CN; gradient: 5% B → 95% B ;

- 10 runtime: 1.5 min ; flow: 4.5 mL/min ; detection: UV/Vis + MS, t_R is given in min.

LC-MS (A): column Zorbax SB-AQ, 3.5 μ m, 4.6x50 mm

LC-MS (B): column Waters XBridge C18, 2.5 μ m, 4.6x30 mm

LC-MS (C): column Waters Atlantis T3, 5 μ m, 4.6x30 mm ;

Eluents (basic conditions): A: H₂O + 13 mmol/L NH₄OH; B: CH₃CN ; gradient: 5% B →

- 15 95% B ; runtime: 1.5 min ; flow: 4.5 mL/min:

LC-MS (D): column Waters XBridge C18, 5 μ m, 4.6x50 mm.

LC-MS (D*): column Zorbax Extend C18, 5 μ m, 4.6x50 mm.

LC-MS (II): Dionex Ultimate 3000 with Thermo MSQ MS, HPG-3000 pump and photodiode array detector

- 20 Eluents (basic conditions): A: H₂O + 0.05% NH₄OH + 2% CH₃CN ; B: CH₃CN; gradient: 5% B → 95% B ; runtime: 2.0 min ; flow: 1.8 mL/min ; detection: UV/Vis + MS, t_R is given in min.

LC-MS (E): column Ascentis Express C18, 2.7 μ m, 2.1x50 mm

LC-MS (F): similar to E except that runtime is 1.1 min

- 25 Eluents (acidic conditions): A: H₂O + 0.05% HCOOH; B: CH₃CN + 0.05% HCOOH; gradient: 5% B → 95% B ; runtime: 2.0 min ; flow: 1.4 mL/min ; detection: UV/Vis + MS, t_R is given in min.

LC-MS (G): column Ascentis Express C18, 2.7 μ m, 2.1x50 mm

B. Purification methods used

- 30 **Preparative LC-MS (A):** flow: 75 mL/min. Detection: UV/Vis and/or MS.

Additional informations for the purification are summerized in the tables below using following explanations:

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XBridge: column Waters XBridge C18, 10 μ m, 30x75 mmAtlantis: column Waters Atlantis T3, 10 μ m, 30x75 mmAcidic: eluant: A = H₂O with 0.5% HCOOH, B = CH₃CNBasic: eluant: A = H₂O with 0.125% NH₄OH, B = CH₃CN

- 5 Lipophilic gradient: 30% B → 95% B over 4 min then 95%B over 2 min
 Normal gradient: 20% B → 95% B over 4 min then 95%B over 2 min
 Polar gradient: 10% B → 95% B over 4 min then 95%B over 2 min
 Very polar gradient: 5% B → 50% B over 3 min then 50% B → 95% B over 1 min and finally 95%B over 2 min

	XBridge		Atlantis
	acidic	basic	acidic
Lipophilic gradient	Method II		
Normal gradient	Method VII	Method IV	Method I
Polar gradient	Method VI	Method V	Method VIII
Very polar gradient	Method III		Method IX

- 10 **Preparative LC-MS (B):** flow: mL/min. Detection: UV/Vis and/or MS.

XBridge: column Waters XBridge C18 OBD™, 5 μ m, 19x50 mmAcidic: eluant: A = H₂O with 0.1% HCOOH, B = CH₃CN with 0.1% HCOOHBasic: eluant: A = H₂O with 0.1% NH₄OH, B = CH₃CN with 0.1% NH₄OH

- Normal gradient: 25% B over 0.2 min, 25% → 35% B over 0.1 min, 35% → 65% B over 2.9 min, 65% → 95% B over 0.1 min and finally 95%B over 1 min
 15 Polar gradient: 10% B over 0.2 min, 10% → 20% B over 0.1 min, 20% → 50% B over 2.9 min, 50% → 95% B over 0.1 min and finally 95%B over 1 min
 Very polar gradient: 5% B over 0.3 min, 5% → 35% B over 2.9 min, 35% → 95% B over 0.1 min and finally 95%B over 1 min.

	acidic	basic
Normal gradient		Method 5
Polar gradient	Method 2	Method 4
Very polar gradient	Method 1	Method 3

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Column chromatography (CC) was performed using *silica gel 60 Merck* (0.063-0.200mm) or using prepacked cartridges (SNAP KP-SIL™, SNAP KP-NH™, Isolute™ Silica II, Isolute™ NH₂ or Isolute™ C¹⁸) from Biotage. Additional information for the purification are summarized in the table below:

	SNAP KP-SIL™	Isolute™ Silica II	SNAP KP-NH™
Hept/EtOAc	Method b	Method c	
EtOAc/MeOH	Method e	Method g	Method f
DCM/MeOH	Method i	Method d	Method a
Hept/EtOAc/MeOH	Method h		

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The following examples illustrate the invention but do not at all limit the scope thereof.

PREPARATION OF PRECURSORS AND INTERMEDIATES

A. Synthesis of carboxylic acids

A.1. Synthesis of 4-chloro-1H-indole-5-carboxylic acid

10 A.1.a. Methyl 4-amino-2-chlorobenzoate

To a solution of 4-amino-2-chlorobenzoic acid (54.2 mmol) in MeOH (325 mL) was added dropwise acetylchloride (163 mmol) and the mixture was refluxed for 5h. It was concentrated in vacuo and partitioned between EtOAc and a sat. solution of NaHCO₃. The organic phase was washed with a sat. solution of NaHCO₃, dried over MgSO₄ and concentrated in vacuo to give the title compound as beige solid.

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LC-MS (B): t_R = 0.57 min; [M+CH₃CN+H]⁺: 227.30

A.1.b. Mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate

To a suspension of methyl 4-amino-2-chlorobenzoate (55.8 mmol) in EtOH (558 mL) was added iodine (58.6 mmol) and silver sulfate (55.8 mmol). The mixture was stirred for 15 min, filtered and the filtrate was concentrated in vacuo. The residue was partitioned between DCM and a 1M aq. solution of NaOH. The organic phase was washed with a 1M aq. solution of NaOH, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SIL™ from Biotage) using Hept/EtOAc/MeOH from 89/11/1 to 81/19/1 to give the mixture of regioisomers as salmon solid. The mixture was enriched

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from 59 to 66% in methyl 4-amino-2-chloro-3-iodobenzoate by recrystallisation in Hept/EtOAc 75/25, separation of the solid methyl 4-amino-2-chloro-5-iodobenzoate by filtration and evaporation of the mother liquid.

LC-MS (B): t_R = 0.72 min; $[M+CH_3CN+H]^+$: 352.79

- 5 In addition, pure methyl 4-amino-2-chloro-5-iodobenzoate regioisomer was isolated as pink to orange solid.

LC-MS (B): t_R = 0.75 min; $[M+CH_3CN+H]^+$: 352.80

A.1.c. Methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate

- A solution of mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate from previous step (13.3 mmol) in Et₃N (110 mL) and toluene (110 mL) was heated to 60°C under argon and treated with PPh₃ (1.33 mmol), CuI (1.33 mmol), Pd(PPh₃)₂Cl₂ (0.66 mmol) and trimethylsilylacetylene (19.9 mmol). The mixture was stirred for 30 min at 60°C and 1h at 70°C, quenched with a 10% aq. solution of NH₄Cl and extracted with EtOAc. The organic phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SIL™ from Biotage) using Hept/EtOAc from 1/0 to 8/2 to give the title compound (second eluting product) as light yellow solid.
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LC-MS (B): t_R = 0.93 min; $[M+CH_3CN+H]^+$: 322.70

- In addition, methyl 4-amino-2-chloro-5-((trimethylsilyl)ethynyl)benzoate was isolated as orange solid (first eluting product).
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LC-MS (B): t_R = 0.97 min; $[M+CH_3CN+H]^+$: 323.22

A.1.d. Methyl 4-amino-2-chloro-3-ethynylbenzoate

- To a solution of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate (8.81 mmol) in MeOH (8.81 mL) was added K₂CO₃ (9.69 mmol). The mixture was stirred for 15 min and the solvent was evaporated off. The residue was partitioned between DCM and water. The organic phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (Isolute™ Silica II from Biotage) using DCM to give the title compound as yellowish solid.
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LC-MS (B): t_R = 0.66 min; $[M+H]^+$: 210.04

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A.1.e. Methyl 4-chloro-1H-indole-5-carboxylate

To a mixture of methyl 4-amino-2-chloro-3-ethynylbenzoate (5.57 mmol), chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.28 mmol) and tris(4-fluorophenyl)phosphine (3.34 mmol) was added under argon degassed DMF (28 mL). The mixture was heated to 85°C for 50 min, cooled to RT and partitioned between Et₂O and water. The organic phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SILTM from Biotage) using Hept/DCM 1/0 to 0/1 to give the title compound as brownish solid.

LC-MS (B): t_R = 0.69 min; [M+H]⁺: 210.14

10 *A.1.f. 4-Chloro-1H-indole-5-carboxylic acid (Saponification I)*

To a suspension of methyl 4-chloro-1H-indole-5-carboxylate (4 mmol) in MeOH (24 mL) was added a 2M aq. solution of LiOH (4 mL). The mixture was stirred for 5h at 65°C then ON at 45°C. It was evaporated off and partitioned between EtOAc and H₂O. The aq. phase was acidified with a 25% solution of HCl and extracted 3 times with DCM. The combined organic phases were dried over MgSO₄ and concentrated in vacuo to give the title compound as off-white solid.

LC-MS (A): t_R = 0.65 min; [M+H]⁺: 196.06

*A.2. Synthesis of 4-chloro-7-methyl-1H-indole-5-carboxylic acid**A.2.a. Methyl 4-chloro-7-iodo-3-(methylthio)-1H-indole-5-carboxylate (Gassman indole)*

To a suspension of methyl 4-amino-2-chloro-5-iodobenzoate (6.21 mmol) in anh. DCM (29 mL) was added at -60°C NCS (7.45 mmol) and the mixture was stirred for 10 min. A solution of (methylthio)acetaldehyde dimethyl acetal (7.45 mmol) in anh. DCM (5.8 mL) was added at -60°C and the mixture was stirred allowing temperature to reach -30°C. A solution of Et₃N (7.45 mmol) in anh. DCM (5 mL) was added at -30°C and the mixture was stirred allowing temperature to reach RT. It was concentrated in vacuo, PhCl (17.4 mL) and Et₃N (20.5 mmol) were added and the mixture was heated to 125°C and stirred for 2h. The volatiles were evaporated off and the residue was taken up in Et₂O (28.7 mL) and treated with a 4M solution of HCl in dioxane (11 mL) for 30 min. It was partitioned between EtOAc and a sat. solution of NaHCO₃, the organic phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SILTM from Biotage) using Hept/EtOAc from 9/1 to 65/35 to give the title compound as yellow solid.

LC-MS (A): t_R = 0.93 min; [M+H]⁺: 381.71

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A.2.b. Methyl 4-chloro-7-methyl-3-(methylthio)-1H-indole-5-carboxylate

To a solution of methyl 4-chloro-7-iodo-3-(methylthio)-1H-indole-5-carboxylate (0.42 mmol) in dioxane (1 mL) was added under argon a 2M solution of methylzinc chloride in THF (1.04 mmol) and a solution of Pd(dppf)Cl₂.DCM (0.03 mmol) in dioxane (0.5 mL). The mixture was stirred ON at 65°C in a sealed vial, diluted with EtOAc and washed with a sat. solution of Rochelle salt and brine. The organic phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SIL™ from Biotage) using DCM to give the title compound as yellow solid.

LC-MS (A): t_R = 0.86 min; [M+H]⁺: 270.11

10 *A.2.c. Methyl 4-chloro-7-methyl-1H-indole-5-carboxylate*

To a solution of methyl 4-chloro-7-methyl-3-(methylthio)-1H-indole-5-carboxylate (0.24 mmol) in EtOH (4.11 mL) was added Actimet M Raney Nickel (14 mg). The mixture was stirred for 2h at RT and filtered over a pad of celite. The filtrate was concentrated in vacuo to give the title compound as white solid.

15 LC-MS (A): t_R = 0.82 min; [M+H]⁺: 224.16

A.2.d. 4-Chloro-7-methyl-1H-indole-5-carboxylic acid (Saponification II)

To a solution of methyl 4-chloro-7-methyl-1H-indole-5-carboxylate (0.11 mmol) in MeOH (0.4 mL), THF (0.4 mL) and H₂O (0.4 mL) was added LiOH.H₂O (0.44 mmol). The mixture was stirred for 2h at 60°C. It was evaporated off and partitioned between EtOAc and H₂O. The aq. phase was acidified with a 25% solution of HCl and extracted 3 times with EtOAc. The combined organic phases were dried over MgSO₄ and concentrated in vacuo to give the title compound as pink solid.

LC-MS (A): t_R = 0.69 min; [M+H]⁺: 209.98

A.3. Synthesis of 4-chloro-2-methyl-1H-indole-5-carboxylic acid

25 *A.3.a. Methyl 2-chloro-4-hydrazinyl-5-iodobenzoate*

To a solution of methyl 4-amino-2-chloro-5-iodobenzoate (6.42 mmol) in 37% HCl (4.40 mL) was added dropwise at 0°C a solution of sodium nitrite (7.49 mmol) in water (2.15 mL). The mixture was stirred for 15 min at 0°C and a solution of tin(II) chloride dihydrate (16 mmol) in water (1 mL) and 37% HCl (4.28 mL) was added dropwise at 0°C. The mixture was stirred for 15 min and quenched with consecutive addition of water, a 10% solution of Na₂CO₃ and a 20% solution of NaOH. It was extracted 3 times with DCM, the combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude

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was purified by CC (SNAP KP-SIL™ from Biotage) using Hept/EtOAc from 95/5 to 62/38 to give the title compound as beige solid.

LC-MS (A): t_R = 0.73 min; $[M+CH_3CN+H]^+$: 367.75

A.3.b. Methyl 4-chloro-7-iodo-2-methyl-3-(methylthio)-1H-indole-5-carboxylate

- 5 To a solution of methyl 2-chloro-4-hydrazinyl-5-iodobenzoate (0.76 mmol) in a 1.25 M solution of HCl in EtOH (1.8 mL) was added 1-methylthio-2-propanone (1.38 mmol). The mixture was stirred for 2h at 65°C and filtered. The filtrate was concentrated in vacuo and the crude was purified by preparative LC-MS using method I.

LC-MS (A): t_R = 0.96 min; $[M+H]^+$: 395.73

10 *A.3.c. Methyl 4-chloro-2-methyl-1H-indole-5-carboxylate*

This compound was prepared using a method analogous to that of methyl 4-chloro-7-methyl-1H-indole-5-carboxylate, methyl 4-chloro-7-iodo-2-methyl-3-(methylthio)-1H-indole-5-carboxylate replacing 4-chloro-7-methyl-3-(methylthio)-1H-indole-5-carboxylate except that the reaction mixture was stirred for 48h at RT and further additions of Actimet
15 M Raney Nickel was required until completion of the reaction.

LC-MS (A): t_R = 0.83 min; $[M+H]^+$: 224.10

A.3.d. 4-Chloro-2-methyl-1H-indole-5-carboxylic acid

- This compound was prepared using a method analogous to that of 4-chloro-1H-indole-5-carboxylic acid, methyl 4-chloro-2-methyl-1H-indole-5-carboxylate replacing methyl 4-
20 chloro-1H-indole-5-carboxylate.

LC-MS (A): t_R = 0.69 min; $[M+H]^+$: 210.04

A.4. Synthesis of 4,6-dichloro-1H-indole-5-carboxylic acid

A.4.a. 2,6-Dichloro-4-nitrobenzoic acid

- A solution of 1,3-dichloro-2-methyl-5-nitrobenzene (4.85 mmol) in pyridine (5 mL) and
25 water (10 mL) was heated to 90°C and $KMnO_4$ (29.1 mmol) was added portionwise. The mixture was refluxed for 2h and stirred ON at RT. It was heated to 90°C, additional amount of $KMnO_4$ (12.7 mmol) was added and it was refluxed for 7h. The mixture was filtered, the filtrate was basified with a 1M solution of NaOH until pH 12-13 and washed with EtOAc. The aq. phase was acidified with a 1M solution of HCl until pH 1-2 and
30 extracted 3 times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the crude acid as orange solid.

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LC-MS (A): t_R = 0.45 minLC-MS (D*): t_R = 0.17 min; [M-H]⁻: 234.01*A.4.b. Methyl 2,6-dichloro-4-nitrobenzoate*

To a solution of 2,6-dichloro-4-nitrobenzoic acid (1.63 mmol) in DMF (5 mL) was added cesium carbonate (2.44 mmol). The suspension was stirred for 30 min at RT and MeI (1.63 mmol) was added. The mixture was stirred for 2h, quenched with water and extracted 3 times with EtOAc. The combined organic phases were dried and concentrated in vacuo to give the title compound as yellow solid.

LC-MS (A): t_R = 0.88 min10 ¹H NMR ((CD₃)₂SO) δ : 8.48 (s, 2 H), 3.99 (s, 3 H)*A.4.c. Methyl 4-amino-2,6-dichlorobenzoate*

To a solution of methyl 2,6-dichloro-4-nitrobenzoate (1.44 mmol) in DMF (2 mL) was added tin(II) chloride dihydrate (5.04 mmol). The mixture was stirred at 100°C for 40 min under microwave condition and quenched with water. It was basified with a 1M solution of NaOH until pH 11-12 and extracted 3 times with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-NHTM from Biotage) using Hept/EtOAc from 1/0 to 1/1 to give the title compound as yellow solid.

LC-MS (A): t_R = 0.78 min; [M+H]⁺: 220.0720 *A.4.d. Methyl 4-amino-2,6-dichloro-3-iodobenzoate*

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2,6-dichlorobenzoate replacing methyl 4-amino-2-chlorobenzoate except that no purification was done.

