



- (51) **International Patent Classification:**
A61K 31/4985 (2006.01)
- (21) **International Application Number:**
PCT/US2014/043577
- (22) **International Filing Date:**
23 June 2014 (23.06.2014)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
13173487.3 25 June 2013 (25.06.2013) EP
- (71) **Applicant (for all designated States except US):** **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).
- (71) **Applicant (for US only):** **HOFFMANN-LA ROCHE INC.** [US/US]; Great Notch, 150 Clove Road, 8th Floor, Little Falls, New Jersey 07424 (US).
- (71) **Applicant:** **PTC THERAPEUTICS INC.** [US/US]; 100 Corporate Court, South Plainfield, New Jersey 07080 (US).
- (72) **Inventors:** **DAKKA, Amal**; 3 Gleim Road, Whitehouse Station, New Jersey 08889 (US). **GREEN, Luke**; Oetlingerstrasse 52, CH-4057 Basel (CH). **KARP, Gary**; 37 Cartwright Drive, Princeton Junction, New Jersey 08550 (US). **NARASIMHAN, Jana**; 2257 New York Avenue, Scotch Plains, New Jersey 07076 (US). **NARYSHKIN, Nikolai**; 101 Windsong Circle, East Brunswick, New Jersey 08816 (US). **PINARD, Emmanuel**; 7, rue de Pujo, F-68480 Linsdorf (FR). **QI, Hongyan**; 30 Birch Drive, Plainsboro, New Jersey 08536 (US). **RATNI, Hasane**; 4,

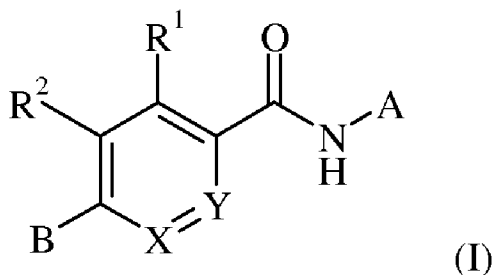
Louis Pasteur, F-68440 Habsheim (FR). **RISHER, Nicole**; 14 Deriemer Road, Hillsborough, New Jersey 08844 (US). **WEETALL, Marla**; 70 Burnham Parkway, Morristown, New Jersey 07960 (US). **WOLL, Matthew**; 413 Mountainview Terrace, Dunellen, New Jersey 08812 (US).

- (74) **Agent:** **MEGERDITCHIAN, Samuel**; Gibbons P.C., 1 Gateway Center, Newark, New Jersey 07102 (US).
- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) **Title:** COMPOUNDS FOR TREATING SPINAL MUSCULAR ATROPHY

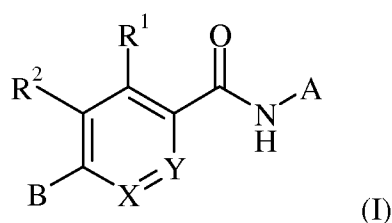


(57) **Abstract:** The present invention provides compounds of formula (I) wherein A, B, X, Y, R₁ and R₂ are as described herein, as well as pharmaceutically acceptable salts thereof. Further the present invention is concerned with the manufacture of the compounds of formula (I), pharmaceutical compositions comprising them and their use as medicaments.

Case 31539**Compounds for treating spinal muscular atrophy****Introduction**

The present invention provides compounds which are SMN2 gene splicing modulators, their manufacture, pharmaceutical compositions comprising them and their use as medicaments for the treatment of spinal muscular atrophy (SMA).

5 In particular, the present invention relates to compounds of formula (I)



wherein A, B, X, Y, R¹ and R² are as described herein, and pharmaceutically acceptable salts thereof.

Background

10 Spinal muscular atrophy (SMA), in its broadest sense, describes a collection of inherited and acquired central nervous system (CNS) diseases characterized by progressive motor neuron loss in the spinal cord and brainstem causing muscle weakness and muscle atrophy. The most common form of SMA is caused by mutations in the Survival Motor Neuron (SMN) gene and manifests over a wide range of severity affecting infants through adults (*Crawford and Pardo,*
15 *Neurobiol. Dis., 1996, 3:97*).

Infantile SMA is the most severe form of this neurodegenerative disorder. Symptoms include muscle weakness, poor muscle tone, weak cry, limpness or a tendency to flop, difficulty sucking or swallowing, accumulation of secretions in the lungs or throat, feeding difficulties, and increased susceptibility to respiratory tract infections. The legs tend to be weaker than the arms
20 and developmental milestones, such as lifting the head or sitting up, cannot be reached. In general, the earlier the symptoms appear, the shorter the lifespan. As the motor neuron cells deteriorate, symptoms appear shortly afterward. The severe forms of the disease are fatal and all forms have no known cure. The course of SMA is directly related to the rate of motor neuron cell deterioration and the resulting severity of weakness. Infants with a severe form of SMA
25 frequently succumb to respiratory disease due to weakness in the muscles that support breathing.

Children with milder forms of SMA live much longer, although they may need extensive medical support, especially those at the more severe end of the spectrum. The clinical spectrum of SMA disorders has been divided into the following five groups.

- 5 (a) Type 0 SMA (In Utero SMA) is the most severe form of the disease and begins before birth. Usually, the first symptom of Type 0 SMA is reduced movement of the fetus that can first be observed between 30 and 36 weeks of pregnancy. After birth, these newborns have little movement and have difficulties with swallowing and breathing.
- 10 (b) Type 1 SMA (Infantile SMA or Werdnig-Hoffmann disease) presents symptoms between 0 and 6 months. form of SMA is also very severe. Patients never achieve the ability to sit, and death usually occurs within the first 2 years without ventilatory support.
- 15 (c) Type 2 SMA (Intermediate SMA) has an age of onset at 7-18 months. Patients achieve the ability to sit unsupported, but never stand or walk unaided. Prognosis in this group is largely dependent on the degree of respiratory involvement.
- (d) Type 3 SMA (Juvenile SMA or Kugelberg-Welander disease) is generally diagnosed after 18 months. Type 3 SMA individuals are able to walk independently at some point during their disease course but often become wheelchair-bound during youth or adulthood.
- 20 (e) Type 4 SMA (Adult onset SMA). Weakness usually begins in late adolescence in the tongue, hands, or feet, then progresses to other areas of the body. The course of adult SMA is much slower and has little or no impact on life expectancy.

The SMN gene has been mapped by linkage analysis to a complex region in chromosome 5q. In humans, this region contains an approximately 500 thousand base pairs (kb) inverted
25 duplication resulting in two nearly identical copies of the SMN gene. SMA is caused by an inactivating mutation or deletion of the telomeric copy of the gene (SMN1) in both chromosomes, resulting in the loss of SMN1 gene function. However, all patients retain the centromeric copy of the gene (SMN2), and the copy number of the SMN2 gene in SMA patients generally correlates inversely with the disease severity; i.e., patients with less severe SMA have
30 more copies of SMN2. Nevertheless, SMN2 is unable to compensate completely for the loss of SMN1 function due to alternative splicing of exon 7 caused by a translationally silent C to T mutation in exon 7. As a result, the majority of transcripts produced from SMN2 lack exon 7 ($\Delta 7$ SMN2), and encode a truncated SMN protein that has an impaired function and is rapidly degraded.

35 The SMN protein is thought to play a role in RNA processing and metabolism, having a well characterized function of mediating the assembly of a specific class of RNA-protein

complexes termed snRNPs. SMN may have other functions in motor neurons, however its role in preventing the selective degeneration of motor neurons is not well established.