25 LC-MS (A): t_R = 0.86 min; [M+CH₃CN+H]⁺: 386.57*A.4.e. Methyl 4-amino-2,6-dichloro-3-((trimethylsilyl)ethynyl)benzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2,6-dichloro-3-iodobenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

30 LC-MS (A): t_R = 1.00 min; [M+H]⁺: 316.07

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A.4.f. Methyl 4-amino-2,6-dichloro-3-ethynylbenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2,6-dichloro-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

5 LC-MS (A): t_R = 0.83 min; $[M+H]^+$: 243.91

A.4.g. Methyl 4,6-dichloro-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-2,6-dichloro-3-ethynylbenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

10 LC-MS (A): t_R = 0.84 min

^1H NMR ($(CD_3)_2SO$) δ : 11.79 (s, 1 H), 7.62 (dd, J_1 = 2.9 Hz, J_2 = 2.5 Hz, 1 H), 7.59 (d, J = 0.9 Hz, 1 H), 6.58 (m, 1 H), 3.91 (s, 3 H)

A.4.h. 4,6-Dichloro-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4,6-dichloro-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

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LC-MS (A): t_R = 0.68 min

LC-MS (D*): t_R = 0.15 min; $[M-H]^-$: 228.06

A.5. Synthesis of 4-chloro-7-isobutyl-1H-indole-5-carboxylic acid

20 *A.5.a. Methyl 4-amino-2-chloro-5-isobutylbenzoate*

To a solution of methyl 4-amino-2-chloro-5-iodobenzoate (3.36 mmol) in toluene/water 20/1 (40 mL) was added under argon K_3PO_4 (11.8 mmol), $PdCl_2(PPh_3)_2$ (0.34 mmol) and (2-methylpropyl)boronic acid (6.72 mmol). The mixture was heated ON at 110°C in a sealed vial, quenched with water and extracted with EtOAc. The organic phase was

25 washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SilTM from Biotage) using Hept/EtOAc from 1/0 to 0/1 to give the title compound as yellow oil.

LC-MS (A): t_R = 0.90 min; $[M+CH_3CN+H]^+$: 283.06

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A.5.b. Methyl 4-amino-2-chloro-3-iodo-5-isobutylbenzoate

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2-chloro-5-isobutylbenzoate replacing methyl 4-amino-2-chlorobenzoate.

5 LC-MS (A): $t_R = 0.97$ min; $[M+CH_3CN+H]^+$: 408.77

A.5.c. Methyl 4-amino-2-chloro-5-isobutyl-3-((trimethylsilyl)ethynyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2-chloro-3-iodo-5-isobutylbenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and
10 methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): $t_R = 1.07$ min; $[M+H]^+$: 337.90

A.5.d. Methyl 4-amino-2-chloro-3-ethynyl-5-isobutylbenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2-chloro-5-isobutyl-3-((trimethylsilyl)ethynyl)
15 benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): $t_R = 0.94$ min; $[M+H]^+$: 266.07

A.5.e. Methyl 4-chloro-7-isobutyl-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-2-chloro-3-ethynyl-5-isobutylbenzoate replacing
20 methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): $t_R = 0.94$ min; $[M+H]^+$: 266.16

A.5.f. 4-Chloro-7-isobutyl-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4-chloro-7-isobutyl-1H-indole-5-carboxylate replacing
25 methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

LC-MS (A): $t_R = 0.82$ min, $[M+H]^+$: 252.06

A.6. Synthesis of 4-chloro-7-(3-methoxypropyl)-1H-indole-5-carboxylic acid*A.6.a. Methyl 4-amino-2-chloro-5-(3-methoxyprop-1-yn-1-yl)benzoate*

To a mixture of methyl 4-amino-2-chloro-5-iodobenzoate (3.51 mmol), $Pd(PPh_3)_2Cl_2$ (0.18
30 mmol) and CuI (0.18 mmol) was sequentially added under argon THF (12 mL), Et_3N (14

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mmol) and methyl propargyl ether (14 mmol). The mixture was stirred for 1h at RT, diluted with EtOAc and filtered. The filtrate was concentrated in vacuo and the crude was purified by CC (SNAP KP-Sil™ from Biotage) using Hept/EtOAc from 85/15 to 40/60 to give the title compound as orange solid.

5 LC-MS (A): t_R = 0.82 min, $[M+H]^+$: 253.99

A.6.b. Methyl 4-amino-2-chloro-5-(3-methoxypropyl)benzoate

To a solution of methyl 4-amino-2-chloro-5-(3-methoxyprop-1-yn-1-yl)benzoate (3.48 mmol) in EtOH (14 mL) was added PtO_2 (0.35 mmol). The mixture was stirred under a hydrogen atmosphere for 2h. It was filtered over Celite, washed with EtOH and
10 concentrated in vacuo. The crude was purified by CC (SNAP KP-Sil™ from Biotage) using Hept/EtOAc from 1/0 to 8/2 to give the title compound as yellow oil.

LC-MS (A): t_R = 0.80 min, $[M+H]^+$: 257.90

A.6.c. Methyl 4-amino-2-chloro-3-iodo-5-(3-methoxypropyl)benzoate

This compound was prepared using a method analogous to that of the mixture of methyl
15 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2-chloro-5-(3-methoxypropyl)benzoate replacing methyl 4-amino-2-chlorobenzoate.

LC-MS (A): t_R = 0.90 min; $[M+H]^+$: 383.91

A.6.d. Methyl 4-amino-2-chloro-5-(3-methoxypropyl)-3-((trimethylsilyl)ethynyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2-chloro-3-iodo-5-(3-methoxypropyl)benzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate
20 and methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): t_R = 1.00 min; $[M+H]^+$: 353.85

A.6.e. Methyl 4-amino-2-chloro-3-ethynyl-5-(3-methoxypropyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2-chloro-5-(3-methoxypropyl)-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.
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LC-MS (A): t_R = 0.85 min; $[M+H]^+$: 281.83

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A.6.f. Methyl 4-chloro-7-(3-methoxypropyl)-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-2-chloro-3-ethynyl-5-(3-methoxypropyl)benzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

5 LC-MS (A): t_R = 0.86 min; $[M+H]^+$: 282.07

A.6.g. 4-Chloro-7-(3-methoxypropyl)-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4-chloro-7-(3-methoxypropyl)-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

10 LC-MS (A): t_R = 0.72 min, $[M+H]^+$: 268.07

A.7. Synthesis of 4-methyl-1H-indole-5-carboxylic acid**A.7.a. Methyl 4-methyl-1H-indole-5-carboxylate**

Methyl 4-chloro-1H-indole-5-carboxylate (0.48 mmol), K_2CO_3 (1.91 mmol) and PEPPSITM-IPr (0.05 mmol) were placed in a pressure vessel and anh. dioxane (2 mL) and
15 trimethylboroxine (0.23 mL) were added sequentially. The tube was sealed under argon and heated at 115°C. After 17h, the reaction mixture was cooled to RT, filtered over a pad of Celite and the cake was washed with EtOAc. The filtrate was concentrated in vacuo and the crude was purified by CC (SNAP KP-SilTM from Biotage) using Hept/EtOAc from 96/4 to 50/50 to give the title compound as white solid.

20 LC-MS (A): t_R = 0.78 min, $[M+H]^+$: 190.10

A.7.b. 4-Methyl-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4-methyl-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate except that the reaction mixture was stirred for
25 16h at 60°C.

LC-MS (A): t_R = 0.64 min

LC-MS (D*): t_R = 0.15 min, $[M-H]^-$: 173.91

A.8. Synthesis of 4-ethyl-1H-indole-5-carboxylic acid**A.8.a. Methyl 4-vinyl-1H-indole-5-carboxylate**

30 This compound was prepared using a method analogous to that of methyl 4-methyl-1H-indole-5-carboxylate, vinylboronic acid pinacol ester replacing trimethylboroxine.

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LC-MS (A): t_R = 0.80 min, $[M+H]^+$: 202.20*A.8.b. Methyl 4-ethyl-1H-indole-5-carboxylate*

To a solution of methyl 4-vinyl-1H-indole-5-carboxylate (0.21 mmol) in EtOH (2 mL) was added platinum dioxide (0.021 mmol). The mixture was stirred under a hydrogen atmosphere for 2h, filtered over Celite and concentrated in vacuo to give the title compound as pinkish solid.

LC-MS (A): t_R = 0.83 min, $[M+H]^+$: 204.18*A.8.c. 4-Ethyl-1H-indole-5-carboxylic acid*

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4-methyl-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

LC-MS (A): t_R = 0.70 min, $[M+CH_3CN+H]^+$: 231.08**A.9. Synthesis of 4-chloro-7-acetyl-1H-indole-5-carboxylic acid***A.9.a. Methyl 4-amino-2-chloro-3,5-diiodobenzoate*

To a suspension of methyl 4-amino-2-chlorobenzoate (10.8 mmol) in EtOH (100 mL) was added iodine (23.7 mmol) and silver sulfate (10.8 mmol) under argon. The mixture was stirred for 2h, filtered and the filtrate was treated with a 10% aq. solution of sodium thiosulfate. After evaporation of EtOH, the residue was partitioned between EtOAc and a 1M aq. solution of NaOH. The organic phase was washed with a 1M aq. solution of NaOH and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using DCM and the solid was triturated in CH_3CN and filtered to give the title compound as beige solid.

LC-MS (A): t_R = 0.92 min ^1H NMR ($(CD_3)_2SO$) δ : 8.13 (s, 1 H), 6.02 (s, 2 H), 3.79 (s, 3 H)*A.9.b. Methyl 4-amino-2-chloro-3-iodo-5-((trimethylsilyl)ethynyl)benzoate*

A solution of methyl 4-amino-2-chloro-3,5-diiodobenzoate (9.6 mmol) in Et_3N (80 mL) and toluene (80 mL) was treated under argon with PPh_3 (0.96 mmol), CuI (4.80 mmol), $Pd(PPh_3)_2Cl_2$ (0.48 mmol) and trimethylsilylacetylene (10.1 mmol). The mixture was stirred for 2h at RT, quenched with a 10% aq. solution of NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The

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crude was purified by CC (SNAP KP-SIL™ from Biotage) using Hept/EtOAc from 100/0 to 85/15 to give the title compound as light orange solid.

LC-MS (A): t_R = 1.05 min; $[M+H]^+$: 408.02

A.9.c. Methyl 5-acetyl-4-amino-2-chloro-3-iodobenzoate

- 5 A solution of methyl 4-amino-2-chloro-3-iodo-5-((trimethylsilyl)ethynyl)benzoate (4.39 mmol) in toluene (20 mL) was treated with 4-toluene sulfonic acid monohydrate (11 mmol). The mixture was stirred for 3h at 80°C and poured into water. The aq. phase was basified with a 32% aq. solution of NaOH until pH=12-13 and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The
- 10 crude was purified by CC (SNAP KP-SIL™ from Biotage) using Hept/EtOAc from 100/0 to 75/25 to give the title compound as light yellow solid.

LC-MS (A): t_R = 0.88 min

^1H NMR ($(CD_3)_2SO$) δ : 8.37 (s, 1 H), 8.00 (s br, 2 H), 3.83 (s, 3 H), 2.63 (s, 3 H)

A.9.d. Methyl 5-acetyl-4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate

- 15 This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 5-acetyl-4-amino-2-chloro-3-iodobenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): t_R = 1.03 min; $[M+H]^+$: 324.25

- 20 A.9.e. Methyl 5-acetyl-4-amino-2-chloro-3-ethynylbenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 5-acetyl-4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): t_R = 0.84 min; $[M+H]^+$: 251.99

- 25 A.9.f. Methyl 7-acetyl-4-chloro-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 5-acetyl-4-amino-2-chloro-3-ethynylbenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): t_R = 0.83 min

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¹H NMR ((CD₃)₂SO) δ: 11.96 (s, 1 H), 8.32 (s, 1 H), 7.56 (dd, $J_1 = J_2 = 2.9$ Hz, 1 H), 6.74 (dd, $J_1 = 2.1$ Hz, $J_2 = 3.2$ Hz, 1 H), 3.92 (s, 3 H), 2.72 (s, 3 H)

A.9.g. 7-Acetyl-4-chloro-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 7-acetyl-4-chloro-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

LC-MS (A): $t_R = 0.69$ min

¹H NMR ((CD₃)₂SO) δ: 13.25 (s, 1 H), 11.91 (s, 1 H), 8.34 (s, 1 H), 7.54 (dd, $J_1 = J_2 = 2.9$ Hz, 1 H), 6.72 (dd, $J_1 = 2.1$ Hz, $J_2 = 3.1$ Hz, 1 H), 2.72 (s, 3 H)

10 **A.10. Synthesis of 7-methyl-4-(trifluoromethyl)-1H-indole-5-carboxylic acid**

A.10.a. Methyl 4-amino-2-(trifluoromethyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chlorobenzoate, 4-amino-2-(trifluoromethyl)benzoic acid replacing 4-amino-2-chlorobenzoic acid.

15 LC-MS (A): $t_R = 0.77$ min, $[M+H]^+$: 220.04

A.10.b. Methyl 4-amino-5-iodo-2-(trifluoromethyl)benzoate

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2-(trifluoromethyl)benzoate replacing methyl 4-amino-2-chlorobenzoate except that
20 only the 5-iodo regioisomer was isolated.

LC-MS (A): $t_R = 0.88$ min, $[M+H]^+$: 345.7

A.10.c. Methyl 4-amino-5-methyl-2-(trifluoromethyl)benzoate

To a solution of methyl 4-amino-5-iodo-2-(trifluoromethyl)benzoate (24.6 mmol) in dioxane (49 mL) was added under argon a 2M solution of methylzinc chloride in THF (61.6 mmol)
25 followed by Pd(dppf)Cl₂.DCM (1.72 mmol). The mixture was stirred for 30 min at 65°C in a sealed vial, diluted with EtOAc and filtered. The filtrate was washed with a sat. solution of Rochelle salt and with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SIL™ from Biotage) using DCM to give the title compound as brown solid.

30 LC-MS (A): $t_R = 0.81$ min; $[M+H]^+$: 234.01

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A.10.d. Methyl 4-amino-3-iodo-5-methyl-2-(trifluoromethyl)benzoate

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-5-methyl-2-(trifluoromethyl)benzoate replacing methyl 4-amino-2-chlorobenzoate
5 except that the reaction mixture was stirred for 7h at 50°C.

LC-MS (A): t_R = 0.88 min, $[M+H]^+$: 400.78

A.10.e. Methyl 4-amino-5-methyl-2-(trifluoromethyl)-3-((trimethylsilyl)ethynyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-3-iodo-5-methyl-2-
10 (trifluoromethyl)benzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate except that the reaction mixture was stirred for 3h30 at 70°C.

LC-MS (A): t_R = 1.02 min; $[M+H]^+$: 330.09

A.10.f. Methyl 4-amino-3-ethynyl-5-methyl-2-(trifluoromethyl)benzoate

15 This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-5-methyl-2-(trifluoromethyl)-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): t_R = 0.85 min; $[M+H]^+$: 257.90

A.10.g. Methyl 7-methyl-4-(trifluoromethyl)-1H-indole-5-carboxylate

20 This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-3-ethynyl-5-methyl-2-(trifluoromethyl)benzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): t_R = 0.86 min

^1H NMR ($(CD_3)_2SO$) δ : 11.87 (s, 1 H), 7.68 (dd, $J_1 = J_2 = 2.8$ Hz, 1 H), 7.22 (s, 1 H), 6.65
25 (m, 1 H), 3.85 (s, 3 H), 2.58 (s, 3 H)

A.10.h. 7-Methyl-4-(trifluoromethyl)-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 7-methyl-4-(trifluoromethyl)-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate except that the reaction
30 mixture was stirred ON at 60°C.

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LC-MS (A): t_R = 0.73 min

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 13.07 (s br, 1 H), 11.79 (s, 1 H), 7.65 (dd, $J_1 = J_2 = 2.7$ Hz, 1 H), 7.21 (s, 1 H), 6.63 (m, 1 H), 2.57 (s, 3 H)

A.11. Synthesis of 4,7-dimethyl-1H-indole-5-carboxylic acid5 A.11.a. 4-Amino-2,5-dimethylbenzonitrile

4-Bromo-2,5-dimethylaniline (5 mmol), zinc cyanide (6 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.1 mmol) were placed in a pressure vessel and anh. DMF (3 mL) was added. The tube was sealed under argon and heated at 110°C. After 35h, it was quenched with a 10% Na_2CO_3 solution and extracted three times with EtOAc. The organic phase was washed with a sat. NaHCO₃ solution, dried over MgSO_4 and concentrated in vacuo. The crude was purified by CC (SNAP KP-SilTM from Biotage) using Hept/EtOAc from 92/8 to 40/60 to give the title compound as white solid.

LC-MS (A): t_R = 0.72 min, $[\text{M}+\text{H}]^+$: 147.16A.11.b. 4-Amino-3-iodo-2,5-dimethylbenzonitrile

15 This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, 4-amino-2,5-dimethylbenzonitrile replacing methyl 4-amino-2-chlorobenzoate.

LC-MS (A): t_R = 0.85 min; $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$: 313.83A.11.c. 4-Amino-2,5-dimethyl-3-((trimethylsilyl)ethynyl)benzonitrile

20 This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, 4-amino-3-iodo-2,5-dimethylbenzonitrile replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): t_R = 1.00 min; $[\text{M}+\text{H}]^+$: 243.1325 A.11.d. 4-Amino-3-ethynyl-2,5-dimethylbenzonitrile

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, 4-amino-2,5-dimethyl-3-((trimethylsilyl)ethynyl)benzonitrile replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): t_R = 0.81 min; $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$: 212.12

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A.11.e. 4,7-Dimethyl-1H-indole-5-carbonitrile

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, 4-amino-3-ethynyl-2,5-dimethylbenzonitrile replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

5 LC-MS (A): t_R = 0.81 min; $[M+CH_3CN+H]^+$: 212.13

^1H NMR ($(CD_3)_2SO$) δ : 11.64 (s br, 1 H), 7.52 (dd, $J_1 = J_2 = 2.8$ Hz, 1 H), 7.17 (s, 1 H), 6.67 (dd, $J_1 = 2.9$ Hz, $J_2 = 1.9$ Hz, 1 H), 2.63 (s, 3 H), 2.47 (s, 3 H)

A.11.f. 4,7-Dimethyl-1H-indole-5-carboxylic acid

To a solution of 4,7-dimethyl-1H-indole-5-carbonitrile (0.19 mmol) in EtOH (1 mL) was
10 added a 4M KOH solution (3.9 mL) and the mixture was heated for 18h at 120°C. It was partitioned between water and EtOAc, the aqueous phase was acidified with a 25% HCl solution until pH 1-2 and extracted three times with EtOAc. The organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the title compound as white solid.

LC-MS (A): t_R = 0.68 min; $[M+H]^+$: 190.18

15 **A.12. Synthesis of 4-chloro-7-ethyl-1H-indole-5-carboxylic acid**

A.12.a. Methyl 4-amino-2-chloro-5-ethynyl-3-iodobenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2-chloro-3-iodo-5-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

20 LC-MS (A): t_R = 0.88 min

^1H NMR ($(CD_3)_2SO$) δ : 7.76 (s, 1 H), 6.17 (s, 2 H), 4.65 (s, 1 H), 3.78 (s, 3 H)

A.12.b. Methyl 4-amino-2-chloro-5-ethyl-3-iodobenzoate

To a solution of methyl 4-amino-2-chloro-5-ethynyl-3-iodobenzoate (0.99 mmol) in EtOH (4 mL) was added platinum dioxide (0.099 mmol). The mixture was stirred under a
25 hydrogen atmosphere for 1h, filtered over Celite and concentrated in vacuo. The crude was purified by CC using DCM to give the title compound as light yellow solid.

LC-MS (A): t_R = 0.90 min, $[M+H]^+$: 339.83

A.12.c. Methyl 4-amino-2-chloro-5-ethyl-3-((trimethylsilyl)ethynyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2-chloro-5-ethyl-3-iodobenzoate
30

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replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate except that the reaction was stirred for 30 min at 80°C.

LC-MS (A): t_R = 1.03 min; $[M+H]^+$: 310.22

A.12.d. Methyl 4-amino-2-chloro-5-ethyl-3-ethynylbenzoate

- 5 This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2-chloro-5-ethyl-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): t_R = 0.86 min; $[M+H]^+$: 238.21

A.12.e. Methyl 4-chloro-7-ethyl-1H-indole-5-carboxylate

- 10 This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-2-chloro-5-ethyl-3-ethynylbenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): t_R = 0.86 min, $[M+H]^+$: 238.05

A.12.f. 4-Chloro-7-ethyl-1H-indole-5-carboxylic acid

- 15 This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 7-methyl-4-(trifluoromethyl)-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

LC-MS (A): t_R = 0.73 min, $[M+H]^+$: 224.20

A.13. Synthesis of 7-chloro-4-methyl-1H-indole-5-carboxylic acid

- 20 *A.13.a. Methyl 4-acetamido-5-chloro-2-(((trifluoromethyl)sulfonyl)oxy)benzoate*

To a solution of methyl 4-acetamido-5-chloro-2-hydroxybenzoate (20.5 mmol) in DCM (100 mL) was added at 0°C Et₃N (22.6 mmol) and trifluoromethanesulfonic anhydride (22.6 mmol). The mixture was stirred for 1h at RT, quenched with a sat. solution of NaHCO₃ and extracted with DCM. The organic phase was washed with brine, dried over
25 MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-SilTM from Biotage) using Hept/EtOAc from 100/0 to 65/35 to give the title compound as light yellow solid.

LC-MS (A): t_R = 0.90 min

¹H NMR ((CD₃)₂SO) δ : 9.94 (s, 1 H), 8.35 (s, 1 H), 8.14 (s, 1 H), 3.88 (s, 3 H), 2.23 (s, 3
30 H)

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A.13.b. Methyl 4-acetamido-5-chloro-2-methylbenzoate

A suspension of methyl 4-acetamido-5-chloro-2-(((trifluoromethyl)sulfonyl)oxy)benzoate (2.61 mmol), K₃PO₄ (5.23 mmol), methylboronic acid (5.23 mmol) and Pd(dppf)Cl₂.DCM (0.26 mmol) in THF (26 mL) was stirred under argon for 2h at 65°C. The reaction mixture
5 was quenched with a sat. solution of NaHCO₃ and extracted three times with EtOAc. The organic phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-Sil™ from Biotage) using Hept/EtOAc from 100/0 to 60/40 to give the title compound as white solid.

LC-MS (A): t_R = 0.77 min, [M+H]⁺: 241.90

10 *A.13.c. Methyl 4-amino-5-chloro-2-methylbenzoate*

To a solution of methyl 4-acetamido-5-chloro-2-methylbenzoate (2.25 mmol) in MeOH (14 mL) was added K₂CO₃ (2.48 mmol). The suspension was stirred for 3 days at RT, MeOH was evaporated off and the residue was partitioned between EtOAc and a 1M solution of HCl. The aq. phase was extracted twice with EtOAc and the combined organic phases
15 were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-Sil™ from Biotage) using Hept/EtOAc from 100/0 to 80/20 to give the title compound as white solid.

LC-MS (A): t_R = 0.81 min, [M+H]⁺: 200.12

A.13.d. Methyl 4-amino-5-chloro-3-iodo-2-methylbenzoate

20 This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-5-chloro-2-methylbenzoate replacing methyl 4-amino-2-chlorobenzoate except that the reaction mixture was stirred for 1h at RT.

LC-MS (A): t_R = 0.91 min

25 ¹H NMR ((CD₃)₂SO) δ: 7.76 (s, 1 H), 6.02 (s, 2 H), 3.77 (s, 3 H), 2.65 (s, 3 H)

A.13.e. Methyl 4-amino-5-chloro-2-methyl-3-((trimethylsilyl)ethynyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-5-chloro-3-iodo-2-methyl benzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-
30 amino-2-chloro-5-iodobenzoate.

LC-MS (A): t_R = 1.06 min; [M+H]⁺: 296.14

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A.13.f. Methyl 4-amino-5-chloro-3-ethynyl-2-methylbenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-5-chloro-2-methyl-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

- 5 LC-MS (A): t_R = 0.88 min; $[M+H]^+$: 224.03

A.13.g. Methyl 7-chloro-4-methyl-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-5-chloro-3-ethynyl-2-methylbenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

- 10 LC-MS (A): t_R = 0.86 min, $[M+H]^+$: 223.46

A.13.h. 7-Chloro-4-methyl-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 7-chloro-4-methyl-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

- 15 LC-MS (A): t_R = 0.72 min

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 12.62 (s, 1 H), 11.77 (s, 1 H), 7.67 (s, 1 H), 7.49 (dd, $J_1 = J_2 = 2.8$ Hz, 1 H), 6.78 (dd, $J_1 = 2.0$ Hz, $J_2 = 3.0$ Hz, 1 H), 2.75 (s, 3 H)

*A.14. Synthesis of 7-methoxy-4-methyl-1H-indole-5-carboxylic acid**A.14.a. 5-Methoxy-2-methyl-4-nitrobenzonitrile*

- 20 To a solution of CuCN (25.2 mmol) in CH_3CN (32 mL) was added *tert*-butylnitrite (19.8 mmol) at RT followed by a suspension of 5-methoxy-2-methyl-4-nitroaniline (11 mmol) in CH_3CN (5 mL) at 0°C. The mixture was stirred for 1 h at 85°C then ON at RT, quenched with a 10% solution of Na_2CO_3 and extracted three times with EtOAc. The organic phases were washed with brine, dried over MgSO_4 and concentrated in vacuo. The crude was
- 25 purified by CC (SNAP KP-SilTM from Biotage) using Hept/EtOAc from 100/0 to 85/15 to give the title compound as orange solid.

LC-MS (A): t_R = 0.82 min

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 8.00 (s, 1 H), 7.88 (s, 1 H), 3.95 (s, 3 H), 2.47 (s, 3 H)

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A.14.b. 5-Methoxy-2-methyl-4-nitrobenzoic acid

To a suspension of 5-methoxy-2-methyl-4-nitrobenzonitrile (1.92 mmol) in 2-propanol (4.3 mL) and water (4.3 mL) was added KOH (9.6 mmol). The mixture was stirred for 2h at 70°C, diluted with water and extracted three times with EtOAc. The organic phases were
5 washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was dissolved in water (1 mL) and H₂SO₄ (2.9 mL) and the mixture was heated to 80°C. Sodium nitrite (3.46 mmol) was added dropwise and the reaction mixture was stirred for 45 min at 80°C. It was diluted with water and extracted three times with EtOAc. The organic phase was dried over MgSO₄ and concentrated in vacuo to give the crude title
10 compound as orange solid.

LC-MS (A): t_R = 0.82 minLC-MS (D*): t_R = 0.17 min; [M-H]⁻: 210.19*A.14.c. Methyl 5-methoxy-2-methyl-4-nitrobenzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chlorobenzoate, 5-methoxy-2-methyl-4-nitrobenzoic acid replacing 4-amino-2-chloro-
15 benzoic acid.

LC-MS (A): t_R = 0.85 min¹H NMR ((CD₃)₂SO) δ: 7.87 (s, 1 H), 7.64 (s, 1 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 2.46 (s, 3 H)*20 A.14.d. Methyl 4-amino-5-methoxy-2-methylbenzoate*

To a solution of methyl 5-methoxy-2-methyl-4-nitrobenzoate (2.13 mmol) in MeOH (21 mL) was added zinc dust (21.3 mmol) at RT followed by ammonium formate (21.3 mmol) at 0°C. The mixture was stirred for 1h at RT, filtered over Celite and the filtrate was concentrated in vacuo. The residue was partitioned between EtOAc and a sat. solution of
25 NaHCO₃. The organic phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH from 100/0 to 99/1 to give the title compound as light yellow solid.

LC-MS (A): t_R = 0.71 min; [M+H]⁺: 196.15*A.14.e. Methyl 4-amino-3-iodo-5-methoxy-2-methylbenzoate*

This compound was prepared using a method analogous to that of the mixture of methyl
30 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-

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amino-5-methoxy-2-methylbenzoate replacing methyl 4-amino-2-chlorobenzoate except that the reaction mixture was stirred for 1h at RT.

LC-MS (A): t_R = 0.87 min, $[M+H]^+$: 321.73

A.14.f. Methyl 4-amino-5-methoxy-2-methyl-3-((trimethylsilyl)ethynyl)benzoate

- 5 This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-3-iodo-5-methoxy-2-methylbenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): t_R = 1.01 min; $[M+H]^+$: 292.21

10 *A.14.g. Methyl 4-amino-3-ethynyl-5-methoxy-2-methylbenzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-5-methoxy-2-methyl-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): t_R = 0.83 min; $[M+H]^+$: 220.13

15 *A.14.h. Methyl 7-methoxy-4-methyl-1H-indole-5-carboxylate*

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-3-ethynyl-5-methoxy-2-methylbenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): t_R = 0.81 min; $[M+H]^+$: 220.07

20 *A.14.i. 7-Methoxy-4-methyl-1H-indole-5-carboxylic acid*

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 7-methoxy-4-methyl-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

LC-MS (A): t_R = 0.67 min; $[M+H]^+$: 206.15

25 ***A.15. Synthesis of 4-chloro-7-ethoxy-1H-indole-5-carboxylic acid***

A.15.a. 4-Amino-2-chloro-5-methoxybenzonitrile

This compound was prepared using a method analogous to that of 4-amino-2,5-dimethylbenzonitrile, 4-bromo-5-chloro-2-methoxyaniline replacing 4-bromo-2,5-dimethyl aniline except that the reaction mixture was stirred ON at 110°C.

- 30 LC-MS (A): t_R = 0.76 min, $[M+H]^+$: 183.19

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A. 15.b. 4-Amino-2-chloro-3-iodo-5-methoxybenzonitrile

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, 4-amino-2-chloro-5-methoxybenzonitrile replacing methyl 4-amino-2-chlorobenzoate except that
5 the reaction mixture was stirred for 45 min at RT.

LC-MS (A): t_R = 0.86 min

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 7.33 (s, 1 H), 6.11 (s, 2 H), 3.85 (s, 3 H)

A. 15.c. 4-Amino-2-chloro-5-methoxy-3-((trimethylsilyl)ethynyl)benzonitrile

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, 4-amino-2-chloro-3-iodo-5-methoxybenzonitrile
10 replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): t_R = 1.00 min; $[\text{M}+\text{H}]^+$: 279.04

A. 15.d. 4-Amino-2-chloro-3-ethynyl-5-methoxybenzonitrile

15 This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, 4-amino-2-chloro-5-methoxy-3-((trimethylsilyl)ethynyl)benzonitrile replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): t_R = 0.82 min; $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$: 248.23

A. 15.e. 4-Chloro-7-methoxy-1H-indole-5-carbonitrile

20 This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, 4-amino-2-chloro-3-ethynyl-5-methoxybenzonitrile replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): t_R = 0.83 min, $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$: 248.23

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 12.23 (s, 1 H), 7.56 (d, J = 3.1 Hz, 1 H), 7.14 (s, 1 H), 6.61 (d, J =
25 3.1 Hz, 1 H), 3.99 (s, 3 H)

A. 15.f. 4-Chloro-7-hydroxy-1H-indole-5-carbonitrile

To a solution of 4-chloro-7-methoxy-1H-indole-5-carbonitrile (2.53 mmol) in DCM (106 mL) was added dropwise a 1M solution of BBr_3 in DCM (14.8 mmol) at -78°C . The mixture was allowed to warm up to RT and stirred for 15h at 45°C then for 4h30 at 55°C . It was
30 quenched with MeOH (40 mL) and concentrated in vacuo. The crude was purified by CC

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(SNAP KP-Sil™ from Biotage) using EtOAc/MeOH from 100/0 to 90/10 to give the title compound as brownish solid.

LC-MS (A): t_R = 0.75 min

¹H NMR ((CD₃)₂SO) δ : 11.99 (s, 1 H), 10.69 (s, 1 H), 7.54 (dd, $J_1 = J_2 = 2.8$ Hz, 1 H), 6.80
5 (s, 1 H), 6.57 (m, 1 H)

A. 15.g. 4-Chloro-7-ethoxy-1H-indole-5-carbonitrile

To a solution of 4-chloro-7-hydroxy-1H-indole-5-carbonitrile (1.31 mmol) in DMF (2.6 mL) was added at 0°C K₂CO₃ (1.58 mmol) and ethyl bromide (1.44 mmol). The mixture was stirred ON at RT, quenched with water and extracted with EtOAc. The organic phase was
10 dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (SNAP KP-Sil™ from Biotage) using Hept/EtOAc from 100/0 to 50/50 to give the title compound as white solid.

LC-MS (A): t_R = 0.88 min, [M+CH₃CN+H]⁺: 262.10

A. 15.h. 4-Chloro-7-ethoxy-1H-indole-5-carboxylic acid

15 This compound was prepared using a method analogous to that of 4,7-dimethyl-1H-indole-5-carboxylic acid, 4-chloro-7-ethoxy-1H-indole-5-carbonitrile replacing 4,7-dimethyl-1H-indole-5-carbonitrile.

LC-MS (A): t_R = 0.73 min; [M+H]⁺: 240.05

A. 16. Synthesis of 4-chloro-7-propyl-1H-indole-5-carboxylic acid

20 *A. 16.a. Methyl 4-amino-2-chloro-5-propylbenzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-5-isobutylbenzoate, 1-propylboronic acid replacing (2-methylpropyl)boronic acid.

LC-MS (A): t_R = 0.86 min; [M+H]⁺: 228.15

A. 16.b. Methyl 4-amino-2-chloro-3-iodo-5-propylbenzoate

25 This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2-chloro-5-propylbenzoate replacing methyl 4-amino-2-chlorobenzoate.

LC-MS (A): t_R = 0.94 min; [M+H]⁺: 353.66

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A.16.c. Methyl 4-amino-2-chloro-5-propyl-3-((trimethylsilyl)ethynyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2-chloro-3-iodo-5-propylbenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and
5 methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): t_R = 1.05 min; $[M+H]^+$: 324.10

A.16.d. Methyl 4-amino-2-chloro-3-ethynyl-5-propylbenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2-chloro-5-propyl-3-((trimethylsilyl)ethynyl)
10 benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): t_R = 0.90 min; $[M+H]^+$: 252.25

A.16.e. Methyl 4-chloro-7-propyl-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-2-chloro-3-ethynyl-5-propylbenzoate replacing
15 methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): t_R = 0.91 min; $[M+H]^+$: 252.21

A.16.f. 4-Chloro-7-propyl-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4-chloro-7-propyl-1H-indole-5-carboxylate replacing
20 methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

LC-MS (A): t_R = 0.78 min, $[M+H]^+$: 238.19

A.17. Synthesis of 7-(2-(tert-butoxy)ethoxy)-4-chloro-1H-indole-5-carboxylic acid*A.17.a. 7-(2-(tert-Butoxy)ethoxy)-4-chloro-1H-indole-5-carbonitrile*

This compound was prepared using a method analogous to that of 4-chloro-7-ethoxy-1H-indole-5-carbonitrile, 2-(2-bromoethoxy)-2-methylpropane replacing ethyl bromide except
25 that the reaction mixture was stirred for 8h at 80°C.

LC-MS (A): t_R = 0.94 min, $[M+CH_3CN+H]^+$: 334.12

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A.17.b. 7-(2-(tert-Butoxy)ethoxy)-4-chloro-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4,7-dimethyl-1H-indole-5-carboxylic acid, 7-(2-(tert-butoxy)ethoxy)-4-chloro-1H-indole-5-carbonitrile replacing 4,7-dimethyl-1H-indole-5-carbonitrile.

5 LC-MS (A): t_R = 0.80 min; $[M+CH_3CN+H]^+$: 353.16

^1H NMR ($(CD_3)_2SO$) δ : 12.86 (s very br, 1 H), 11.74 (s, 1 H), 7.43 (dd, $J_1 = J_2 = 2.7$ Hz, 1 H), 7.17 (s, 1 H), 6.58 (m, 1 H), 4.26 (m, 2 H), 3.74 (m, 2 H), 1.18 (s, 9 H)

*A.18. Synthesis of 4-chloro-7-methoxy-1H-indole-5-carboxylic acid**A.18.a. 1-Chloro-4-methoxy-2-methyl-5-nitrobenzene*

10 To a suspension of 4-chloro-5-methyl-2-nitrophenol (5.33 mmol) and K_2CO_3 (10.70 mmol) in DMF (11 mL) was added methyl iodide (5.86 mmol) and the mixture was stirred for 6h at RT. It was quenched with half saturated $NaHCO_3$ solution and extracted three times with EtOAc. The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC (Isolute Flash Si II from Biotage) using Hept/EtOAc from 85/15
15 to 80/20 to give the title compound as yellow solid.