In most cases, SMA is diagnosed based on clinical symptoms and by the presence of at least one copy of the SMN1 gene test. However, in approximately 5% of cases SMA is caused by mutation in genes other than the inactivation of SMN 1, some known and others not yet defined. In some cases, when the SMN 1 gene test is not feasible or does not show any abnormality, other tests such as an electromyography (EMG) or muscle biopsy may be indicated.

Medical care for SMA patients at present is limited to supportive therapy including respiratory, nutritional and rehabilitation care; there is no drug known to address the underlying cause of the disease. Current treatment for SMA consists of prevention and management of the secondary effects of chronic motor unit loss. The major management issue in Type 1 SMA is the prevention and early treatment of pulmonary problems, which are the cause of death in the majority of the cases. While some infants afflicted with SMA grow to be adults, those with Type 1 SMA have a life expectancy of less than two years.

Several mouse models of SMA have been developed. In particular, the SMN delta exon 7 ($\Delta 7$ SMN) model (*Le et al., Hum. Mol. Genet., 2005, 14:845*) carries both the SMN2 gene and several copies of the $\Delta 7$ SMN2 cDNA and recapitulates many of the phenotypic features of Type 1 SMA. The $\Delta 7$ SMN model can be used for both SMN2 expression studies as well as the evaluation of motor function and survival. The C/C-allele mouse model (*Jackson Laboratory strain #008714, The Jackson Laboratory, Bar Harbor, ME*) provides a less severe SMA disease model, with mice having reduced levels of both SMN2 full length (FL SMN2) mRNA and SMN protein. The C/C-allele mouse phenotype has the SMN2 gene and a hybrid mSMN1-SMN2 gene that undergoes alternative splicing, but does not have overt muscle weakness. The C/C-allele mouse model is used for SMN2 expression studies.

As a result of improved understanding of the genetic basis and pathophysiology of SMA, several strategies for treatment have been explored, but none have yet demonstrated success in the clinic.

Gene replacement of SMN1, using viral delivery vectors, and cell replacement, using differentiated SMN1^{+/+} stem cells, have demonstrated efficacy in animal models of SMA. More research is needed to determine the safety and immune response and to address the requirement for the initiation of treatment at the neonatal stage before these approaches can be applied to humans.

Correction of alternative splicing of SMN2 in cultured cells has also been achieved using synthetic nucleic acids as therapeutic agents: (i) antisense oligonucleotides that target sequence

elements in SMN2 pre-mRNA and shift the outcome of the splicing reaction toward the generation of full length SMN2 mRNA (*Passini et al., Sci. Transl. Med., 2011, 3:72ra18*; and, *Hua et al., Nature, 2011, 478:123*) and (ii) trans-splicing RNA molecules that provide a fully functional RNA sequence that replace the mutant fragment during splicing and generate a full length SMN1 mRNA (*Coady and Lorson, J Neurosci., 2010, 30:126*).

Other approaches under exploration include searching for drugs that increase SMN levels, enhance residual SMN function, or compensate for its loss. Aminoglycosides have been shown to enhance expression of a stabilized SMN protein produced from $\Delta 7$ SMN2 mRNA by promoting the translational read-through of the aberrant stop codon, but have poor central nervous system penetration and are toxic after repeat dosing. Chemotherapeutic agents, such as aclarubicin, have been shown to increase SMN protein in cell culture; however, the toxicity profile of these drugs prohibits long-term use in SMA patients. Some drugs under clinical investigation for the treatment of SMA include transcription activators such as histone deacetylase ("HDAC") inhibitors (e.g., butyrates, valproic acid, and hydroxyurea), and mRNA stabilizers (mRNA decapping inhibitor RG3039 from Repligen), the goal being to increase the amount of total RNA transcribed from the SMN2 gene. However, the use of the HDAC inhibitors or mRNA stabilizers does not address the underlying cause of SMA and may result in a global increase in transcription and gene expression with potential safety problems in humans.

In an alternative approach, neuroprotective agents such as Olesoxime have been chosen for investigation. Such strategies are not aimed at SMN for the treatment of SMA, but instead are being explored to protect the SMN-deficient motor neurons from neurodegeneration.

A system designed for identifying compounds that increase the inclusion of exon 7 of SMN into RNA transcribed from the SMN2 gene and certain benzoxazole and benzoisoxazole compounds identified thereby have been described in *International Patent Application WO2009/151546A1*. A system designed for identifying compounds that cause ribosomal frameshifting to produce a stabilized SMN protein from $\Delta 7$ SMN2 mRNA and certain isoindolinone compounds identified thereby have been described in *International Patent Application WO2010/019236A1*.

Despite the progress made in understanding the genetic basis and pathophysiology of SMA, there remains a need to identify compounds that alter the course of spinal muscular atrophy, one of the most devastating childhood neurological diseases.

Detailed description of the invention

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen, unless indicated otherwise.

The definitions described herein apply irrespective of whether the terms in question appear alone or in combination. It is contemplated that the definitions described herein can be appended to form chemically-relevant combinations, such as e.g. “heterocycloalkylaryl”, “haloalkylheteroaryl”, “arylalkylheterocycloalkyl”, or “alkoxyalkyl”. The last member of the combination is the radical which is binding to the rest of the molecule. The other members of the combination are attached to the binding radical in reversed order in respect of the literal sequence, e.g. the combination arylalkylheterocycloalkyl refers to a heterocycloalkyl-radical which is substituted by an alkyl which is substituted by an aryl.

The term “moiety” refers to an atom or group of chemically bonded atoms that is attached to another atom or molecule by one or more chemical bonds thereby forming part of a molecule. For example, the variables R^1 and R^2 of formula (I) refer to moieties that are attached to the core structure of formula I by a covalent bond.

When indicating the number of substituents, the term “one or more” refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The term “optional” or “optionally” denotes that a subsequently described event or circumstance can but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term “substituent” denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

The term “substituted” denotes that a specified group bears one or more substituents. Where any group can carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term “unsubstituted” means that the specified group bears no substituents. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term “one or more” means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The term “compound(s) of this invention” and “compound(s) of the present invention” refers to compounds of formula (I) as disclosed herein and stereoisomers, tautomers, solvates, and salts (e.g., pharmaceutically acceptable salts) thereof. When the compounds of the invention are solids, it is understood by those skilled in the art that these compounds, and their solvates and salts, may exist in different solid forms, particularly different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

The term “pharmaceutically acceptable salts” denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

The term “pharmaceutically acceptable acid addition salt” denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. Particular pharmaceutically acceptable salts of the present invention are salts formed with hydrochloric acid yielding a hydrochloride, dihydrochloride, or trihydrochloride salt.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc., New York, 1994. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The substituents attached to the chiral center under consideration are ranked in accordance with the

Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al. *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511). The prefixes D and L or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or L designating that the compound is levorotatory. A compound prefixed with (+) or D is dextrorotatory.

- 5 The “basicity” of a compound is expressed herein by the negative decadic logarithm of the acidity constant of the conjugate acid ($\text{pK}_a = -\log K_a$). The larger the pK_a of the conjugate acid, the stronger the base ($\text{pK}_a + \text{pK}_b = 14$). In this application, an atom or functional group is denoted “basic” if it is suitable to accept a proton and if the calculated pK_a of its conjugate acid is at least 7, more particularly if the calculated pK_a of its conjugate acid is at least 7.8, most particularly if the calculated pK_a of its conjugate acid is at least 8. pK_a values were calculated in-silico as described in F. Milletti et al., *J. Chem. Inf. Model* (2007) 47:2172-2181.