LC-MS (A): t_R = 0.88 min

^1H NMR ($(CD_3)_2SO$) δ : 8.01 (s, 1 H), 7.44 (s, 1 H), 3.93 (s, 3 H), 2.42 (s, 3 H)

A.18.b. 2-Chloro-5-methoxy-4-nitrobenzoic acid

To a suspension of 1-chloro-4-methoxy-2-methyl-5-nitrobenzene (4.32 mmol) in H_2O (207
20 mL) was added $KMnO_4$ (17.30 mmol) and the mixture was refluxed for 3h and filtered to remove solids. The filtrate was quenched with a 40% $NaHSO_3$ solution, acidified with a 1M HCl solution until pH 1-2 and extracted three times with EtOAc. The organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the title compound as light yellow solid.

25 LC-MS (A): t_R = 0.69 min

LC-MS (D*): t_R = 0.26 min, $[M-H]^-$: 230.04

A.18.c. 4-Amino-2-chloro-5-methoxybenzoic acid

This compound was prepared using a method analogous to that of methyl 4-amino-2,6-dichlorobenzoate, 2-chloro-5-methoxy-4-nitrobenzoic acid replacing methyl 2,6-dichloro-4-
30 nitrobenzoate except that the mixture was heated for 15 min at 100°C under microwave conditions.

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LC-MS (A): $t_R = 0.59$ min; $[M+CH_3CN+H]^+$: 242.70*A.18.d. Methyl 4-amino-2-chloro-5-methoxybenzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chlorobenzoate, 4-amino-2-chloro-5-methoxybenzoic acid replacing 4-amino-2-chlorobenzoic acid.

LC-MS (A): $t_R = 0.75$ min; $[M+H]^+$: 216.14*A.18.e. Methyl 4-amino-2-chloro-3-iodo-5-methoxybenzoate*

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2-chloro-5-methoxybenzoate replacing methyl 4-amino-2-chlorobenzoate.

LC-MS (A): $t_R = 0.85$ min; $[M+H]^+$: 341.67*A.18.f. Methyl 4-amino-2-chloro-5-methoxy-3-((trimethylsilyl)ethynyl)benzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2-chloro-3-iodo-5-methoxybenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): $t_R = 0.99$ min; $[M+H]^+$: 311.94*A.18.g. Methyl 4-amino-2-chloro-3-ethynyl-5-methoxybenzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2-chloro-5-methoxy-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): $t_R = 0.81$ min; $[M+H]^+$: 240.02*A.18.h. Methyl 4-chloro-7-methoxy-1H-indole-5-carboxylate*

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-2-chloro-3-ethynyl-5-methoxybenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): $t_R = 0.82$ min; $[M+H]^+$: 239.95

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A.18.i. 4-Chloro-7-methoxy-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4-chloro-7-methoxy-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

5 LC-MS (A): t_R = 0.68 min, $[M+H]^+$: 226.08

*A.19. Synthesis of 4,7-difluoro-1H-indole-5-carboxylic acid**A.19.a. Methyl 2,5-difluoro-4-nitrobenzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chlorobenzoate, 2,5-difluoro-4-nitrobenzoic acid replacing 4-amino-2-chlorobenzoic acid.

10 LC-MS (A): t_R = 0.80 min

^1H NMR ($(CD_3)_2SO$) δ : 8.31 (dd, J_1 = 6.0 Hz, J_2 = 9.7 Hz, 1 H), 8.07 (dd, J_1 = 5.8 Hz, J_2 = 10.9 Hz, 1 H), 3.92 (s, 3 H)

A.19.b. Methyl 4-amino-2,5-difluorobenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-5-methoxy-2-methylbenzoate, methyl 2,5-difluoro-4-nitrobenzoate replacing methyl 5-methoxy-2-methyl-4-nitrobenzoate.

15 LC-MS (A): t_R = 0.70 min, $[M+H]^+$: 188.22

A.19.c. Methyl 4-amino-2,5-difluoro-3-iodobenzoate

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2,5-difluorobenzoate replacing methyl 4-amino-2-chlorobenzoate except that the reaction mixture was stirred for 1h at RT.

LC-MS (A): t_R = 0.81 min

^1H NMR ($(CD_3)_2SO$) δ : 7.52 (dd, J_1 = 6.7 Hz, J_2 = 11.7 Hz, 1 H), 6.43 (s, 2 H), 3.78 (s, 3 H)

25 *A.19.d. Methyl 4-amino-2,5-difluoro-3-((trimethylsilyl)ethynyl)benzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2,5-difluoro-3-iodobenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

30 LC-MS (A): t_R = 0.98 min; $[M+H]^+$: 284.22

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A.19.e. Methyl 4-amino-3-ethynyl-2,5-difluorobenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2,5-difluoro-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

5 LC-MS (A): t_R = 0.78 min

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 7.48 (dd, J_1 = 6.6 Hz, J_2 = 11.8 Hz, 1 H), 6.66 (s, 2 H), 4.80 (s, 1 H), 3.78 (s, 3 H)

A.19.f. Methyl 4,7-difluoro-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-3-ethynyl-2,5-difluorobenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

10 LC-MS (A): t_R = 0.79 min, $[\text{M}+\text{H}]^+$: 212.21

A.19.g. 4,7-Difluoro-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4,7-difluoro-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

15 LC-MS (A): t_R = 0.64 min

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 12.96 (s, 1 H), 12.29 (s, 1 H), 7.56 (dd, J_1 = J_2 = 2.6 Hz, 1 H), 7.32 (dd, J_1 = 4.9 Hz, J_2 = 11.3 Hz, 1 H), 6.73 (m, 1 H)

20 **A.20. Synthesis of 4-fluoro-7-methoxy-1H-indole-5-carboxylic acid**

A.20.a. 2-Fluoro-5-methoxy-4-nitrobenzoic acid

To a suspension of 2,5-difluoro-4-nitrobenzoic acid (2.46 mmol) and Cs_2CO_3 (12.3 mmol) in DMF was added MeOH (16.5 mmol) and the mixture was stirred for 3h30 at RT. It was diluted with water, acidified with a 1M solution of HCl until pH=1-2 and extracted three times with EtOAc. The organic phases were washed with brine, dried over MgSO_4 and concentrated in vacuo to give the title compound as light yellow solid.

25 LC-MS (A): t_R = 0.67 min

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 13.96 (s br, 1 H), 8.03 (d, J = 9.6 Hz, 1 H), 7.68 (d, J = 5.8 Hz, 1 H), 3.97 (s, 3 H)

30 *A.20.b. Methyl 2-fluoro-5-methoxy-4-nitrobenzoate*

This compound was prepared using a method analogous to that of methyl 4-amino-2-chlorobenzoate, 2-fluoro-5-methoxy-4-nitrobenzoic acid replacing 4-amino-2-chlorobenzoic acid.

LC-MS (A): t_R = 0.81 min

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^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 8.09 (d, $J = 9.7$ Hz, 1 H), 7.70 (d, $J = 5.7$ Hz, 1 H), 3.98 (s, 3 H), 3.92 (s, 3 H)

A.20.c. Methyl 4-amino-2-fluoro-5-methoxybenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-5-methoxy-2-methylbenzoate, methyl 2-fluoro-5-methoxy-4-nitrobenzoate replacing methyl 5-methoxy-2-methyl-4-nitrobenzoate.

LC-MS (A): $t_R = 0.70$ min, $[\text{M}+\text{H}]^+$: 200.19

A.20.d. Methyl 4-amino-2-fluoro-3-iodo-5-methoxybenzoate

This compound was prepared using a method analogous to that of the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate, methyl 4-amino-2-fluoro-5-methoxybenzoate replacing methyl 4-amino-2-chlorobenzoate except that the reaction mixture was stirred for 2h at RT.

LC-MS (A): $t_R = 0.83$ min, $[\text{M}+\text{H}]^+$: 325.97

A.20.e. Methyl 4-amino-2-fluoro-5-methoxy-3-((trimethylsilyl)ethynyl)benzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate, methyl 4-amino-2-fluoro-3-iodo-5-methoxybenzoate replacing the mixture of methyl 4-amino-2-chloro-3-iodobenzoate and methyl 4-amino-2-chloro-5-iodobenzoate.

LC-MS (A): $t_R = 0.97$ min; $[\text{M}+\text{H}]^+$: 296.03

A.20.f. Methyl 4-amino-3-ethynyl-2-fluoro-5-methoxybenzoate

This compound was prepared using a method analogous to that of methyl 4-amino-2-chloro-3-ethynylbenzoate, methyl 4-amino-2-fluoro-5-methoxy-3-((trimethylsilyl)ethynyl)benzoate replacing methyl 4-amino-2-chloro-3-((trimethylsilyl)ethynyl)benzoate.

LC-MS (A): $t_R = 0.78$ min; $[\text{M}+\text{H}]^+$: 223.92

A.20.g. Methyl 4-fluoro-7-methoxy-1H-indole-5-carboxylate

This compound was prepared using a method analogous to that of methyl 4-chloro-1H-indole-5-carboxylate, methyl 4-amino-3-ethynyl-2-fluoro-5-methoxybenzoate replacing methyl 4-amino-2-chloro-3-ethynylbenzoate.

LC-MS (A): $t_R = 0.78$ min, $[\text{M}+\text{H}]^+$: 223.76

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ : 11.96 (s, 1 H), 7.41 (dd, $J_1 = J_2 = 2.6$ Hz, 1 H), 6.99 (d, $J = 4.9$ Hz, 1 H), 6.62 (m, 1 H), 3.95 (s, 3 H), 3.85 (s, 3 H)

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A.20.h. 4-Fluoro-7-methoxy-1H-indole-5-carboxylic acid

This compound was prepared using a method analogous to that of 4-chloro-7-methyl-1H-indole-5-carboxylic acid, methyl 4-fluoro-7-methoxy-1H-indole-5-carboxylate replacing methyl 4-chloro-7-methyl-1H-indole-5-carboxylate.

5 LC-MS (A): $t_R = 0.64$ min, $[M+H]^+$: 210.15

B. Synthesis of amines***B.1. Synthesis of 2-alkyl/(hetero)aryl-2-aminoethanamine******B.1.a. Strecker reaction (general procedure I)***

To a suspension of the corresponding aldehyde (24.6 mmol) in anh. Et₂O (8 mL) was slowly added at RT, TMSCN (27 mmol) followed by ZnI₂ (1.23 mmol). The mixture was cooled to 0°C and a solution of the corresponding amine (24.6 mmol) in anh. MeOH (20 mL) was added dropwise (when the amine was a HCl salt, 24.6 mmol of TEA were additionally added). The mixture was heated at 70°C for 1 to 6h then cooled to RT. It was quenched with a 10% Na₂CO₃ aq. solution and extracted 3 times with EtOAc. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (KP-NH™ from Biotage) to isolate the desired α-amino-nitrile (see table below).

Name	LC-MS		
	type	t_R (min)	$[M+H]^+$
2-morpholino-2-(2-(trifluoromethyl)pyrimidin-5-yl)acetonitrile	B	0.65	$[M+MeCN+H]^+$: 313.99
2-(6-chloropyridin-3-yl)-2-(4,4-difluoropiperidin-1-yl)acetonitrile	B	0.76	272.25
2-(2-methylpyrimidin-5-yl)-2-morpholinoacetonitrile	B	0.39	219.41
2-(4,4-difluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	B	0.59	253.05
2-(6-methylpyridin-3-yl)-2-morpholinoacetonitrile	B	0.29	218.11
2-(4,4-difluoropiperidin-1-yl)-2-(2-(trifluoromethyl)pyrimidin-5-yl)acetonitrile	B	0.80	$[M+MeCN+H]^+$: 347.93

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2-(2-cyclopropylpyrimidin-5-yl)-2-morpholinoacetonitrile	B	0.55	245.06
2-morpholino-2-(6-(trifluoromethyl)pyridin-3-yl)acetonitrile	B	0.68	272.01
2-(6-methoxypyridin-3-yl)-2-morpholinoacetonitrile	B	0.57	234.33
2-(dimethylamino)-2-(2-methylpyrimidin-5-yl)acetonitrile	B	0.39	177.46
2-(azetidin-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	B	0.35	189.47
2-(2-methylpyrimidin-5-yl)-2-(pyrrolidin-1-yl)acetonitrile	B	0.44	203.46
2-(diethylamino)-2-(2-methylpyrimidin-5-yl)acetonitrile	B	0.58	205.14
2-(2-methylpyrimidin-5-yl)-2-(piperidin-1-yl)acetonitrile	B	0.59	217.11
2-(4-fluorophenyl)-2-morpholinoacetonitrile	B	0.70	221.06
2-(3,5-difluorophenyl)-2-morpholinoacetonitrile	B	0.74	239.05
2-(6-chloropyridin-3-yl)-2-morpholinoacetonitrile	A	0.70	238.26
2-morpholino-2-(pyrimidin-5-yl)acetonitrile	E	0.30	205.3
2-(piperidin-1-yl)-2-(pyrimidin-5-yl)acetonitrile	E	0.72	203.26
2-(1-methyl-1H-pyrazol-4-yl)-2-morpholinoacetonitrile	E	0.35	207.27
2-(1-methyl-1H-pyrazol-4-yl)-2-(piperidin-1-yl)acetonitrile	F	0.56	205.3
2-(piperidin-1-yl)-2-(2,4,6-	F	0.89	255.16

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trifluorophenyl)acetonitrile			
2-(2,4-difluorophenyl)-2-(piperidin-1-yl)acetonitrile	F	0.91	237.23
2-(5-fluoropyridin-2-yl)-2-(piperidin-1-yl)acetonitrile	F	0.74	220.26
2-morpholino-2-(2,4,6-trifluorophenyl)acetonitrile	F	0.66	257.12
2-(2,4-difluorophenyl)-2-morpholinoacetonitrile	F	0.68	239.21
2-(2-fluorophenyl)-2-morpholinoacetonitrile	F	0.64	221.26
2-(5-fluoropyridin-2-yl)-2-morpholinoacetonitrile	F	0.48	222.26
2-(3-fluorophenyl)-2-morpholinoacetonitrile	F	0.68	221.25
2-(4-chlorophenyl)-2-morpholinoacetonitrile	A	0.83	237.08
2-(2,4-dichlorophenyl)-2-morpholinoacetonitrile	A	0.89	270.98
2-(4-chloro-2-fluorophenyl)-2-morpholinoacetonitrile	A	0.84	255.02
2-(2,6-dimethylmorpholino)-2-(2-methylpyrimidin-5-yl)acetonitrile	A	0.66	247.32
2-(3-fluorophenyl)-2-(piperidin-1-yl)acetonitrile	F	0.93	219.28
2-(piperidin-1-yl)-2-(4-(trifluoromethyl)phenyl)acetonitrile	F	1.02	269.14
2-(3,4-difluorophenyl)-2-(piperidin-1-yl)acetonitrile	F	0.96	237.22
2-(6-chloropyridin-3-yl)-2-(piperidin-1-yl)acetonitrile	F	0.82	236.21
2-morpholino-2-(p-tolyl)acetonitrile	F	0.74	217.28

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2-morpholino-2-(4-(trifluoromethoxy)phenyl)acetonitrile	F	0.84	287.08
2-morpholino-2-(4-(trifluoromethyl)phenyl)acetonitrile	F	0.81	271.1
2-(3,4-difluorophenyl)-2-morpholinoacetonitrile	F	0.72	239.2
2-(3,5-dimethylisoxazol-4-yl)-2-morpholinoacetonitrile	E	0.63	222.25
2-(3,5-dimethylisoxazol-4-yl)-2-(piperidin-1-yl)acetonitrile	E	1.07	220.28
2-(piperidin-1-yl)-2-(p-tolyl)acetonitrile	F	0.98	215.29
2-(6-chloropyridin-3-yl)-2-(piperidin-1-yl)acetonitrile	F	0.82	236.21
2-(4-phenoxyphenyl)-2-(piperidin-1-yl)acetonitrile	F	1.09	293.16
2-morpholino-2-(4-phenoxyphenyl)acetonitrile	F	0.89	295.13
2-(4-methoxyphenyl)-2-morpholinoacetonitrile	F	0.67	233.24
2-(5-methylpyrazin-2-yl)-2-(piperidin-1-yl)acetonitrile	F	0.64	217.3
2-(isothiazol-5-yl)-2-(piperidin-1-yl)acetonitrile	F	0.76	208.2
2-(piperidin-1-yl)-2-(thiazol-5-yl)acetonitrile	F	0.66	208.22
2-(5-methylpyrazin-2-yl)-2-morpholinoacetonitrile	F	0.39	219.26
2-morpholino-2-(thiazol-5-yl)acetonitrile	F	0.39	210.2
2-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	A	0.54	231.16

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2-(piperidin-1-yl)-2-(pyridazin-3-yl)acetonitrile	E	0.65	203.27
2-(2-hydroxypyridin-4-yl)-2-(piperidin-1-yl)acetonitrile	E	0.64	218.25
<i>tert</i> -butyl 1-(cyano(2-methylpyrimidin-5-yl)methyl)piperidine-4-carboxylate	E	1.09	317.23
2-(4-methylpiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.95	231.27
2-(2-methylpiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.93	231.26
2-(4-fluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.64	235.24
2-(3,3-difluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.75	253.16
2-(azepan-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	F	0.71	231.26
2-(2-methylpyrimidin-5-yl)-2-(1,4-oxazepan-4-yl)acetonitrile	E	0.50	233.24
2-(3,3-difluoropyrrolidin-1-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.66	239.19
2-(cyclopentylamino)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.71	217.28
2-((cyclopentylmethyl)amino)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.90	231.28
2-(isobutylamino)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.72	205.29
2-(isobutyl(methyl)amino)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.97	219.29
2-(benzyl(methyl)amino)-2-(2-methylpyrimidin-5-yl)acetonitrile	E	0.99	253.17

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<i>tert</i> -butyl 4-(cyano(2-methylpyrimidin-5-yl)methyl)piperazine-1-carboxylate	F	0.68	318.2
2-morpholino-2-(pyridazin-3-yl)acetonitrile	E	0.24	205.24
2-morpholino-2-(2-hydroxypyridin-4-yl)acetonitrile	E	0.25	220.23
2-(1,1-dioxidothiomorpholino)-2-(2-methylpyrimidin-5-yl)acetonitrile	F	0.28	267.09
2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-2-(2-methylpyrimidin-5-yl)acetonitrile	A	0.56	231.13

B.1.b. Hydrogenation of nitrile (general procedure II)

To a solution of the α -amino-nitrile (4.38 mmol) from the previous step in a 7M solution of NH₃ in MeOH (32 mL) were added at 0°C a 4% solution of thiophene in diisopropylether (0.16 mL) and Actimet M Raney nickel. The mixture was allowed to warm to RT and stirred under a hydrogen atmosphere for 30h. It was filtered over Celite, washed with MeOH and concentrated in vacuo. The amine was optionally transformed to its HCl salt by dissolution in Et₂O (8.8 mL), addition of a 4M HCl solution in dioxane (4.4 mL) at 0°C and filtration of the formed solid.

Name	LC-MS		
	type	tr (min)	[M+H] ⁺
2-morpholino-2-(2-(trifluoromethyl)pyrimidin-5-yl)ethanamine	B	0.40	277.09
2-(6-chloropyridin-3-yl)-2-(4,4-difluoropiperidin-1-yl)ethanamine	B	0.50	276.30
2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine	B	0.21	223.10
2-(4,4-difluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	B	0.40	257.07
2-(6-methylpyridin-3-yl)-2-morpholinoethanamine	B	0.12	222.12

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2-(4,4-difluoropiperidin-1-yl)-2-(2-(trifluoromethyl)pyrimidin-5-yl)ethanamine	B	0.55	311.39
2-(2-cyclopropylpyrimidin-5-yl)-2-morpholinoethanamine	B	0.34	249.10
2-morpholino-2-(6-(trifluoromethyl)pyridin-3-yl)ethanamine	B	0.41	276.10
2-(6-methoxypyridin-3-yl)-2-morpholinoethanamine	B	0.28	238.09
N1,N1-dimethyl-1-(2-methylpyrimidin-5-yl)ethane-1,2-diamine	B	0.10	181.20
2-(azetidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	B	0.10	193.18
2-(2-methylpyrimidin-5-yl)-2-(pyrrolidin-1-yl)ethanamine	B	0.13	207.15
N1,N1-diethyl-1-(2-methylpyrimidin-5-yl)ethane-1,2-diamine	B	0.15	209.19
2-(2-methylpyrimidin-5-yl)-2-(piperidin-1-yl)ethanamine	B	0.19	221.19
2-(4-fluorophenyl)-2-morpholinoethanamine	B	0.31	225.12
2-(3,5-difluorophenyl)-2-morpholinoethanamine	B	0.41	242.98
2-(6-chloropyridin-3-yl)-2-morpholinoethanamine	A	0.43	242.11
2-(pyridin-3-yl)-2-morpholinoethanamine (side-product from hydrogenation of 2-(6-chloropyridin-3-yl)-2-morpholinoacetonitrile)	A	0.17	208.48
2-morpholino-2-(pyrimidin-5-yl)ethanamine	F	0.16	209.3

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2-(piperidin-1-yl)-2-(pyrimidin-5-yl)ethanamine	F	0.41	207.3
2-(1-methyl-1H-pyrazol-4-yl)-2-morpholinoethanamine	F	0.19	211.28
2-(1-methyl-1H-pyrazol-4-yl)-2-(piperidin-1-yl)ethanamine	F	0.53	209.32
2-(piperidin-1-yl)-2-(2,4,6-trifluorophenyl)ethanamine	F	0.79	259.16
2-(2,4-difluorophenyl)-2-(piperidin-1-yl)ethanamine	F	0.78	241.25
2-(5-fluoropyridin-2-yl)-2-(piperidin-1-yl)ethanamine	F	0.55	224.3
2-morpholino-2-(2,4,6-trifluorophenyl)ethanamine	F	0.56	261.13
2-(2,4-difluorophenyl)-2-morpholinoethanamine	F	0.53	243.23
2-(2-fluorophenyl)-2-morpholinoethanamine	F	0.49	225.27
2-(5-fluoropyridin-2-yl)-2-morpholinoethanamine	F	0.35	226.27
2-(3-fluorophenyl)-2-morpholinoethanamine	F	0.50	225.27
2-(4-chlorophenyl)-2-morpholinoethanamine	A	0.46	241.23
2-(2,4-dichlorophenyl)-2-morpholinoethanamine	A	0.57	275.33
2-(4-chloro-2-fluorophenyl)-2-morpholinoethanamine	A	0.54	259.29
2-(2,6-dimethylmorpholino)-2-(2-methylpyrimidin-5-yl)ethanamine	A	0.41	251.36

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2-(3-fluorophenyl)-2-(piperidin-1-yl)ethanamine	F	0.78	223.3
2-(piperidin-1-yl)-2-(4-(trifluoromethyl)phenyl)ethanamine	F	0.91	273.2
2-(3,4-difluorophenyl)-2-(piperidin-1-yl)ethanamine	F	0.87	241.24
2-(6-chloropyridin-3-yl)-2-(piperidin-1-yl)ethanamine	F	0.63	240.21
2-(pyridin-3-yl)-2-(piperidin-1-yl)ethanamine (side-product from hydrogenation of 2-(6-chloropyridin-3-yl)-2-(piperidin-1-yl)acetonitrile)	F	0.54	206.3
2-morpholino-2-(p-tolyl)ethanamine	F	0.58	221.31
2-morpholino-2-(4-(trifluoromethoxy)phenyl)ethanamine	F	0.70	291.12
2-morpholino-2-(4-(trifluoromethyl)phenyl)ethanamine	F	0.67	275.11
2-(3,4-difluorophenyl)-2-morpholinoethanamine	F	0.58	243.22
2-(3,5-dimethylisoxazol-4-yl)-2-morpholinoethanamine	F	0.38	226.3
2-(3,5-dimethylisoxazol-4-yl)-2-(piperidin-1-yl)ethanamine	F	0.58	224.3
2-(piperidin-1-yl)-2-(p-tolyl)ethanamine	F	0.93	219.33
2-(6-chloropyridin-3-yl)-2-(piperidin-1-yl)ethanamine	F	0.62	240.21
2-(4-phenoxyphenyl)-2-(piperidin-1-yl)ethanamine	F	1.05	297.19
2-morpholino-2-(4-phenoxyphenyl)ethanamine	F	0.76	299.17

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2-(4-methoxyphenyl)-2-morpholinoethanamine	F	0.50	237.27
2-(5-methylpyrazin-2-yl)-2-(piperidin-1-yl)ethanamine	F	0.52	221.33
2-(isothiazol-5-yl)-2-(piperidin-1-yl)ethanamine	F	0.54	212.29
2-(piperidin-1-yl)-2-(thiazol-5-yl)ethanamine	F	0.50	212.26
2-(5-methylpyrazin-2-yl)-2-morpholinoethanamine	F	0.27	223.3
2-morpholino-2-(thiazol-5-yl)ethanamine	F	0.23	214.25
2-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	A	0.27	235.17
2-(piperidin-1-yl)-2-(pyridazin-3-yl)ethanamine	F	0.43	207.3
4-(2-amino-1-(piperidin-1-yl)ethyl)pyridin-2-ol	F	0.37	222.26
<i>tert</i> -butyl 1-(2-amino-1-(2-methylpyrimidin-5-yl)ethyl)piperidine-4-carboxylate	F	0.62	321.25
2-(4-methylpiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	F	0.53	235.28
2-(2-methylpiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	F	0.52	235.28
2-(4-fluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	F	0.38	239.23
2-(3,3-difluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	F	0.44	257.17
2-(azepan-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	F	0.56	235.28

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2-(2-methylpyrimidin-5-yl)-2-(1,4-oxazepan-4-yl)ethanamine	F	0.31	237.25
2-(3,3-difluoropyrrolidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	F	0.38	243.2
N1-cyclopentyl-1-(2-methylpyrimidin-5-yl)ethane-1,2-diamine	F	0.44	221.29
N1-(cyclopentylmethyl)-1-(2-methylpyrimidin-5-yl)ethane-1,2-diamine	F	0.54	235.3
N1-isobutyl-1-(2-methylpyrimidin-5-yl)ethane-1,2-diamine	F	0.44	209.3
N1-isobutyl-N1-methyl-1-(2-methylpyrimidin-5-yl)ethane-1,2-diamine	F	0.57	223.3
N1-benzyl-N1-methyl-1-(2-methylpyrimidin-5-yl)ethane-1,2-diamine	F	0.61	257.18
<i>tert</i> -butyl 4-(2-amino-1-(2-methylpyrimidin-5-yl)ethyl)piperazine-1-carboxylate	F	0.54	322.25
2-morpholino-2-(pyridazin-3-yl)ethanamine	F	0.17	209.3
4-(2-amino-1-morpholinoethyl)pyridin-2-ol	F	0.12	224.3
4-(2-amino-1-(2-methylpyrimidin-5-yl)ethyl)thiomorpholine 1,1-dioxide	F	0.15	271.1
2-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-2-(2-methylpyrimidin-5-yl)ethanamine	A	0.33	235.22

B.2. Synthesis of 2-alkyl/cycloalkyl-2-heteroaryl-ethanamine

B.2.a. Synthesis of *tert*-butyl 4-(2-amino-1-(pyridin-3-yl)ethyl)piperidine-1-carboxylate

B.2.a.1. *tert*-Butyl 4-((6-chloropyridin-3-yl)(cyano)methylene)piperidine-1-carboxylate

To a solution of 2-(6-chloro-3-pyridinyl)acetonitrile (6.52 mmol) in MeOH (26 mL) was added a 30% solution of NaOMe in MeOH (13 mmol) followed by 1-Boc-4-piperidone (6.52 mmol). The mixture was heated to 70°C for 5h, poured into cold H₂O and extracted

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3 times with EtOAc. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC (KP-Sil™ from Biotage) using Hept/EtOAc from 1/0 to 7/3 to give the title compound as colorless oil.

LC-MS (B): t_R = 0.85 min; [M+CH₃CN+H]⁺: 375.32

5 B.2.a.2. tert-Butyl 4-(2-amino-1-(pyridin-3-yl)ethylidene)piperidine-1-carboxylate

This compound was prepared using a method analogous to that of general procedure II (hydrogenation of nitrile), *tert*-butyl 4-((6-chloropyridin-3-yl)(cyano)methylene)piperidine-1-carboxylate replacing α -amino-nitrile. The crude was purified by preparative LC-MS method I to give the title compound as white solid.

10 LC-MS (B): t_R = 0.43 min; [M+ H]⁺: 304.11

 B.2.a.3. tert-Butyl 4-(2-amino-1-(pyridin-3-yl)ethyl)piperidine-1-carboxylate

To a solution of *tert*-butyl 4-(2-amino-1-(pyridin-3-yl)ethylidene)piperidine-1-carboxylate (1.27 mmol) in a 7M solution of NH₃ in MeOH (20 mL) was added 10% palladium on activated charcoal (135 mg). The mixture was stirred under a hydrogen atmosphere for 2 h 30 min. It was filtered over Celite, washed with MeOH and concentrated in vacuo to give the title compound as white foam.

LC-MS (B): t_R = 0.42 min; [M+ H]⁺: 306.31

 B.2.b. Synthesis of 2-(2-methylpyrimidin-5-yl)-2-(tetrahydro-2H-pyran-4-yl)ethanamine

 B.2.b.1. 2-(2-Methylpyrimidin-5-yl)acetonitrile

20 This compound was synthesized according to JACS, 2011, 133, 6948-6951

To a solution of 5-bromo-2-methylpyrimidine (5.78 mmol) and 4-isoxazoleboronic acid pinacol ester (6.07 mmol) in DMSO (40 mL) was added a solution of potassium fluoride (17.30 mmol) in water (17 mL). The mixture was flushed with argon, Pd(dppf)Cl₂.DCM (0.58 mmol) was added and the mixture was heated for 48h at 130°C. It was filtered over a pad of Celite and washed with EtOAc. The filtrate was partitioned between water and EtOAc and the aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH from 1/0 to 95/5 to give the title compound as brown oil.

LC-MS (A): t_R = 0.43 min; [M+ H]⁺: 134.10

30 B.2.b.2. 2-(Dihydro-2H-pyran-4(3H)-ylidene)-2-(2-methylpyrimidin-5-yl)acetonitrile

This compound was prepared using a method analogous to that of *tert*-butyl 4-((6-chloropyridin-3-yl)(cyano)methylene)piperidine-1-carboxylate, 2-(2-methylpyrimidin-5-yl)acetonitrile replacing 2-(6-chloro-3-pyridinyl)acetonitrile and tetrahydro-4H-pyran-4-one

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replacing 1-Boc-4-piperidone except that the reaction mixture was stirred for 20 min at 50°C.

LC-MS (A): t_R = 0.61 min; $[M+H]^+$: 216.09

B.2.b.3. 2-(2-Methylpyrimidin-5-yl)-2-(tetrahydro-2H-pyran-4-yl)ethanamine

- 5 To a solution of 2-(dihydro-2H-pyran-4(3H)-ylidene)-2-(2-methylpyrimidin-5-yl)acetonitrile (0.22 mmol) in a 7M solution of NH_3 in MeOH (3 mL) was added 10% palladium on activated charcoal (24 mg). The mixture was stirred under a hydrogen atmosphere for 24h. It was filtered over Celite and the filtrate was treated with Actimet M Raney nickel (25 mg) at 0°C. The mixture was allowed to warm to RT and stirred under a hydrogen
10 atmosphere for 4h. It was filtered over Celite, washed with DCM/MeOH 8/2 and concentrated in vacuo to give the title compound as orange oil.

LC-MS (A): t_R = 0.38 min; $[M+H]^+$: 222.14

B.2.c. Synthesis of 2-(6-chloropyridin-3-yl)-2-cyclohexylethanamine

B.2.c.1. 2-(6-Chloropyridin-3-yl)-2-cyclohexylideneacetonitrile

- 15 To a solution of KOH (1.32 mmol) in MeOH (1.5 mL) was added at 0°C 2-(6-chloro-3-pyridinyl)acetonitrile (1.32 mmol) followed by cyclohexanone (1.32 mmol). The mixture was stirred ON allowing temperature to reach RT. It was quenched with a sat. solution of NH_4Cl , diluted with water and extracted 3 times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the crude as orange oil.
- 20 LC-MS (A): t_R = 0.90 min; $[M+H]^+$: 233.15

B.2.c.2. 2-(6-Chloropyridin-3-yl)-2-cyclohexylethanamine

- To a solution of 2-(6-chloropyridin-3-yl)-2-cyclohexylideneacetonitrile (1.28 mmol) in THF (3 mL) was added a 1M solution of BH_3 in THF (3.83 mmol). The mixture was heated for 3h at 60°C and quenched at 0°C with MeOH followed by water. The volatiles were
25 evaporated off and the residue diluted with water and acidified with a 1M solution of HCl until pH 1-2. The aqueous phase was washed 3 times with EtOAc, acidified with a 32% solution of NaOH until pH 13-14 and extracted 3 times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the title compound as light yellow oil.
- 30 LC-MS (A): t_R = 0.63 min; $[M+H]^+$: 239.17

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*B.2.d. Synthesis of 2-(6-chloropyridin-3-yl)-4-methylpentan-1-amine**B.2.d.1. 2-(6-Chloropyridin-3-yl)-4-methylpent-2-enenitrile*

This compound was prepared using a method analogous to that of 2-(6-chloropyridin-3-yl)-2-cyclohexylideneacetone, isobutyraldehyde replacing cyclohexanone except that
5 the reaction mixture was stirred for 30 min at 0°C.

LC-MS (A): t_R = 0.88 min; $[M+H]^+$: 207.16

B.2.d.2. 2-(6-Chloropyridin-3-yl)-4-methylpentan-1-amine

This compound was prepared using a method analogous to that of 2-(6-chloropyridin-3-yl)-2-cyclohexylethanamine, 2-(6-chloropyridin-3-yl)-4-methylpent-2-enenitrile replacing 2-
10 (6-chloropyridin-3-yl)-2-cyclohexylideneacetone except that the reaction mixture was stirred for 30 min at 60°C.

LC-MS (A): t_R = 0.59 min; $[M+H]^+$: 213.16

*B.2.e. Synthesis of 3-Ethyl-2-(pyrimidin-5-yl)pentan-1-amine**B.2.e.1. 3-Ethyl-2-(pyrimidin-5-yl)pent-2-enenitrile*

This compound was prepared using a method analogous to that of *tert*-butyl 4-((6-chloropyridin-3-yl)(cyano)methylene)piperidine-1-carboxylate, 5-pyrimidineacetone
15 replacing 2-(6-chloro-3-pyridinyl)acetone and 3-pentanone replacing 1-Boc-4-piperidone except that the reaction mixture was stirred ON at 50°C.

LC-MS (A): t_R = 0.76 min; $[M+H]^+$: 188.24

20 *B.2.e.2. 3-Ethyl-2-(pyrimidin-5-yl)pentan-1-amine*

This compound was prepared using a method analogous to that of 2-(2-methylpyrimidin-5-yl)-2-(tetrahydro-2H-pyran-4-yl)ethanamine, 3-ethyl-2-(pyrimidin-5-yl)pent-2-enenitrile
replacing 2-(dihydro-2H-pyran-4(3H)-ylidene)-2-(2-methylpyrimidin-5-yl)acetone.