The term “halo”, “halogen”, and “halide” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo. Particular examples of halo are fluoro and chloro, most particularly fluoro.

- 15 The term “alkyl” denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 7 carbon atoms. In particular embodiments, alkyl has 1 to 4 carbon atoms, and in more particular embodiments 1 to 2 carbon atoms. Examples of alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. Particular examples of alkyl are methyl and ethyl.

- 20 The term “alkoxy” denotes a group of the formula $-\text{O}-\text{R}'$, wherein R' is an alkyl group. Examples of alkoxy moieties include methoxy, ethoxy, isopropoxy, and tert-butoxy. Particular examples of alkoxy are methoxy and ethoxy.

- 25 The term “haloalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl. The term “perhaloalkyl” denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms. Particular example of haloalkyl is trifluoromethyl.

- 30 The term “haloalkoxy” denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkoxyl include monofluoro-, difluoro- or trifluoro-methoxy, -ethoxy or -propoxy, for example 3,3,3-trifluoropropoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, fluoromethoxy, or trifluoromethoxy. The term “perhaloalkoxy” denotes an alkoxy group where

all hydrogen atoms of the alkoxy group have been replaced by the same or different halogen atoms. Particular example of haloalkoxy is 2,2,2-trifluoroethoxy.

The term “bicyclic ring system” denotes two rings which are fused to each other via a common single or double bond (annelated bicyclic ring system), via a sequence of three or more
5 common atoms (bridged bicyclic ring system) or via a common single atom (spiro bicyclic ring system). Bicyclic ring systems can be saturated, partially unsaturated, unsaturated or aromatic. Bicyclic ring systems can comprise heteroatoms selected from N, O and S.

The term “cycloalkyl” denotes a monovalent saturated monocyclic hydrocarbon group of 3
10 to 7 ring carbon atoms. Examples for cycloalkyl are cyclopropyl, cyclobutanyl, cyclopentyl, cyclohexyl or cycloheptyl. Particular example for cycloalkyl is cyclopropyl.

The term “heterocycloalkyl” denotes a monovalent saturated or partly unsaturated mono-
or bicyclic ring system of 3 to 9 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. In particular embodiments, heterocycloalkyl
15 is a monovalent saturated monocyclic ring system of 4 to 7 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples for monocyclic saturated heterocycloalkyl are aziridinyl, oxiranyl, azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or
20 oxazepanyl. Examples for bicyclic saturated heterocycloalkyl are 8-aza-bicyclo[3.2.1]octyl, quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-aza-bicyclo[3.3.1]nonyl, 3-oxa-9-aza-bicyclo[3.3.1]nonyl, or 3-thia-9-aza-bicyclo[3.3.1]nonyl. Examples for partly unsaturated heterocycloalkyl are dihydrofuryl, imidazoliny, dihydro-oxazolyl, tetrahydro-pyridinyl, or dihydropyranyl. Particular examples of heterocycloalkyl are saturated or partially unsaturated
25 mono- or bicyclic 4 to 9-membered heterocycloalkyl comprising one or two ring nitrogen atoms, the remaining ring atoms being carbon. Particular examples for monocyclic saturated heterocycloalkyl are piperidinyl and piperazinyl. Particular example for monocyclic partially unsaturated heterocycloalkyl is 1,2,3,6-tetrahydropyridin-4-yl. Particular examples for bicyclic saturated heterocycloalkyl are hexahydropyrrolo[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-
30 c]pyrrol-2-yl, and 2,6-diazaspiro[3.3]heptan-2-yl. Most particular examples for heterocycloalkyl is piperazinyl.

The term “located opposite of the site of attachment” denotes the position of an atom in a cyclic ring system. If the point of attachment of a monocyclic ring to the rest of the molecular backbone is termed position 1, then “located opposite of the site of attachment” denotes position
35 3 for a monocyclic 4-membered ring, positions 3 or 4 for a monocyclic 5-membered ring, position

4 for a monocyclic 6-membered ring, and positions 4 or 5 for a monocyclic 7-membered ring. For bicyclic ring systems, "located opposite of the site of attachment" denotes a ring atom of the second fused ring (including bridgehead atoms).

5 The term "aromatic" denotes the conventional idea of aromaticity as defined in the literature, in particular in IUPAC - Compendium of Chemical Terminology, 2nd, A. D. McNaught & A. Wilkinson (Eds). Blackwell Scientific Publications, Oxford (1997).

10 The term "heteroaryl" denotes a monovalent aromatic heterocyclic mono- or bicyclic ring system of 5 to 12 ring atoms, comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples of heteroaryl moieties include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, benzofuranyl, isothiazolyl, benzothienyl, indolyl, isoindolyl, isobenzofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzooxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolyl, isoquinolyl, quinazolinyl, or
15 quinoxalinyl. Particular examples for heteroaryl are bicyclic 9-membered heteroaryl comprising 2 or 3 heteroatoms selected from N or O. More particular examples for heteroaryl are imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyridin-6-yl, and benzo[d]oxazol-6-yl. Most particular heteroaryl is imidazo[1,2-a]pyridin-6-yl.

20 The term "alkylene" denotes a linear saturated divalent hydrocarbon group of 2 to 7 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 7 carbon atoms. Examples of alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene. Particular examples of alkylene are methylene and ethylene.

25 The term "protecting group" denotes the group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Protecting groups can be removed at the appropriate point. Exemplary protecting groups are amino-protecting groups, carboxy-protecting groups or hydroxy-protecting groups.

30 The term "amino-protecting group" denotes groups intended to protect an amino group and includes benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), Fmoc (9-Fluorenylmethyloxycarbonyl), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl. Particular amino-protecting group is tert-butoxycarbonyl (BOC). Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York,
35 NY, 1991, chapter 7; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie,

Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. The term "protected amino group" refers to an amino group substituted by an amino-protecting groups.

5 The term "deprotection" or "deprotecting" denotes the process by which a protective group is removed after the selective reaction is completed. Deprotecting reagents include acids, bases or hydrogen, in particular potassium or sodium carbonates, lithium hydroxide in alcoholic solutions, zinc in methanol, acetic acid, trifluoroacetic acid, palladium catalysts, or boron tribromide. Most particular deprotecting reagent is hydrochloric acid.

10 The term "active pharmaceutical ingredient" (or "API") denotes the compound or molecule in a pharmaceutical composition that has a particular biological activity.

The term "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the composition would be administered.

15 The term "pharmaceutically acceptable" denotes an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use.

20 The term "pharmaceutically acceptable excipient" denotes any ingredient having no therapeutic activity and being non-toxic such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants or lubricants used in formulating pharmaceutical products.

25 A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical composition, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

30 An "individual" or "subject" is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human. In a particular embodiment of the invention the subject is a human with spinal muscular atrophy (SMA). In another specific embodiment, the subject is a human with SMA caused by an inactivating mutation or deletion in the SMN1 gene on both chromosomes, resulting in a loss of SMN1 gene function.

The term “spinal muscular atrophy” (or SMA) relates to a disease caused by an inactivating mutation or deletion in the SMN1 gene on both chromosomes, resulting in a loss of SMN1 gene function.

Symptoms of SMA include muscle weakness, poor muscle tone, weak cry, weak cough,

- 5 limpness or a tendency to flop, difficulty sucking or swallowing, difficulty breathing, accumulation of secretions in the lungs or throat, clenched fists with sweaty hand, flickering/vibrating of the tongue, head often tilted to one side, even when lying down, legs that tend to be weaker than the arms, legs frequently assuming a “frog legs” position, feeding difficulties, increased susceptibility to respiratory tract infections, bowel/bladder weakness,
- 10 lower-than-normal weight, inability to sit without support, failure to walk, failure to crawl, and hypotonia, areflexia, and multiple congenital contractures (arthrogryposis) associated with loss of anterior horn cells.

The term “treating spinal muscular atrophy (SMA)” or “treatment of spinal muscular atrophy (SMA)” includes one or more of the following effects: (i) reduction or amelioration of

15 the severity of SMA; (ii) delay of the onset of SMA; (iii) inhibition of the progression of SMA; (iv) reduction of hospitalization of a subject; (v) reduction of hospitalization length for a subject; (vi) increase of the survival of a subject; (vii) improvement of the quality of life of a subject; (viii) reduction of the number of symptoms associated with SMA; (ix) reduction of or amelioration of the severity of one or more symptoms associated with SMA; (x) reduction of the

20 duration of a symptom associated with SMA; (xi) prevention of the recurrence of a symptom associated with SMA; (xii) inhibition of the development or onset of a symptom of SMA; and/or (xiii) inhibition of the progression of a symptom associated with SMA.

More particular, “treating SMA” denotes one or more of the following beneficial effects: (i) a reduction in the loss of muscle strength; (ii) an increase in muscle strength; (iii) a reduction in

25 muscle atrophy; (iv) a reduction in the loss of motor function; (v) an increase in motor neurons; (vii) a reduction in the loss of motor neurons; (viii) protection of SMN deficient motor neurons from degeneration; (ix) an increase in motor function; (x) an increase in pulmonary function; and/or (xi) a reduction in the loss of pulmonary function.

In detail, “treating SMA” results in the functional ability or helps retain the functional ability for

30 a human infant or a human toddler to sit up unaided or for a human infant, a human toddler, a human child or a human adult to stand up unaided, to walk unaided, to run unaided, to breathe unaided, to turn during sleep unaided, or to swallow unaided.

An “effective amount” of an agent, e.g., a pharmaceutical composition, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or

35 prophylactic result.

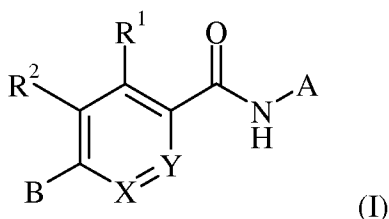
-12-

The term “preventing” or “prevention” of a disease state denotes causing the clinical symptoms of the disease state not to develop in a subject that can be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state.

The term “EC_{1.5x} concentration for production of full length SMN2 minigene mRNA” (or “EC_{1.5x} minigene”) is defined as that concentration of test compound that is effective in increasing the amount of full length SMN2 minigene mRNA to a level 1.5-fold greater relative to that in vehicle-treated cells.

The term “EC_{1.5x} concentration for SMN protein expression” (or “EC_{1.5x} SMN protein”) is defined as that concentration of test compound that is effective in producing 1.5 times the amount of SMN protein in an SMA patient fibroblast cell compared to the amount produced from the vehicle control.

In detail, the present invention relates to compounds of formula (I)



wherein

X is N or CR³;

Y is N or CR⁴; with the proviso that not both X and Y are N;

A is a bicyclic 9-membered heteroaryl comprising two or three heteroatoms independently selected from N or O, wherein A can be optionally substituted with one, two or three R⁵;

B is a saturated or partially unsaturated mono- or bicyclic 4 to 9-membered heterocycloalkyl comprising one or two ring nitrogen atoms, the remaining ring atoms being carbon, wherein B can be optionally substituted with one, two or three R⁶;

R¹ is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;

R² is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;

R³ is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;

R⁴ is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;

each R⁵ is independently selected from halo, cyano, C₁₋₇-alkyl, C₁₋₇-haloalkyl or C₃₋₇-cycloalkyl;

each R⁶ is independently selected from C₁₋₇-alkyl, or two R⁶ together form a C₂₋₇-alkylene;

5 and pharmaceutically acceptable salts thereof.

Particular embodiments of the present invention are compounds of formula (I) and pharmaceutically acceptable salts thereof.

Further, it is to be understood that every embodiment relating to a specific A, B, X, Y, R¹, R², R³, R⁴, R⁵ or R⁶ as disclosed herein may be combined with any other embodiment relating to another A, B, X, Y, R¹, R², R³, R⁴, R⁵ or R⁶ as disclosed herein.

A particular embodiment of the present invention relates to compounds of formula (I), wherein A is selected from the group of imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyridinyl, and benzo[d]oxazolyl, which can be optionally substituted with one, two or three R⁵.

15 A particular embodiment of the present invention relates to compounds of formula (I), wherein A is selected from the group of imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyridin-6-yl, and benzo[d]oxazol-6-yl, which can be optionally substituted with one, two or three R⁵.

20 A particular embodiment of the present invention relates to compounds of formula (I), wherein A is selected from the group of imidazo[1,2-a]pyrazin-2-yl substituted with two C₁₋₇-alkyl, imidazo[1,2-a]pyridin-6-yl substituted with one or two C₁₋₇-alkyl, imidazo[1,2-a]pyridin-6-yl substituted with one C₁₋₇-alkyl and one halo, imidazo[1,2-a]pyridin-6-yl substituted with one C₁₋₇-alkyl and one C₁₋₇-haloalkyl, benzo[d]oxazol-6-yl substituted with one C₁₋₇-alkyl, and benzo[d]oxazol-6-yl substituted with one C₁₋₇-alkyl and one halo.

A particular embodiment of the present invention relates to compounds of formula (I), wherein A is imidazo[1,2-a]pyridinyl which can be optionally substituted with one or two R⁵.

25 A particular embodiment of the present invention relates to compounds of formula (I), wherein A is imidazo[1,2-a]pyridin-6-yl substituted with one C₁₋₇-alkyl and one halo.

30 A particular embodiment of the present invention relates to compounds of formula (I), wherein A is selected from 2-methylbenzo[d]oxazol-6-yl, 4-fluoro-2-methylbenzo[d]oxazol-6-yl, 6,8-dimethylimidazo[1,2-a]pyrazin-2-yl, 2-methylimidazo[1,2-a]pyridin-6-yl, 2,7-dimethylimidazo[1,2-a]pyridin-6-yl, 2,8-dimethylimidazo[1,2-a]pyridin-6-yl, 2-methyl-8-

(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl, 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl, and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl.