LC-MS (A): t_R = 0.50 min; $[M+CH_3CN+H]^+$: 235.18

25 *B.2.f. 2-(4,4-Difluorocyclohexyl)-2-(2-methylpyrimidin-5-yl)ethanamine*

B.2.f.1. 2-(4,4-Difluorocyclohexylidene)-2-(2-methylpyrimidin-5-yl)acetone

This compound was prepared using a method analogous to that of 2-(6-chloropyridin-3-yl)-2-cyclohexylideneacetone, 2-(2-methylpyrimidin-5-yl)acetone replacing 2-(6-chloro-3-pyridinyl)acetone and 4,4-difluorocyclohexanone replacing cyclohexanone
30 except that the reaction mixture was stirred for 2h 30 min at 50°C.

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LC-MS (A): t_R = 0.76 min; $[M+H]^+$: 250.11**B.2.f.2. 2-(4,4-Difluorocyclohexyl)-2-(2-methylpyrimidin-5-yl)ethanamine**

This compound was prepared using a method analogous to that of 2-(2-methylpyrimidin-5-yl)-2-(tetrahydro-2H-pyran-4-yl)ethanamine, 2-(4,4-difluorocyclohexylidene)-2-(2-methylpyrimidin-5-yl)acetonitrile replacing 2-(dihydro-2H-pyran-4(3H)-ylidene)-2-(2-methylpyrimidin-5-yl)acetonitrile.

LC-MS (A): t_R = 0.50 min; $[M+CH_3CN+H]^+$: 297.26**B.3. *Synthesis of 2-alkoxy/cycloalkoxy-2-heteroarylethanamine*****B.3.a. Synthesis of 2-(cyclopentyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine****10 B.3.a.1. 1-(2-Methylpyrimidin-5-yl)-2-nitroethanol**

To a mixture of 2-methyl-pyrimidine-5-carbaldehyde (13.9 mmol) and nitromethane (22.2 mmol) in THF (8.33 mL) and tBuOH (8.33 mL) was added portionwise at 0°C tBuOK (0.83 mmol). The mixture was stirred for 5 min at 0°C, quenched with water and volatiles were evaporated off. The residue was partitioned between water and EtOAc. The organic phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc from 1/1 to 0/1 to give the title compound as yellowish solid.

LC-MS (A): t_R = 0.40 min; $[M+H]^+$: 184.13**B.3.a.2. 2-Methyl-5-(2-nitrovinyl)pyrimidine**

To a solution of 1-(2-methylpyrimidin-5-yl)-2-nitroethanol (6.73 mmol) in DCM (33.6 mL) was added DMAP (0.34 mmol) followed by Ac₂O (7.40 mmol). The mixture was stirred for 3 days at RT, quenched with a sat. solution of NaHCO₃ and extracted 3 times with DCM. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc from 75/25 to 30/70 to give the title compound as yellow solid.

25 LC-MS (A): t_R = 0.56 min; $[M+CH_3CN+H]^+$: 207.42**B.3.a.3. 5-(1-(Cyclopentyloxy)-2-nitroethyl)-2-methylpyrimidine**

To a suspension of tBuOK (1.31 mmol) in THF (3.84 mL) and tBuOH (0.77 mL) under argon was added cyclopentanol (1.15 mmol). The mixture was cooled to 0°C and a solution of 2-methyl-5-(2-nitrovinyl)pyrimidine (0.77 mmol) in THF (0.5 mL) was added dropwise. It was stirred for 5 min at 0°C then for 30 min at RT, quenched with a 2M solution of HCl and filtered over a pad of celite. The filtrate was diluted with water and

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extracted twice with EtOAc. The combined organic phases were dried over MgSO_4 and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc from 1/0 to 0/1 to give the title compound as white solid.

LC-MS (A): t_R = 0.79 min; $[\text{M}+\text{H}]^+$: 252.16

5 B.3.a.4. 2-(Cyclopentyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine

To a solution of 5-(1-(cyclopentyloxy)-2-nitroethyl)-2-methylpyrimidine (0.22 mmol) in EtOH (1.45 mL) was added 10% palladium on activated charcoal (7.8 mg). The mixture was stirred under a hydrogen atmosphere for 3h. It was filtered over Celite and the filtrate was concentrated in vacuo to give the title compound as yellow oil.

10 LC-MS (B): t_R = 0.49 min; $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$: 263.22

B.3.b. Synthesis of 2-ethoxy-2-(2-methylpyrimidin-5-yl)ethanamine

B.3.b.1. 5-(1-Ethoxy-2-nitroethyl)-2-methylpyrimidine

This compound was prepared using a method analogous to that of 5-(1-(cyclopentyloxy)-2-nitroethyl)-2-methylpyrimidine, ethanol replacing cyclopentanol.

15 LC-MS (A): t_R = 0.63 min; $[\text{M}+\text{H}]^+$: 212.17

B.3.b.2. 2-Ethoxy-2-(2-methylpyrimidin-5-yl)ethanamine

This compound was prepared using a method analogous to that of 2-(cyclopentyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine, 5-(1-ethoxy-2-nitroethyl)-2-methylpyrimidine replacing 5-(1-(cyclopentyloxy)-2-nitroethyl)-2-methylpyrimidine except that 10%
20 palladium on activated charcoal was replaced by platinum dioxide and the reaction mixture was stirred ON.

LC-MS (C): t_R = 0.31 min; $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$: 223.21

B.3.c. Synthesis of 2-(cyclohexyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine

B.3.c.1. 5-(1-(Cyclohexyloxy)-2-nitroethyl)-2-methylpyrimidine

25 To a suspension of NaH (1.70 mmol) in THF (1.89 mL) was added at 0°C cyclohexanol (6 mmol). The mixture was stirred for 5 min and a solution of 2-methyl-5-(2-nitrovinyl)pyrimidine (0.30 mmol) in THF (2 mL) was added dropwise at 0°C. It was stirred for 5 min at 0°C then for 1,5 h allowing temperature to reach 10°C. It was quenched with AcOH and filtered over a pad of celite. The cake was washed with EtOAc and the filtrate
30 was concentrated in vacuo. The crude was purified by CC using Hept/EtOAc from 8/2 to 25/75 to give the title compound as yellow oil.

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LC-MS (A): t_R = 0.83 min; $[M+H]^+$: 266.24**B.3.c.2. 2-(Cyclohexyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine**

This compound was prepared using a method analogous to that of 2-(cyclopentyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine, 5-(1-(cyclohexyloxy)-2-nitroethyl)-2-methylpyrimidine replacing 5-(1-(cyclopentyloxy)-2-nitroethyl)-2-methylpyrimidine except that platinum dioxide was used as catalyst instead of 10% palladium on activated charcoal and the reaction mixture was stirred ON.

LC-MS (A): t_R = 0.52 min; $[M+H]^+$: 235.91

10 **B.3.d. Synthesis of 2-(2-methylpyrimidin-5-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)ethanamine**

B.3.d.1. 2-Methyl-5-(2-nitro-1-((tetrahydro-2H-pyran-4-yl)oxy)ethyl)pyrimidine

This compound was prepared using a method analogous to that of 5-(1-(cyclohexyloxy)-2-nitroethyl)-2-methylpyrimidine, tetrahydro-2H-pyran-4-ol replacing cyclohexanol.

LC-MS (A): t_R = 0.62 min; $[M+H]^+$: 267.93

15 **B.3.d.2. 2-(2-Methylpyrimidin-5-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)ethanamine**

This compound was prepared using a method analogous to that of 2-(cyclopentyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine, 2-methyl-5-(2-nitro-1-((tetrahydro-2H-pyran-4-yl)oxy)ethyl)pyrimidine replacing 5-(1-(cyclopentyloxy)-2-nitroethyl)-2-methylpyrimidine except that platinum dioxide was used as catalyst instead of 10% palladium on activated charcoal and the reaction mixture was stirred for 1.5h.

LC-MS (A): t_R = 0.39 min; $[M+H]^+$: 238.20**B.3.e. Synthesis of 2-(2-methylpyrimidin-5-yl)-2-(pentan-3-yloxy)ethanamine****B.3.e.1. 2-Methyl-5-(2-nitro-1-(pentan-3-yloxy)ethyl)pyrimidine**

This compound was prepared using a method analogous to that of 5-(1-(cyclohexyloxy)-2-nitroethyl)-2-methylpyrimidine, 3-pentanol replacing cyclohexanol.

LC-MS (A): t_R = 0.81 min; $[M+H]^+$: 254.18**B.4. 2-(2-methylpyrimidin-5-yl)-2-(pentan-3-yloxy)ethanamine**

This compound was prepared using a method analogous to that of 2-(cyclopentyloxy)-2-(2-methylpyrimidin-5-yl)ethanamine, 2-methyl-5-(2-nitro-1-(pentan-3-yloxy)ethyl)pyrimidine replacing 5-(1-(cyclopentyloxy)-2-nitroethyl)-2-methylpyrimidine except that platinum

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dioxide was used as catalyst instead of 10% palladium on activated charcoal and the reaction mixture was stirred ON.

LC-MS (A): t_R = 0.51 min; $[M+H]^+$: 225.04

C. Chiral separation of amines of formula (III)

5 **C.1. Synthesis of 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine (enantiomer A) and 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine (enantiomer B)**

2-(2-Methylpyrimidin-5-yl)-2-morpholinoethanamine as racemate was separated into the two enantiomers using preparative chiral HPLC (Daicel, ChiralPak IC, 5 μ m, 20x250 mm, CH₃CN/(EtOH+0.1%DEA) 90/10, flow: 18 mL/min, detection: UV 210 nm).

10 Both enantiomers were characterized by analytical chiral HPLC (Daicel, ChiralPak IC, 5 μ m, 4.6x250 mm, CH₃CN/(EtOH+0.1%DEA) 90/10, flow: 0.8 mL/min, detection: UV 210 to 280 nm)

Enantiomer A: t_R = 12.63 min

Enantiomer B: t_R = 17.92 min

15 Both enantiomers were transformed to their HCl salt following the procedure described above (under B.1.b)

Enantiomer A: LC-MS (A): t_R = 0.36 min; $[M+H]^+$: 223.21

Enantiomer B: LC-MS (A): t_R = 0.36 min; $[M+H]^+$: 223.18

PREPARATION OF EXAMPLES

20 A. Synthesis of compounds of formula I (general procedure for amide coupling)

To a solution of the respective carboxylic acid precursor of formula II (0.23 mmol) in a mixture of DCM/DMF (0.4 mL) were consecutively added DIPEA (0.69 mmol), HOBt (0.28 mmol) and EDC.HCl (0.28 mmol) followed by a solution of the respective amine precursor of formula III (0.25 mmol) in DCM (0.1 mL). The mixture was stirred ON at RT, diluted with
25 DCM and washed twice with a 5% solution of KHSO₄ (when appropriate), with a sat. solution of NaHCO₃ and with brine (when appropriate). The organic phase was dried over MgSO₄ and concentrated in vacuo. The crude was purified using conditions which are detailed in the table below.

30 All compounds in the following table were synthesized according to the aforementioned general procedure except compounds which are marked with "see below under section B"

or “see below under section C”; such compounds were synthesized according to the specific procedures given in sections “B. Chiral separation of compounds of formula (I)” or “C. Post amide coupling steps” below.

Compound	Name	Purification method	LC-MS		
			type	t _R (min)	[M+H] ⁺
Example 1	rac-4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide	a+IV	C	0.65	453.94
Example 2	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-(4,4-difluoro-piperidin-1-yl)-ethyl]-amide	b	B	0.61	452.88
Example 3	4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A)	see below under section B.			
Example 4	4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)	see below under section B.			
Example 5	4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide (enantiomer A)	see below under section B.			
Example 6	4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide (enantiomer B)	see below under section B.			
Example 7	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(6-methyl-pyridin-3-yl)-2-morpholin-4-yl-	IV	B	0.40	398.83

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	ethyl]-amide				
Example 8	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoropiperidin-1-yl)-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide	c+d	B	0.77	488.45
Example 9	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2-cyclopropylpyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	IV	B	0.48	425.78
Example 10	rac-4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide	IV	B	0.56	453.25
Example 11	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(6-methoxypyridin-3-yl)-2-morpholin-4-yl-ethyl]-amide	IV	B	0.48	414.98
Example 12	rac-4-Chloro-1H-indole-5-carboxylic acid [2-dimethylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	V+d	B	0.40	358.00
Example 13	rac-4-Chloro-1H-indole-5-carboxylic acid [2-azetidin-1-yl-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	V+d	B	0.42	369.80
Example 14	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2-methylpyrimidin-5-yl)-2-pyrrolidin-1-yl-ethyl]-amide	V+d	B	0.42	384.05
Example 15	rac-4-Chloro-1H-indole-5-carboxylic acid [2-diethylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	IV	B	0.43	385.79
Example 16	rac-4-Chloro-1H-indole-5-	IV	B	0.43	398.37

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	carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-piperidin-1-yl-ethyl]-amide				
Example 17	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4-fluorophenyl)-2-morpholin-4-yl-ethyl]-amide	IV+e	B	0.53	401.73
Example 18	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-difluorophenyl)-2-morpholin-4-yl-ethyl]-amide	IV+e	B	0.56	420.01
Example 19	rac-4-{2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-pyridin-3-yl-ethyl}-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	f	B	0.61	483.56
Example 20	rac-4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-4-yl-2-pyridin-3-yl-ethyl)-amide	see below under section C.			
Example 21	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide formic acid salt	see below under section C.			
Example 22	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-acetyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide	see below under section C.			
Example 23	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-methanesulfonyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide	see below under section C.			
Example 24	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloropyridin-3-yl)-2-morpholin-4-yl-ethyl]-amide	e	A	0.60	418.95
Example 25	rac-4-Chloro-1H-indole-5-	e	A	0.61	385.05

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	carboxylic acid (2-morpholin-4-yl-2-pyridin-3-yl-ethyl)-amide				
Example 26	rac-4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyrimidin-5-yl-ethyl)-amide	3	E	0.62	386.17
Example 27	rac-4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyrimidin-5-yl-ethyl)-amide	4	E	0.89	384.17
Example 28	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-1H-pyrazol-4-yl)-2-morpholin-4-yl-ethyl]-amide	4	E	0.67	388.18
Example 29	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-1H-pyrazol-4-yl)-2-piperidin-1-yl-ethyl]-amide	4	E	0.96	386.16
Example 30	rac-4-Chloro-1H-indole-5-carboxylic acid [2-piperidin-1-yl-2-(2,4,6-trifluoro-phenyl)-ethyl]-amide	5	E	1.41	436.05
Example 31	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-difluoro-phenyl)-2-piperidin-1-yl-ethyl]-amide	5	E	1.39	418.08
Example 32	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-2-piperidin-1-yl-ethyl]-amide	5	E	1.18	401.16
Example 33	rac-4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2,4,6-trifluoro-phenyl)-ethyl]-amide	5	E	1.08	437.71
Example 34	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-difluoro-phenyl)-2-morpholin-4-yl-ethyl]-	5	E	1.06	420.05

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	amide				
Example 35	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2-fluorophenyl)-2-morpholin-4-yl-ethyl]-amide	4	E	1.02	402.11
Example 36	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(5-fluoropyridin-2-yl)-2-morpholin-4-yl-ethyl]-amide	4	E	0.86	403.11
Example 37	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3-fluorophenyl)-2-morpholin-4-yl-ethyl]-amide	4	E	1.03	402.11
Example 38	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4-chlorophenyl)-2-morpholin-4-yl-ethyl]-amide	b+VI	A	0.65	418.22
Example 39	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-dichlorophenyl)-2-morpholin-4-yl-ethyl]-amide	VI	A	0.67	452.40
Example 40	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4-chloro-2-fluorophenyl)-2-morpholin-4-yl-ethyl]-amide	VI	A	0.66	436.41
Example 41	4-Chloro-1H-indole-5-carboxylic acid [2-(2,6-dimethyl-morpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide (mixture A of stereoisomers)	VI	A	0.58	428.06
Example 42	4-Chloro-1H-indole-5-carboxylic acid [2-(2,6-dimethyl-morpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide (mixture B of stereoisomers)	VI	A	0.62	428.05

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Example 43	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3-fluorophenyl)-2-piperidin-1-yl-ethyl]-amide	1	E	1.34	400.14
Example 44	rac-4-Chloro-1H-indole-5-carboxylic acid [2-piperidin-1-yl-2-(4-trifluoromethyl-phenyl)-ethyl]-amide	2	E	1.47	450.08
Example 45	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3,4-difluorophenyl)-2-piperidin-1-yl-ethyl]-amide	1	E	1.37	418.07
Example 46	rac-4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyridin-3-yl-ethyl)-amide	1	E	0.96	383.16
Example 47	rac-4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2- <i>p</i> -tolyl-ethyl)-amide	1	E	1.07	398.14
Example 48	rac-4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-trifluoromethoxy-phenyl)-ethyl]-amide	2	E	1.19	468.06
Example 49	rac-4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-trifluoromethyl-phenyl)-ethyl]-amide	2	E	1.16	452.05
Example 50	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3,4-difluorophenyl)-2-morpholin-4-yl-ethyl]-amide	1	E	1.04	420.06
Example 51	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2-methylpyrimidin-5-yl)-2-(tetrahydropyran-4-yl)-ethyl]-amide	d	A	0.65	399.07
Example 52	rac-4-Chloro-1H-indole-5-	I	A	0.81	399.01

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	carboxylic acid [2-cyclopentyloxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide				
Example 53	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-dimethyl-isoxazol-4-yl)-2-morpholin-4-yl-ethyl]-amide	1	E	0.61	403.12
Example 54	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-dimethyl-isoxazol-4-yl)-2-piperidin-1-yl-ethyl]-amide	1	E	0.54	401.15
Example 55	rac-4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2- <i>p</i> -tolyl-ethyl)-amide	1	E	0.70	396.16
Example 56	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-piperidin-1-yl-ethyl]-amide	1	E	0.57	417.07
Example 57	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4-phenoxy-phenyl)-2-piperidin-1-yl-ethyl]-amide	2	E	0.86	474.12
Example 58	rac-4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-phenoxy-phenyl)-ethyl]-amide	2	E	0.84	476.12
Example 59	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4-methoxy-phenyl)-2-morpholin-4-yl-ethyl]-amide	1	E	0.57	414.08
Example 60	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(5-methyl-pyrazin-2-yl)-2-piperidin-1-yl-ethyl]-amide	1	E	0.50	398.14
Example 61	rac-4-Chloro-1H-indole-5-	1	E	0.54	389.14