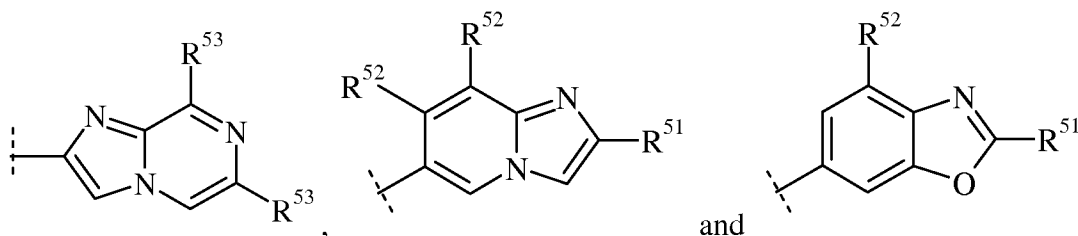
A particular embodiment of the present invention relates to compounds of formula (I), wherein A is selected from 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein each R^5 is independently selected from halo, C_{1-7} -alkyl, or C_{1-7} -haloalkyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein each R^5 is independently selected from methyl, fluoro, chloro, and trifluoromethyl.

10 A particular embodiment of the present invention relates to compounds of formula (I), wherein A is substituted by two R^5 wherein one R^5 is methyl and the other R^5 is fluoro or chloro.

A particular embodiment of the present invention relates to compounds of formula (I), wherein A is selected from the group of



15 wherein R^{51} , R^{52} and R^{53} are independently selected from the group of hydrogen, halo, cyano, C_{1-7} -alkyl, C_{1-7} -haloalkyl and C_{3-7} -cycloalkyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R^{51} , R^{52} and R^{53} are independently selected from the group of hydrogen, methyl, fluoro, chloro, and trifluoromethyl.

20 A particular embodiment of the present invention relates to compounds of formula (I), wherein R^{51} is selected from hydrogen and C_{1-7} -alkyl.

A more particular embodiment of the present invention relates to compounds of formula (I), wherein R^{51} is selected from hydrogen and C_{1-2} -alkyl.

25 A particular embodiment of the present invention relates to compounds of formula (I), wherein each R^{52} is independently selected from hydrogen, halo, cyano, C_{1-7} -alkyl, C_{1-7} -haloalkyl and C_{3-7} cycloalkyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein each R⁵² is independently selected from hydrogen, halo, cyano, C₁₋₂-alkyl, C₁₋₂-haloalkyl and cyclopropyl.

5 A particular embodiment of the present invention relates to compounds of formula (I), wherein each R⁵² is independently selected from hydrogen and fluoro.

A particular embodiment of the present invention relates to compounds of formula (I), wherein each R⁵³ is independently selected from hydrogen, chloro, C₁₋₇-alkyl, C₁₋₇-haloalkyl and C₃₋₇ cycloalkyl.

10 A particular embodiment of the present invention relates to compounds of formula (I), wherein each R⁵³ is independently selected from hydrogen, chloro, C₁₋₂-alkyl, C₁₋₂-haloalkyl and cyclopropyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein B as defined herein is further characterized in that one ring nitrogen atoms is basic.

15 A particular embodiment of the present invention relates to compounds of formula (I), wherein B as defined herein is further characterized in that its one, two or three optional substituent(s) R⁶ are attached at and/or directly adjacent to the basic ring nitrogen atoms.

A particular embodiment of the present invention relates to compounds of formula (I), wherein B is selected from 1,2,3,6-tetrahydropyridinyl, 2,6-diazaspiro[3.3]heptanyl, hexahydropyrrolo[3,4-c]pyrrolyl, hexahydropyrrolo[1,2-a]pyrazinyl, piperazinyl, and piperidinyl,
20 wherein each can be optionally substituted with one, two or three R⁶.

A particular embodiment of the present invention relates to compounds of formula (I), wherein B is selected from 1,2,3,6-tetrahydropyridin-4-yl, 2,6-diazaspiro[3.3]heptan-2-yl, hexahydropyrrolo[3,4-c]pyrrol-2-yl, hexahydropyrrolo[1,2-a]pyrazin-2-yl, piperazin-1-yl, and piperidin-4-yl, wherein each can be optionally substituted with one, two or three R⁶.

25 A particular embodiment of the present invention relates to compounds of formula (I), wherein B is selected from 1,2,3,6-tetrahydropyridin-4-yl, and piperazin-1-yl, wherein each can be optionally substituted with one, two or three R⁶.

A particular embodiment of the present invention relates to compounds of formula (I), wherein B is piperazin-1-yl optionally substituted with one, two or three R⁶.

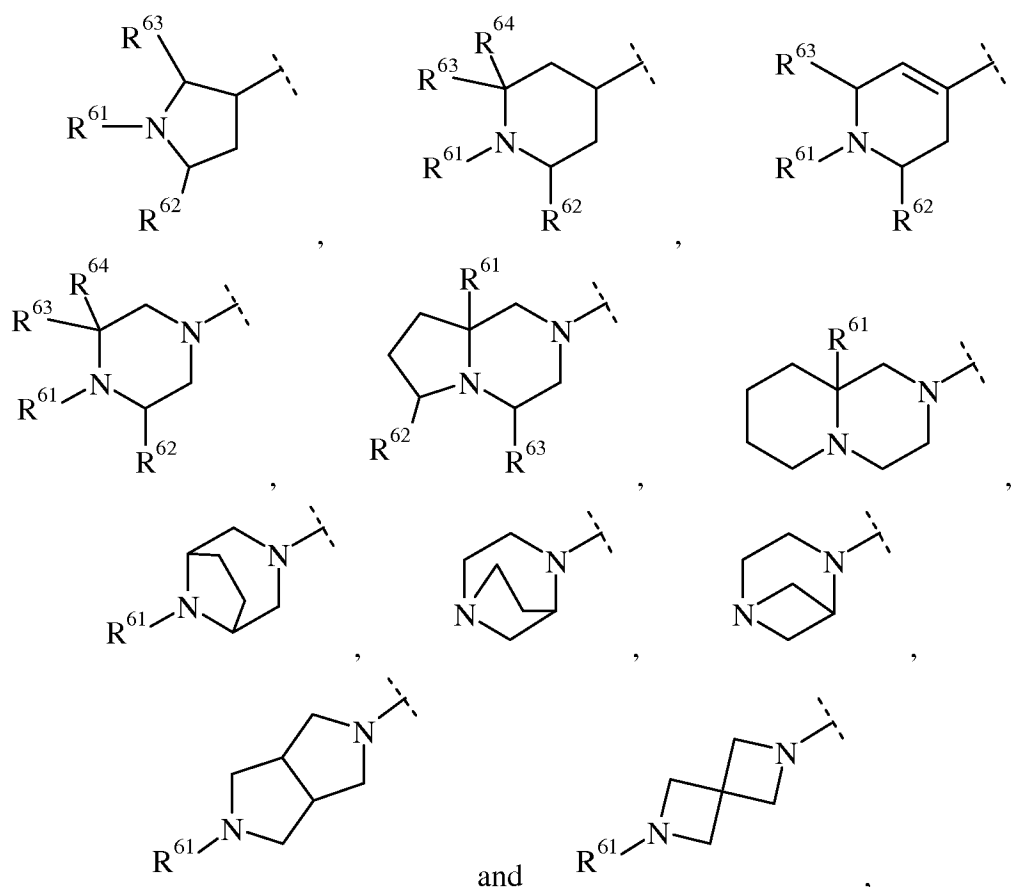
A particular embodiment of the present invention relates to compounds of formula (I), wherein B is selected from piperazin-1-yl, 3-methyl-piperazin-1-yl, and 3,3-dimethylpiperazin-1-yl.

5 A particular embodiment of the present invention relates to compounds of formula (I), wherein each R^6 is C_{1-7} alkyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein each R^6 is independently selected from methyl, and ethyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein each R^6 is independently selected from methyl.

10 A particular embodiment of the present invention relates to compounds of formula (I), wherein B is selected from the group of



wherein R^{61} , R^{62} , R^{63} and R^{64} are independently selected from hydrogen or C_{1-7} -alkyl, or wherein two of R^{61} , R^{62} and R^{63} together are forming a C_{2-7} -alkylene.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R^{61} , R^{62} , R^{63} and R^{64} are independently selected from hydrogen, methyl, and ethyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein X is CR³ and Y is CR⁴, or X is N and Y is CR⁴, or X is CR³ and Y is N.

A particular embodiment of the present invention relates to compounds of formula (I), wherein X is CR³ and Y is CR⁴.

5 A particular embodiment of the present invention relates to compounds of formula (I), wherein X is N and Y is CR⁴.

A particular embodiment of the present invention relates to compounds of formula (I), wherein X is CR³ and Y is N.

10 A particular embodiment of the present invention relates to compounds of formula (I), wherein R¹ is hydrogen, halo, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R¹ is hydrogen, fluoro, methoxy, ethoxy or trifluoroethoxy.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R¹ is hydrogen.

15 A particular embodiment of the present invention relates to compounds of formula (I), wherein R² is hydrogen, halo, or C₁₋₇-alkyl.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R² is hydrogen, fluoro or methyl.

20 A particular embodiment of the present invention relates to compounds of formula (I), wherein R² is hydrogen.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R³ is hydrogen or halo.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R³ is hydrogen or fluoro.

25 A particular embodiment of the present invention relates to compounds of formula (I), wherein R³ is hydrogen.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R⁴ is hydrogen, halo or C₁₋₇-alkoxy.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R⁴ is hydrogen or halo.

A particular embodiment of the present invention relates to compounds of formula (I), wherein R⁴ is hydrogen, fluoro, methoxy, ethoxy or trifluoroethoxy.

5 A particular embodiment of the present invention relates to compounds of formula (I), wherein R⁴ is hydrogen or fluoro.

Particular compounds of formula (I) of the present invention are those selected from the group consisting of:

- N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(piperazin-1-yl)benzamide;
10 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(3-methylpiperazin-1-yl)benzamide;
N-(6,8-Dimethyl-imidazo[1,2-a]pyrazin-2-yl)-4-((S)-3-methyl-piperazin-1-yl)-benzamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(4-methylpiperazin-1-yl)benzamide;
rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
15 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-ethylpiperazin-1-yl)nicotinamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(4-methylpiperazin-1-yl)picolinamide;
rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(piperazin-1-yl)picolinamide;
20 rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
6-(3,3-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
6-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinamide;
25 rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
rac-2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
rac-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
30 (S)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
6-(3,5-dimethylpiperazin-1-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
6-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide;
35 N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
(S)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-

yl)nicotinamide;

N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-piperazin-1-yl-nicotinamide;

rac-N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-(3-methyl-piperazin-1-yl)-nicotinamide;

N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;

5 rac-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

4-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide;

(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;

10 (S)-2-Fluoro-N-(4-fluoro-2-methyl-benzooxazol-6-yl)-4-(S)-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl-benzamide;

(R)-2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide;

(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-

15 (trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;

rac-N-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;

rac-2-fluoro-N-(2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-

20 yl)benzamide;

2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;

rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;

25 2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;

rac-2,3-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

rac-2,5-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

30 rac-5-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;

rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;

rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

35 (S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

(R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-

- yl)benzamide;
rac-N-(2,7-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-6-(3-methylpiperazin-1-yl)nicotinamide;
- 5 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide;
- 10 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2,6-difluoro-4-(3-methylpiperazin-1-yl)benzamide;
2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;
2-fluoro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
- 15 2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;
2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;
N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)picolinamide;
- 20 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(piperazin-1-yl)nicotinamide;
2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-methyl-4-(piperazin-1-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-methyl-6-(piperazin-1-yl)nicotinamide;
4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- 25 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(piperazin-1-yl)nicotinamide;
4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinamide;
2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- 30 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-2-(2,2,2-trifluoroethoxy)nicotinamide;
rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
6-(3,3-dimethylpiperazin-1-yl)-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-
- 35 methoxynicotinamide;
rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;

- N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperidin-4-yl)benzamide;
 5 rac-6-(3,4-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
 and pharmaceutically acceptable salts thereof.

Particular compounds of formula (I) of the present invention are those selected from the group consisting of:

- 10 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(piperazin-1-yl)benzamide;
 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 N-(6,8-Dimethyl-imidazo[1,2-a]pyrazin-2-yl)-4-((S)-3-methyl-piperazin-1-yl)-benzamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(4-methylpiperazin-1-yl)benzamide;
 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
 15 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-ethylpiperazin-1-yl)nicotinamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(4-methylpiperazin-1-yl)picolinamide;
 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 20 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(piperazin-1-yl)picolinamide;
 rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
 6-(3,3-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 6-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide
 25 hydrochloride;
 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinamide
 hydrochloride;
 rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 rac-2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 30 N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 rac-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
 (S)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
 35 6-(3,5-dimethylpiperazin-1-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
 6-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide;

- N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
(S)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide;
N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-piperazin-1-yl-nicotinamide;
5 rac-N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-(3-methyl-piperazin-1-yl)-nicotinamide;
N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;
rac-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
4-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide;
(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)benzamide;
10 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
(S)-2-Fluoro-N-(4-fluoro-2-methyl-benzooxazol-6-yl)-4-(S)-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl-benzamide;
(R)-2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide;
15 (S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide hydrochloride;
rac-N-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide
20 dihydrochloride;
rac-2-fluoro-N-(2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride;
rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride;
25 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide dihydrochloride;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide dihydrochloride;
rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide
30 dihydrochloride;
rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide dihydrochloride;
2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide hydrochloride;
rac-2,3-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride;
35 rac-2,5-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride;
rac-5-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-

- yl)nicotinamide hydrochloride;
rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide hydrochloride;
rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride;
5 (S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride;
(R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride;
10 rac-N-(2,7-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-6-(3-methylpiperazin-1-yl)nicotinamide hydrochloride;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride;
15 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide dihydrochloride;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide dihydrochloride;
20 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2,6-difluoro-4-(3-methylpiperazin-1-yl)benzamide trihydrochloride;
2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;
2-fluoro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
25 2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide hydrochloride;
2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide hydrochloride;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide dihydrochloride;
30 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)picolinamide dihydrochloride;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(piperazin-1-yl)nicotinamide;
2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
35 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-methyl-4-(piperazin-1-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-methyl-6-(piperazin-1-yl)nicotinamide;
4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(piperazin-1-yl)nicotinamide;

- 4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinamide;
 2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 5 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-2-(2,2,2-trifluoroethoxy)nicotinamide;
 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
 6-(3,3-dimethylpiperazin-1-yl)-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxynicotinamide;
 10 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide hydrochloride;
 15 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide dihydrochloride;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperidin-4-yl)benzamide hydrochloride;
 20 rac-6-(3,4-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
 and pharmaceutically acceptable salts thereof.