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	carboxylic acid (2-isothiazol-5-yl-2-piperidin-1-yl-ethyl)-amide				
Example 62	rac-4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-thiazol-5-yl-ethyl)-amide	1	E	0.45	389.11
Example 63	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(5-methyl-pyrazin-2-yl)-2-morpholin-4-yl-ethyl]-amide	1	E	0.51	400.13
Example 64	rac-4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-thiazol-5-yl-ethyl)-amide	1	E	0.57	391.08
Example 65	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-cyclohexyl-ethyl]-amide	b+d	A	0.92	416.12
Example 66	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-4-methyl-pentyl]-amide	b+d	A	0.89	389.90
Example 67	rac-4-Chloro-1H-indole-5-carboxylic acid [2-ethoxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	I	A	0.71	358.96
Example 68	4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethyl]-amide (mixture of stereoisomers)	V+VI	A	0.52	411.99
Example 69	rac-4-Chloro-1H-indole-5-carboxylic acid [2-cyclohexyloxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	b	A	0.84	413.01
Example 70	rac-4-Chloro-1H-indole-5-	precipitate	A	0.69	415.15

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	carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(tetrahydro-pyran-4-yloxy)-ethyl]-amide	from CH ₃ CN			
Example 71	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-ethyl-propoxy)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	precipitate from CH ₃ CN	A	0.83	401.01
Example 72	rac-4-Chloro-2-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	V+e	A	0.56	414.00
Example 73	rac-4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyridazin-3-yl-ethyl)-amide	1	G	0.42	384.17
Example 74	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2-hydroxypyridin-4-yl)-2-piperidin-1-yl-ethyl]-amide	1	G	0.35	399.16
Example 75	rac-1-[2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-(2-methyl-pyrimidin-5-yl)-ethyl]-piperidine-4-carboxylic acid <i>tert</i> -butyl ester	1	G	0.74	498.25
Example 76	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4-methyl-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	1	G	0.50	412.15
Example 77	4-Chloro-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide (mixture of stereoisomers)	1	G	0.49	412.16
Example 78	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4-fluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	1	G	0.50	416.13

Example 79	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3,3-difluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)-ethyl]-amide	2	G	0.91	434.10
Example 80	rac-4-Chloro-1H-indole-5-carboxylic acid [2-azepan-1-yl-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	1	G	0.51	412.14
Example 81	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(2-methylpyrimidin-5-yl)-2-[1,4]oxazepan-4-yl-ethyl]-amide	1	G	0.45	414.13
Example 82	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(3,3-difluoropyrrolidin-1-yl)-2-(2-methylpyrimidin-5-yl)-ethyl]-amide	2	G	0.85	420.12
Example 83	rac-4-Chloro-1H-indole-5-carboxylic acid [2-cyclopentylamino-2-(2-methylpyrimidin-5-yl)-ethyl]-amide	1	G	0.50	398.17
Example 84	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(cyclopentylmethyl-amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	1	G	0.58	412.16
Example 85	rac-4-Chloro-1H-indole-5-carboxylic acid [2-isobutylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	1	G	0.48	386.16
Example 86	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(isobutylmethyl-amino)-2-(2-methylpyrimidin-5-yl)-ethyl]-amide	1	G	0.56	400.17
Example 87	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(benzyl-methyl-	2	G	0.74	434.14

	amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide				
Example 88	rac-4-Chloro-1H-indole-5-carboxylic acid (3-ethyl-2-pyrimidin-5-yl-pentyl)-amide	VII+d	A	0.83	371.01
Example 89	rac-4-[2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-(2-methyl-pyrimidin-5-yl)-ethyl]-piperazine-1-carboxylic acid <i>tert</i> -butyl ester	2	E	0.93	499.23
Example 90	rac-4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyridazin-3-yl-ethyl)-amide	1	E	0.46	386.15
Example 91	rac-4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2-hydroxypyridin-4-yl)-ethyl]-amide	1	E	0.41	401.13
Example 92	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1,1-dioxo-thiomorpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	1	E	0.62	448.11
Example 93	rac-4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluorocyclohexyl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide	e	A	0.79	433.06
Example 94	rac-4,6-Dichloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	III+d	A	0.55	433.82
Example 95	4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(6-oxa-3-aza-bicyclo[3.1.1]hept-3-yl)-ethyl]-amide (mixture of stereoisomers)	VIII	A	0.54	411.98
Example 96	4-Chloro-7-methyl-1H-indole-5-	see below under section B.			

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	carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A)				
Example 97	4-Chloro-7-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)	see below under section B.			
Example 98	rac-4-Chloro-7-isobutyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	IV+g	A	0.65	456.12
Example 99	rac-4-Chloro-7-(3-methoxy-propyl)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	h	A	0.59	472.21
Example 100	rac-4-Methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.51	380.04
Example 101	rac-4-Ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.55	394.06
Example 102	rac-7-Acetyl-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.56	441.93
Example 103	rac-7-Methyl-4-trifluoromethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	e	A	0.58	447.94
Example 104	rac-4,7-Dimethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	e	A	0.54	394.10

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Example 105	4-Methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A)	i	A	0.51	380.01
		For chiral characterization, see below under section B			
Example 106	4-Methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)	i	A	0.51	380.01
		For chiral characterization, see below under section B			
Example 107	rac-4-Chloro-7-ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	e	A	0.58	427.98
Example 108	rac-7-Chloro-4-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.56	414.09
Example 109	rac-7-Methoxy-4-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.54	410.07
Example 110	rac-4-Chloro-7-ethoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	e	A	0.59	443.99
Example 111	rac-4-Chloro-7-propyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.62	442.24
Example 112	rac-7-(2-tert-Butoxy-ethoxy)-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	VIII	A	0.66	516.16
Example 113	rac-4-Chloro-7-(2-hydroxy-ethoxy)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-	see below under section C.			

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	2-morpholin-4-yl-ethyl]-amide				
Example 114	4-Chloro-7-methoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A)	d	A	0.55	430.24
		For chiral characterization, see below under section B			
Example 115	4-Chloro-7-methoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)	d	A	0.55	430.24
		For chiral characterization, see below under section B			
Example 116	rac-4-Chloro-7-(1-hydroxy-1-methyl-ethyl)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	see below under section C.			
Example 117	rac-4,7-Difluoro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.55	402.11
Example 118	rac-4-Fluoro-7-methoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide	d	A	0.55	413.88
Example 119	4-Chloro-7-ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A)	d	A	0.58	428.21
		For chiral characterization, see below under section B			

B. Chiral separation of compounds of formula (I)

Example 3 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A) and

- 5 **Example 4** 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)

4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide as racemate was prepared according to the general procedure for amide coupling

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engaging 4-chloro-1H-indole-5-carboxylic acid as carboxylic acid precursor II and 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine as amine precursor III.

LC-MS (B): t_R = 0.41 min; $[M+H]^+$: 400.02

The racemate was separated into the two enantiomers using preparative chiral HPLC (Daicel, ChiralPak AD-H, 5 μ m, 20x250 mm, Hept/(EtOH+0.1%DEA) 50/50, flow: 16 mL/min, detection: UV 230 nm).

Both enantiomers were characterized by analytical chiral HPLC (Daicel, ChiralPak AD-H, 5 μ m, 4.6x250 mm, (Hept+0.05%DEA)/(EtOH+0.05%DEA) 50/50, flow: 0.8 mL/min, detection: UV 210 to 280 nm)

10 Enantiomer A: t_R = 8.67 min (Example 3)

Enantiomer B: t_R = 10.70 min (Example 4)

Example 5 4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide (enantiomer A) and

Example 6 4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide (enantiomer B)

4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide as racemate was prepared according to the general procedure for amide coupling engaging 4-chloro-1H-indole-5-carboxylic acid as carboxylic acid precursor II and 2-(4,4-difluoropiperidin-1-yl)-2-(2-methylpyrimidin-5-yl)ethanamine as amine precursor III.

LC-MS (B): t_R = 0.52 min; $[M+H]^+$: 434.33

The racemate was separated into the two enantiomers using preparative chiral HPLC (Daicel, ChiralPak AD-H, 5 μ m, 20x250 mm, Hept/(EtOH+0.1%DEA) 50/50, flow: 16 mL/min, detection: UV 210 nm).

25 Both enantiomers were characterized by analytical chiral HPLC (Daicel, ChiralPak AD-H, 5 μ m, 4.6x250 mm, (Hept+0.05%DEA)/(EtOH+0.05%DEA) 50/50, flow: 0.8 mL/min, detection: UV 210 to 280 nm)

Enantiomer A: t_R = 8.72 min (Example 5)

Enantiomer B: t_R = 10.92 min (Example 6)

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Example 96 4-Chloro-7-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A) and

Example 97 4-Chloro-7-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)

- 5 4-Chloro-7-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide as racemate was prepared according to the general procedure for amide coupling engaging 4-chloro-7-methyl-1H-indole-5-carboxylic acid as carboxylic acid precursor II and 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine as amine precursor III.

- 10 LC-MS (A): t_R = 0.55 min; $[M+H]^+$: 414.03

The racemate was separated into the two enantiomers using preparative chiral HPLC (Daicel, ChiralPak AD-H, 5 μ m, 20x250 mm, Hept/(EtOH+0.1%DEA) 70/30, flow: 20 mL/min, detection: UV 230 nm).

- Both enantiomers were characterized by analytical chiral HPLC (Daicel, ChiralPak AD-H,
15 5 μ m, 4.6x250 mm, (Hept+0.05%DEA)/(EtOH+0.05%DEA) 70/30, flow: 1.0 mL/min, detection: UV 210 to 280 nm)

Enantiomer A: t_R = 10.43 min (Example 96)

Enantiomer B: t_R = 13.21 min (Example 97)

- Example 105** 4-Methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-
20 morpholin-4-yl-ethyl]-amide (enantiomer A) and

Example 106 4-Methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)

- Example 105 (or example 106 respectively) was synthesized according to the
aforementioned general amide coupling procedure using 2-(2-methylpyrimidin-5-yl)-2-
25 morpholinoethanamine (enantiomer A) as chiral amines of formula III (or 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine (enantiomer B) respectively).

Both enantiomers were characterized by analytical chiral HPLC (Daicel, ChiralPak AD-H, 5 μ m, 4.6x250 mm, (Hept+0.05%DEA)/(EtOH+0.05%DEA) 50/50, flow: 1.2 mL/min, detection: UV 210 to 280 nm)

- 30 Enantiomer A: t_R = 8.16 min (Example 105)

Enantiomer B: t_R = 6.35 min (Example 106)

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Example 114 4-Chloro-7-methoxy-1H-indole-5-carboxylic acid 2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer A) and

Example 115 4-Chloro-7-methoxy-1H-indole-5-carboxylic acid 2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (enantiomer B)

- 5 Example 114 (or example 115 respectively) was synthesized according to the aforementioned general amide coupling procedure using 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine (enantiomer A) as chiral amines of formula III (or 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine (enantiomer B) respectively).

Both enantiomers were characterized by analytical chiral HPLC (Daicel, ChiralPak ID, 5
10 μm , 4.6x250 mm, $\text{CH}_3\text{CN}/(\text{EtOAc}+0.1\%\text{DEA})$ 40/60, flow: 1.0 mL/min, detection: UV 210 to 280 nm)

Enantiomer A: t_R = 5.40 min (Example 114)

Enantiomer B: t_R = 6.79 min (Example 115)

- Example 119** 4-Chloro-7-ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-
15 morpholin-4-yl-ethyl]-amide (enantiomer A)

Example 119 was synthesized according to the aforementioned general amide coupling procedure using 2-(2-methylpyrimidin-5-yl)-2-morpholinoethanamine (enantiomer A) as chiral amines of formula III.

- It was characterized by analytical chiral HPLC (Daicel, ChiralPak ID, 5 μm , 4.6x250 mm,
20 Hept/(EtOAc+0.1%DEA) 10/90, flow: 1.4 mL/min, detection: UV 210 to 280 nm)

Enantiomer A: t_R = 5.61 min (Example 119) (t_R = 8.09 min for the other enantiomer)

C. Post amide coupling steps

Example 20 rac-4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-4-yl-2-pyridin-3-yl-ethyl)-amide dihydrochloride

- 25 To a solution of 4-{2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-pyridin-3-yl-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester (Example 19) (0.42 mmol) in EtOAc (2 mL) was added dropwise a 4M solution of HCl in dioxane (4.18 mmol). The mixture was stirred for 4h at RT and concentrated in vacuo to give the title compound as light pink solid.

LC-MS (A): t_R = 0.43 min; $[M+H]^+$: 383.01

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Example 21 rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide formate

To a solution of 4-chloro-1H-indole-5-carboxylic acid (2-piperidin-4-yl-2-pyridin-3-yl-ethyl)-amide dihydrochloride (Example 20) (0.13 mmol) in DCM (1 mL) and MeOH (2 mL) was added AcOH (0.16 mmol) followed by a 37% aqueous solution of formaldehyde (0.17 mmol) and by sodium triacetoxyborohydride (0.18 mmol). The mixture was stirred for 5h at RT and an additional amount of sodium triacetoxyborohydride (0.18 mmol) was added. It was stirred ON at RT, quenched with a sat. solution of NaHCO₃ and extracted twice with DCM. The aqueous phase was further basified with a 1M solution of NaOH until pH 13-14 and extracted twice with DCM. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by preparative LC-MS using method III to give the title compound as white solid.

LC-MS (A): t_R = 0.44 min; [M+H]⁺: 397.04

Example 22 rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-acetyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide

To a suspension of 4-chloro-1H-indole-5-carboxylic acid (2-piperidin-4-yl-2-pyridin-3-yl-ethyl)-amide dihydrochloride (Example 20) (0.13 mmol) and Et₃N (0.66 mmol) in DCM (1 mL) was added at 0°C acetyl chloride (0.16 mmol). The mixture was stirred for 1.5h at 0°C, quenched with a sat. solution of NaHCO₃ and extracted 3 times with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by preparative LC-MS using method III to give the title compound as white solid.

LC-MS (A): t_R = 0.54 min; [M+H]⁺: 424.99

Example 23 rac-4-Chloro-1H-indole-5-carboxylic acid [2-(1-methanesulfonyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide

To a suspension of 4-chloro-1H-indole-5-carboxylic acid (2-piperidin-4-yl-2-pyridin-3-yl-ethyl)-amide dihydrochloride (Example 20) (0.13 mmol) and Et₃N (0.66 mmol) in DCM (1 mL) was added at 0°C methanesulfonyl chloride (0.16 mmol). The mixture was stirred for 1.5h at 0°C, quenched with a sat. solution of NaHCO₃ and extracted 3 times with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was purified by preparative LC-MS using method III and additionally by CC (IsoluteTM Silica II from Biotage) using DCM/MeOH 94/6 to give the title compound as white solid.

LC-MS (A): t_R = 0.57 min; [M+H]⁺: 460.94

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Example 113 rac-4-Chloro-7-(2-hydroxy-ethoxy)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide

To a solution of rac-7-(2-tert-butoxy-ethoxy)-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (example 112) (0.047 mmol) in DCM (0.19 mL) was added TFA (0.18 mL). The mixture was stirred for 2h at RT, concentrated in vacuo and coevaporated with toluene. The crude was purified by preparative LC-MS using method IX to give the title compound as beige solid

LC-MS (A): t_R = 0.51 min; $[M+H]^+$: 460.02

Example 116 rac-4-Chloro-7-(1-hydroxy-1-methyl-ethyl)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide

To a solution of rac-7-acetyl-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide (0.05 mmol) in THF (1 mL) was added dropwise at -10°C a 3M solution of methylmagnesium bromide in diethyl ether (0.54 mmol). The mixture was stirred for 2h at RT and cooled to 0°C. It was quenched with a sat. solution of NH_4Cl and extracted three times with EtOAc. The organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC (Isolute™ Silica II from Biotage) using DCM/MeOH 90/10 to give the title compound as light yellow solid.

LC-MS (A): t_R = 0.54 min; $[M+H]^+$: 458.24

BIOLOGICAL ASSAYS

A. In vitro assay

The $P2X_7$ receptor antagonistic activity of the compounds of formula (I) is determined in accordance with the following experimental method.

B. Experimental method:

Cell line generation and YO-PRO assay

Cell line generation was performed in general according to established molecular cloning protocols. Specifically, RNA was extracted from human whole blood using the Qiagen RNeasy kit (Qiagen, CH) according to the manufacturer's instructions. Subsequently cDNA was made (Superscript II, Invitrogen AG, CH) and the human $P2X_7$ gene (genbank ref. BC011913) was amplified with the following primers:

ATCGCGGCCGCTCAGTAAGGACTCTTGAAGCCACT and CGCCGCTAGCACCAACCATGCCGGCCTGCTGCAGCTGCA. The amplified sequence was subsequently ligated into a pcDNA3.1 (+) NotI, NheI digested plasmid. Human

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embryonic kidney (HEK) cells (ATCC CRL – 1573, Manassas, VA, USA) were transfected with the pcDNA3.1 (+).hP2X7 plasmid using lipofectamine 2000 (Invitrogen AG, CH) according to the manufacturer's instructions. Following a 24h exposure to DNA, cells were trypsinized and re-seeded at low density in the presence of 250 µg Geneticin. Geneticin resistant cells were then selected during two consecutive rounds of cloning by serial limiting dilution with visual inspection. Individual clones were screened for P2X7 expression by applying ATP and recording the resultant uptake of YO-PRO1. Specific cell clones were chosen based on RNA and protein expression. HEK cells stably expressing P2X7 were used to screen drugs using the YO-PRO1 assay. Cells were grown to confluency in adherent culture at 37°C in a humidified 5% CO₂ incubator (split 1/5 every 3 – 4 days with DMEM, 10 % FCS, 1% Penicillin/Streptomycin, 250 µg/ml Geneticin). Adherent cells were detached by incubation with Trypsine (1 ml per 165 cm² dish) for 2 minutes, then washed off with 10 ml PBS (without Mg²⁺ and Ca²⁺), and resuspended in DMEM, 10 % FCS, 1 % Penicillin/Streptomycin, no Geneticin. 10'000 cells per well (48 hours before the assay) or 25'000 cells per well (Vi-cell XR (Beckman Coulter) (24 hours before the assay) in 50 µl full medium were seeded on 384-well black-wall, clear bottom plates, that were coated before with 10 µl per well Poly-L-Lysine, incubated for 30 – 60 minutes at 37° C and washed once with PBS. Medium was removed from cells and 50 µl of assay buffer containing 0.5 µM YO-PRO-1 was added into the wells. Solutions of antagonist compounds were prepared by serial dilutions of a 10 mM DMSO solution of the antagonist into PBS using a BioMek (Beckman Coulter). Each concentration was performed in duplicate. For IC₅₀ measurements 10 concentration points were measured (10 µM being the highest concentration followed by 9 serial dilution steps 1/3). The cells were incubated with the antagonists of the present invention together with ATP at a final concentration of 250 µM for 90 minutes. During this time period, four time points were taken. Each time point comprised the average of several measurements made within a few seconds. Fluorescence was measured in the FLIPR tetra (Molecular Devices) using the filters appropriate for YO-PRO-1 fluorescence (excitation 485/20, emission 530/25). The FLIPR tetra was equipped with Molecular Devices Screen Works system control software to define and run experimental protocols. For antagonist activity measurements, the maximal intensity was expressed as a percentage of that induced by the EC₅₀ value for agonist activation (0.25 mM ATP for HEK-293 cells expressing human recombinant P2X7 receptor). For IC₅₀ measurements the maximum intensity is plotted against the concentration of compound to determine IC₅₀ values.