Particular compounds of formula (I) of the present invention are those selected from the group consisting of:

- 25 rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 30 rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 (S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 35 (R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-

yl)benzamide;

rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide;

2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;

4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

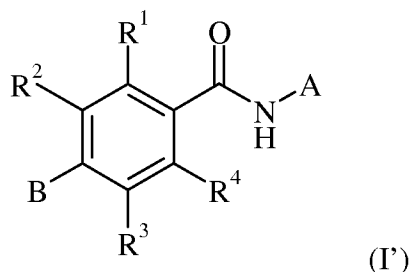
2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;

rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;

and pharmaceutically acceptable salts thereof.

A particular embodiment of the present invention relates to compounds of formula (I')



wherein A, B, R¹, R², R³ and R⁴ are as described herein.

Particular compounds of formula (I') of the present invention are those selected from the group consisting of:

N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(piperazin-1-yl)benzamide;

rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(3-methylpiperazin-1-yl)benzamide;

N-(6,8-Dimethyl-imidazo[1,2-a]pyrazin-2-yl)-4-((S)-3-methyl-piperazin-1-yl)-benzamide;

N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(4-methylpiperazin-1-yl)benzamide;

rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;

rac-2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;

rac-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

4-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide;

(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)benzamide;

(S)-2-Fluoro-N-(4-fluoro-2-methyl-benzooxazol-6-yl)-4-(S)-hexahydro-pyrrolo[1,2-a]pyrazin-2-

yl-benzamide;

(R)-2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide;

(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-

5 (trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;

rac-N-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;

rac-2-fluoro-N-(2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-

10 yl)benzamide;

2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;

2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;

rac-2,3-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

15 rac-2,5-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

(S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-

20 yl)benzamide;

(R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;

rac-N-(2,7-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;

rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-

25 yl)benzamide;

rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2,6-difluoro-4-(3-methylpiperazin-1-yl)benzamide;

2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;

2-fluoro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-

30 yl)benzamide;

2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;

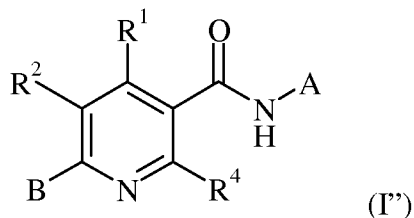
2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-methyl-4-(piperazin-1-yl)benzamide;

35 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperidin-4-yl)benzamide;

and pharmaceutically acceptable salts thereof.

A particular embodiment of the present invention relates to compounds of formula (I'')



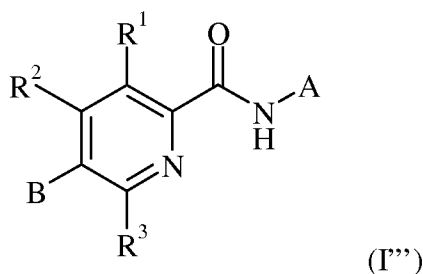
wherein A, B, R¹, R² and R⁴ are as described herein.

Particular compounds of formula (I'') of the present invention are those selected from the group consisting of:

- 5 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
- rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
- N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-ethylpiperazin-1-yl)nicotinamide;
- rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
- 10 6-(3,3-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
- N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- 6-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
- N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinamide;
- N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- 15 rac-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
- (S)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
- 6-(3,5-dimethylpiperazin-1-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
- 20 6-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide;
- N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
- (S)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide;
- 25 N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-piperazin-1-yl-nicotinamide;
- rac-N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-(3-methyl-piperazin-1-yl)-nicotinamide;
- N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
- N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
- 30 rac-5-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
- rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-6-(3-methylpiperazin-1-yl)nicotinamide;

- rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(piperazin-1-yl)nicotinamide;
 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 5 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-methyl-6-(piperazin-1-yl)nicotinamide;
 4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(piperazin-1-yl)nicotinamide;
 4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-4-(2,2,2-
 10 trifluoroethoxy)nicotinamide;
 2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-2-(2,2,2-
 trifluoroethoxy)nicotinamide;
 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-
 15 yl)nicotinamide;
 6-(3,3-dimethylpiperazin-1-yl)-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-
 methoxynicotinamide;
 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-
 yl)nicotinamide;
 20 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;
 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 rac-6-(3,4-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
 25 and pharmaceutically acceptable salts thereof.

A particular embodiment of the present invention relates to compounds of formula (I''')



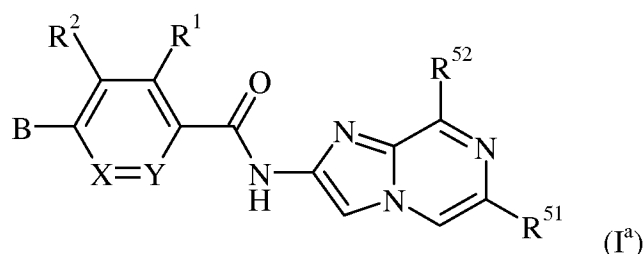
wherein A, B, R¹, R² and R³ are as described herein.

- Particular compounds of formula (I''') of the present invention are those selected from the
 30 group consisting of:

N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(4-methylpiperazin-1-yl)picolinamide;

- rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(piperazin-1-yl)picolinamide;
 rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 5 rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide;
 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)picolinamide;
 10 and pharmaceutically acceptable salts thereof.

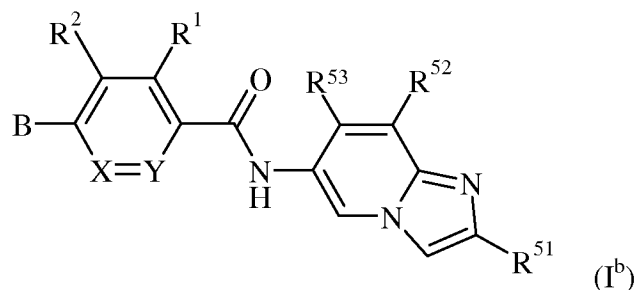
A particular embodiment of the present invention relates to compounds of formula (I^a)



wherein B, X, Y, R¹, R², R⁵¹ and R⁵² are as described herein.

- Particular compounds of formula (I^a) of the present invention are those selected from the
 15 group consisting of:
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(piperazin-1-yl)benzamide;
 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 N-(6,8-Dimethyl-imidazo[1,2-a]pyrazin-2-yl)-4-((S)-3-methyl-piperazin-1-yl)-benzamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(4-methylpiperazin-1-yl)benzamide;
 20 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-ethylpiperazin-1-yl)nicotinamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(4-methylpiperazin-1-yl)picolinamide;
 25 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(piperazin-1-yl)picolinamide;
 and pharmaceutically acceptable salts thereof.

A particular embodiment of the present invention relates to compounds of formula (I^b)



wherein B, X, Y, R¹, R², R⁵¹, R⁵² and R⁵³ are as described herein.