Antagonistic activities with respect to the P2X₇ receptor (IC₅₀ values) of exemplified compounds are displayed in *Table 1*.

Table 1

Compound	IC₅₀ [nM]	Compound	IC₅₀ [nM]	Compound	IC₅₀ [nM]
Example 1	3.9	Example 2	4.3	Example 3	7.9
Example 4	9.4	Example 5	7.9	Example 6	6.8
Example 7	19	Example 8	12	Example 9	7.7
Example 10	5.1	Example 11	14	Example 12	2295
Example 13	831	Example 14	286	Example 15	85
Example 16	9.7	Example 17	9.2	Example 18	19
Example 19	35	Example 20	447	Example 21	584
Example 22	126	Example 23	56	Example 24	4.7
Example 25	32	Example 26	10	Example 27	8.7
Example 28	66	Example 29	161	Example 30	1305
Example 31	251	Example 32	232	Example 33	301
Example 34	61	Example 35	161	Example 36	265
Example 37	32	Example 38	15	Example 39	455
Example 40	73	Example 41	651	Example 42	36
Example 43	163	Example 44	889	Example 45	83
Example 46	39	Example 47	54	Example 48	134
Example 49	34	Example 50	13	Example 51	16
Example 52	32	Example 53	1990	Example 54	1851
Example 55	774	Example 56	8.8	Example 57	187

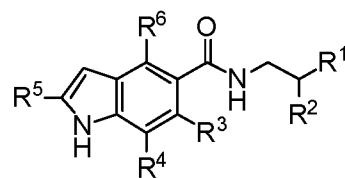
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Example 58	102	Example 59	55	Example 60	232
Example 61	15	Example 62	48	Example 63	257
Example 64	53	Example 65	76	Example 66	32
Example 67	636	Example 68	2057	Example 69	61
Example 70	91	Example 71	22	Example 72	463
Example 73	1014	Example 74	193	Example 75	258
Example 76	348	Example 77	87	Example 78	12
Example 79	9.3	Example 80	25	Example 81	26
Example 82	34	Example 83	162	Example 84	1473
Example 85	303	Example 86	280	Example 87	2647
Example 88	15	Example 89	277	Example 90	1615
Example 91	353	Example 92	98	Example 93	12
Example 94	211	Example 95	28	Example 96	9.6
Example 97	10	Example 98	10	Example 99	21
Example 100	19	Example 101	30	Example 102	33
Example 103	26	Example 104	35	Example 105	20
Example 106	25	Example 107	15	Example 108	11
Example 109	25	Example 110	13	Example 111	18
Example 112	32	Example 113	21	Example 114	14
Example 115	8.2	Example 116	149	Example 117	118
Example 118	20	Example 119	16		

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Claims

1. A compound of the formula (I),



(I)

5 wherein

R¹ represents a heteroaryl or an aryl group which groups are independently unsubstituted, mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₄)alkoxy, (C₁–C₃)fluoroalkyl, (C₁–C₃)fluoroalkoxy, hydroxy, halogen and phenoxy;

10 **R²** represents

- heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from (C₁–C₄)alkyl, (C₁–C₄)alkylcarbonyl, (C₁–C₄)alkoxycarbonyl, (C₁–C₄)alkylsulfonyl, and halogen;
- heterocyclyloxy;
- 15 • (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with halogen;
- (C₃–C₆)cycloalkyloxy;
- *N*-(C₃–C₆)cycloalkyl-amino;
- *N*-(C₃–C₆)cycloalkylmethyl-amino;
- (C₃–C₆)alkyl;
- 20 • (C₂–C₆)alkoxy;
- *N*-(C₁–C₄)alkylamino;
- *N,N*-di-[(C₁–C₄)alkyl]-amino; or
- *N*-arylmethyl-*N*-(C₁–C₄)alkyl-amino;

R³ represents hydrogen or halogen;

25 **R⁴** represents hydrogen, fluoro, chloro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy, (C₁–C₄)alkyl-carbonyl, hydroxy-(C₁–C₄)alkyl, hydroxy-(C₂–C₄)alkoxy, (C₁–C₂)alkoxy-(C₁–C₄)alkyl or (C₁–C₄)alkoxy-(C₂–C₄)alkoxy;

R⁵ represents hydrogen or (C₁–C₄)alkyl; and

R⁶ represents fluoro, chloro, methyl, ethyl or (C₁–C₂)fluoroalkyl;

30 or a salt of such a compound.

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2. A compound of formula (I) according to claim 1, wherein

R^1 represents a 5- or 6-membered monocyclic heteroaryl group which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₄)alkoxy, (C₁–C₃)fluoroalkyl and halogen;

R^2 represents

- heterocyclyl which is unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from methyl and fluoro; or
- (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with fluoro;

R^3 represents hydrogen;

R^4 represents hydrogen or (C₁–C₄)alkyl;

R^5 represents hydrogen; and

R^6 represents chloro or methyl;

or a salt of such a compound.

3. A compound of formula (I) according to claim 1, wherein

R^1 represents a 5- or 6-membered monocyclic heteroaryl or a phenyl group which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₃)fluoroalkyl and halogen;

or a salt of such a compound.

4. A compound of formula (I) according to any one of claims 1 to 3, wherein

R^2 represents heterocyclyl which is unsubstituted or mono- or di-substituted with fluoro; or a salt of such a compound.

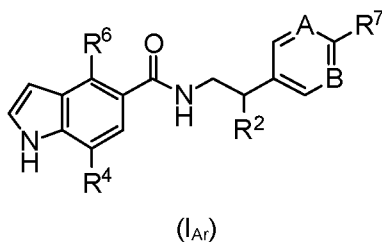
5. A compound of formula (I) according to any one of claims 1 or 3, wherein

R^2 represents (C₃–C₆)alkyl; or (C₃–C₆)cycloalkyl which is unsubstituted or mono- or di-substituted with fluoro; or a salt of such a compound.

6. A compound of formula (I) according to claim 1, which is also a compound of formula

(I_{Ar})

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wherein

A represents N or CH;

5 **B** represents N or CH;

R² represents heterocyclyl which is unsubstituted or mono- or di-substituted with fluoro, wherein the heterocyclyl is selected from pyrrolidinyl, piperidinyl, tetrahydropyranyl, morpholinyl, azepanyl, 1,4-oxazepanyl and 6-oxa-3-azabicyclo[3.1.1]heptanyl; or

R² represents cyclohexyl which is unsubstituted or mono- or di-substituted with fluoro;

10 **R**⁴ represents hydrogen, fluoro, chloro, (C₁–C₄)alkyl, (C₁–C₄)alkoxy, hydroxy-(C₂–C₄)alkoxy or (C₁–C₂)alkoxy-(C₁–C₄)alkyl;

R⁶ represents fluoro, chloro, methyl, ethyl or (C₁–C₂)fluoroalkyl; and

R⁷ represents hydrogen, halogen, (C₁–C₄)alkyl, (C₃–C₆)cycloalkyl, (C₁–C₄)alkoxy or (C₁–C₃)fluoroalkyl;

15 or a salt of such a compound.

7. A compound of formula (I_{Ar}) according to claim 6, wherein

A and **B** represent N and **R**⁷ represents hydrogen, methyl, cyclopropyl or trifluoromethyl; or

20 **A** represents N, **B** represents CH and **R**⁷ represents chloro, methyl, methoxy or trifluoromethyl; or

A and **B** represent CH and **R**⁷ represents fluoro or chloro;

R² represents 3,3-difluoro-pyrrolidin-1-yl, piperidin-1-yl, 4-fluoro-piperidin-1-yl, 3,3-difluoro-piperidin-1-yl, 4,4-difluoro-piperidin-1-yl, tetrahydropyran-4-yl, morpholin-4-yl, azepan-1-yl, 1,4-oxazepan-4-yl, or 6-oxa-3-azabicyclo[3.1.1]heptan-3-yl;

25 **R**⁴ represents hydrogen, chloro, methyl, ethyl, *n*-propyl, *iso*-butyl, methoxy, ethoxy, 2-hydroxy-ethoxy or 3-methoxy-prop-1-yl;

R⁶ represents fluoro, chloro, methyl, ethyl or trifluoromethyl;

or a salt of such a compound.

8. A compound of formula (I_{Ar}) according to any one of claims 6 or 7, wherein

30 **A** and **B** represent N;

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or a salt of such a compound.

9. A compound of formula (I) according to any one of claims 1 to 8, wherein

R^6 represents chloro;

or a salt of such a compound.

5 10. A compound of formula (I) according to any one of claims 1 to 8, wherein

R^6 represents methyl;

or a salt of such a compound.

11. A compound of formula (I) according to claim 1, selected from the group consisting of:

10 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide;

4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-(4,4-difluoro-piperidin-1-yl)-ethyl]-amide;

4-Chloro-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

15 4-Chloro-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

4-Chloro-1H-indole-5-carboxylic acid [(R)-2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;

20 4-Chloro-1H-indole-5-carboxylic acid [(S)-2-(4,4-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;

4-Chloro-1H-indole-5-carboxylic acid [2-(6-methyl-pyridin-3-yl)-2-morpholin-4-yl-ethyl]-amide;

4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-piperidin-1-yl)-2-(2-trifluoromethyl-pyrimidin-5-yl)-ethyl]-amide;

25 4-Chloro-1H-indole-5-carboxylic acid [2-(2-cyclopropyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide;

30 4-Chloro-1H-indole-5-carboxylic acid [2-(6-methoxy-pyridin-3-yl)-2-morpholin-4-yl-ethyl]-amide;

4-Chloro-1H-indole-5-carboxylic acid [2-dimethylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;

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- 4-Chloro-1H-indole-5-carboxylic acid [2-azetidin-1-yl-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-pyrrolidin-1-yl-ethyl]-amide;
- 5 4-Chloro-1H-indole-5-carboxylic acid [2-diethylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 10 4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-difluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-{2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-pyridin-3-yl-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-4-yl-2-pyridin-3-yl-ethyl)-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-acetyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methanesulfonyl-piperidin-4-yl)-2-pyridin-3-yl-ethyl]-amide;
- 20 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyridin-3-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyrimidin-5-yl-ethyl)-amide;
- 25 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyrimidin-5-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-1H-pyrazol-4-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1-methyl-1H-pyrazol-4-yl)-2-piperidin-1-yl-ethyl]-amide;
- 30 4-Chloro-1H-indole-5-carboxylic acid [2-piperidin-1-yl-2-(2,4,6-trifluoro-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-difluoro-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-2-piperidin-1-yl-ethyl]-amide;

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- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2,4,6-trifluoro-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-difluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 5 4-Chloro-1H-indole-5-carboxylic acid [2-(2-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-chloro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 10 4-Chloro-1H-indole-5-carboxylic acid [2-(2,4-dichloro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-chloro-2-fluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(*cis*-2,6-dimethyl-morpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid [2-(*trans*-2,6-dimethyl-morpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3-fluoro-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-piperidin-1-yl-2-(4-trifluoromethyl-phenyl)-ethyl]-amide;
- 20 4-Chloro-1H-indole-5-carboxylic acid [2-(3,4-difluoro-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyridin-3-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-*p*-tolyl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-trifluoromethoxy-phenyl)-ethyl]-amide;
- 25 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-trifluoromethyl-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3,4-difluoro-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 30 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(tetrahydro-pyran-4-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-cyclopentyloxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-dimethyl-isoxazol-4-yl)-2-morpholin-4-yl-ethyl]-amide;
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- 4-Chloro-1H-indole-5-carboxylic acid [2-(3,5-dimethyl-isoxazol-4-yl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-*p*-tolyl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-piperidin-1-yl-ethyl]-amide;
- 5 4-Chloro-1H-indole-5-carboxylic acid [2-(4-phenoxy-phenyl)-2-piperidin-1-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(4-phenoxy-phenyl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-methoxy-phenyl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-methyl-pyrazin-2-yl)-2-piperidin-1-yl-ethyl]-amide;
- 10 4-Chloro-1H-indole-5-carboxylic acid (2-isothiazol-5-yl-2-piperidin-1-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-thiazol-5-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(5-methyl-pyrazin-2-yl)-2-morpholin-4-yl-ethyl]-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-thiazol-5-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-2-cyclohexyl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(6-chloro-pyridin-3-yl)-4-methyl-pentyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-ethoxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethyl]-amide;
- 20 4-Chloro-1H-indole-5-carboxylic acid [2-cyclohexyloxy-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(tetrahydro-pyran-4-yloxy)-ethyl]-amide;
- 25 4-Chloro-1H-indole-5-carboxylic acid [2-(1-ethyl-propoxy)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-2-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (2-piperidin-1-yl-2-pyridazin-3-yl-ethyl)-amide;
- 30 4-Chloro-1H-indole-5-carboxylic acid [2-(2-hydroxypyridin-4-yl)-2-piperidin-1-yl-ethyl]-amide;
- 1-[2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-(2-methyl-pyrimidin-5-yl)-ethyl]-piperidine-4-carboxylic acid *tert*-butyl ester;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-methyl-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
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- 4-Chloro-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(4-fluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 5 4-Chloro-1H-indole-5-carboxylic acid [2-(3,3-difluoro-piperidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-azepan-1-yl-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-[1,4]oxazepan-4-yl-ethyl]-amide;
- 10 4-Chloro-1H-indole-5-carboxylic acid [2-(3,3-difluoro-pyrrolidin-1-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-cyclopentylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 15 4-Chloro-1H-indole-5-carboxylic acid [2-(cyclopentylmethyl-amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-isobutylamino-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(isobutyl-methyl-amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 20 4-Chloro-1H-indole-5-carboxylic acid [2-(benzyl-methyl-amino)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid (3-ethyl-2-pyrimidin-5-yl-pentyl)-amide;
- 4-[2-[(4-Chloro-1H-indole-5-carbonyl)-amino]-1-(2-methyl-pyrimidin-5-yl)-ethyl]-piperazine-
- 25 1-carboxylic acid *tert*-butyl ester;
- 4-Chloro-1H-indole-5-carboxylic acid (2-morpholin-4-yl-2-pyridazin-3-yl-ethyl)-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-morpholin-4-yl-2-(2-hydroxypyridin-4-yl)-ethyl]-amide;
- 4-Chloro-1H-indole-5-carboxylic acid [2-(1,1-dioxo-thiomorpholin-4-yl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 30 4-Chloro-1H-indole-5-carboxylic acid [2-(4,4-difluoro-cyclohexyl)-2-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
- 4,6-Dichloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

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- 4-Chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-(6-oxa-3-aza-bicyclo[3.1.1]hept-3-yl)-ethyl]-amide;
- 4-Chloro-7-methyl-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 5 4-Chloro-7-methyl-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-isobutyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-(3-methoxy-propyl)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 10 4-Methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 15 7-Acetyl-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 7-Methyl-4-trifluoromethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4,7-Dimethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 20 4-Methyl-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Methyl-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 25 4-Chloro-7-ethyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 7-Chloro-4-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 7-Methoxy-4-methyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 30 4-Chloro-7-ethoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-propyl-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;

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- 7-(2-tert-Butoxy-ethoxy)-4-chloro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-(2-hydroxy-ethoxy)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 5 4-Chloro-7-methoxy-1H-indole-5-carboxylic acid [(S)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-methoxy-1H-indole-5-carboxylic acid [(R)-2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 4-Chloro-7-(1-hydroxy-1-methyl-ethyl)-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 10 4,7-Difluoro-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide; and
- 4-Fluoro-7-methoxy-1H-indole-5-carboxylic acid [2-(2-methyl-pyrimidin-5-yl)-2-morpholin-4-yl-ethyl]-amide;
- 15 or a salt of such a compound.

12. A compound of formula (I) according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use as a medicament.

- 13.** A pharmaceutical composition containing, as active principle, a compound of formula (I) according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof,
- 20 and at least one therapeutically inert excipient.

- 14.** Use of a compound of formula (I) according to any one of claims 1 to 11, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a disease selected from pain; neurodegenerative and neuroinflammatory diseases; bone and joint diseases; obstructive diseases of the airways;
- 25 cardiovascular diseases; eye diseases; skin diseases; abdominal and gastrointestinal tract diseases; genitourinary diseases; cancer; other auto-immune and allergic disorders; and other disorders with an inflammatory or immunological component.

- 15.** A compound of formula (I) according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of a disease selected from pain; neurodegenerative and neuroinflammatory diseases; bone and joint diseases; obstructive diseases of the airways; cardiovascular diseases; eye diseases; skin diseases; abdominal and gastrointestinal tract diseases; genitourinary diseases; cancer; other auto-immune and allergic disorders; and other disorders with an inflammatory or immunological component.
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