Particular compounds of formula (I^b) of the present invention are those selected from the

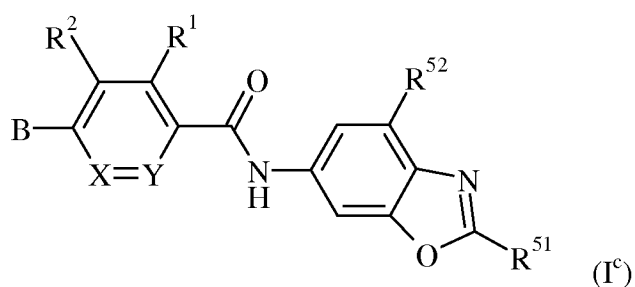
5 group consisting of:

- rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
- 6-(3,3-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
- N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- 6-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
- 10 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinamide;
- rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
- rac-2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
- N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- rac-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-
- 15 yl)nicotinamide;
- (S)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-
- a]pyridin-6-yl)nicotinamide;
- 6-(3,5-dimethylpiperazin-1-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-
- yl)nicotinamide;
- 20 (S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-
- yl)benzamide;
- N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
- (S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-
- (trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)benzamide;
- 25 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
- rac-N-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
- rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-
- yl)benzamide;
- 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
- 30 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
- rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;

- rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
rac-2,3-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
- 5 rac-2,5-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
rac-5-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
- 10 rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
(S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
- 15 (R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
rac-N-(2,7-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-6-(3-methylpiperazin-1-yl)nicotinamide;
- 20 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide;
- 25 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2,6-difluoro-4-(3-methylpiperazin-1-yl)benzamide;
2-fluoro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;
- 30 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;
N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)picolinamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(piperazin-1-yl)nicotinamide;
- 35 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-methyl-4-(piperazin-1-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-methyl-6-(piperazin-1-yl)nicotinamide;
4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

- N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(piperazin-1-yl)nicotinamide;
 4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinamide;
 5 2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-2-(2,2,2-trifluoroethoxy)nicotinamide;
 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
 10 6-(3,3-dimethylpiperazin-1-yl)-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxynicotinamide;
 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;
 15 N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide;
 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;
 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperidin-4-yl)benzamide;
 rac-6-(3,4-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
 20 and pharmaceutically acceptable salts thereof.

A particular embodiment of the present invention relates to compounds of formula (I^c)



wherein B, X, Y, R¹, R², R⁵¹, and R⁵² are as described herein.

- Particular compounds of formula (I^c) of the present invention are those selected from the
 25 group consisting of:
 6-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide;
 N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
 (S)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide;
 30 N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-piperazin-1-yl-nicotinamide;
 rac-N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-(3-methyl-piperazin-1-yl)-nicotinamide;

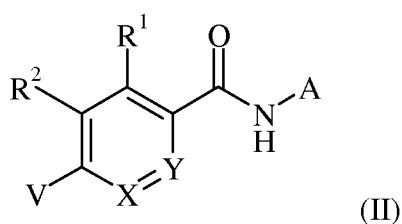
N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;
 rac-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 4-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide;
 (S)-2-Fluoro-N-(4-fluoro-2-methyl-benzooxazol-6-yl)-4-(S)-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl-benzamide;
 (R)-2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide;
 rac-2-fluoro-N-(2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;
 and pharmaceutically acceptable salts thereof.

Manufacturing Processes

Compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above be prepared following standard methods known in the art.

In a particular embodiment, the invention further relates to a process for the manufacture of compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above, comprising:

- a) the Buchwald-Hartwig amination reaction of a compound of formula (II)



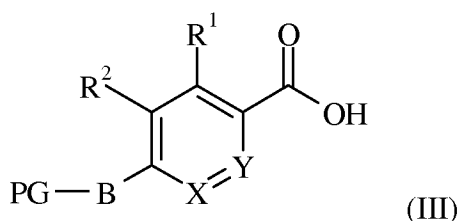
with a compound of formula B-H, in the presence of a catalyst (e.g. tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃)) and a ligand (e.g. 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)) and a base (e.g. cesium carbonate) and a solvent (e.g. toluene), wherein the hydrogen H of the compound of formula B-H is bound to a ring nitrogen atom of B, V is chloro or bromo, and A, B, X, Y, R¹, and R² are as defined above; or

- b) a nucleophilic aromatic substitution reaction between a compound of formula (II) with a compound of formula B-H by heating (e.g. T = 120°C - 200°C) in a solvent (e.g. dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), or dimethylformamide (DMF)), wherein the hydrogen H of the compound of formula B-H is bound to a ring nitrogen atom of B, V

is fluoro if X is CR³ or V is chloro if X is N, and A, B, X, Y, R¹, R² and R³ are as defined above; or

c) the Suzuki coupling reaction of a compound of formula (II) with a compound of formula PG-B-pinB in the presence of a base (e.g. K₂CO₃) and a catalyst (e.g. PdCl₂), followed by removal of PG, wherein pinB is pinacolboranyl (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) which is bound to a ring carbon atom of B, PG is an amino-protecting group such as tert-butoxycarbonyl (BOC), V is fluoro or chloro, and wherein A, B, X, Y, R¹, and R² are as defined above; or

d) the amidation reaction of a compound of formula (III)



with a compound of formula A-NH₂ in the presence of a tertiary amine (e.g. N,N-diisopropylethylamine (DIPEA) or triethylamine (TEA)) and a coupling reagent (e.g. 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium (HATU) or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU)), optionally followed by the removal of PG, wherein PG is an optional amino-protecting group such as tert-butoxycarbonyl (PG), and wherein A, B, X, Y, R¹, and R² are as defined above.

Particularly, compounds of formula (I) and pharmaceutically acceptable salts thereof can be prepared in accordance to the methods described in the examples herein.

Pharmaceutical Compositions

Another embodiment provides pharmaceutical compositions or medicaments comprising the compounds of the invention and a therapeutically inert carrier, diluent or pharmaceutically acceptable excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being

treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

5 The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

10 The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may comprise components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents, antioxidants, and
15 further active agents. They can also comprise still other therapeutically valuable substances.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., *Ansel H.C. et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (2004) Lippincott, Williams & Wilkins, Philadelphia; Gennaro A.R. et al.,
20 Remington: The Science and Practice of Pharmacy (2000) Lippincott, Williams & Wilkins, Philadelphia; and Rowe R.C., Handbook of Pharmaceutical Excipients (2005) Pharmaceutical Press, Chicago*. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents,
25 flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The dosage at which compounds of the invention can be administered can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In
30 general, in the case of oral administration a daily dosage of about 0.01 to 1000 mg per person of a compound of general formula (I) should be appropriate, although the above upper limit can also be exceeded when necessary.

An example of a suitable oral dosage form is a tablet comprising about 100 mg to 500 mg of the compound of the invention compounded with about 30 to 90 mg anhydrous lactose, about
35 5 to 40 mg sodium croscarmellose, about 5 to 30 mg polyvinylpyrrolidone (PVP) K30, and about

1 to 10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment.

5 An example of an aerosol formulation can be prepared by dissolving the compound, for example 10 to 100 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such as sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 μm filter, to remove impurities and contaminants.

10 Uses

As described above, the compounds of formula (I) and their pharmaceutically acceptable salts possess valuable pharmacological properties and have been found to be enhancing inclusion of exon 7 of SMN1 and/or SMN2 into mRNA transcribed from the SMN1 and/or SMN2 gene, thereby increasing expression of SMN protein in a human subject in need thereof.

15 The compounds of the present invention can be used, either alone or in combination with other drugs, for the treatment or prevention of diseases caused by an inactivating mutation or deletion in the SMN1 gene and/or associated with loss or defect of SMN1 gene function. These diseases include, but are not limited to spinal muscular atrophy (SMA).

20 A particular embodiment of the present invention relates to pharmaceutical compositions comprising compounds of formula (I) as defined above or their pharmaceutically acceptable salts as defined above and one or more pharmaceutically acceptable excipients.

25 A particular embodiment of the present invention relates to pharmaceutical compositions comprising compounds of formula (I) or their pharmaceutically acceptable salts as defined above and one or more pharmaceutically acceptable excipients for the treatment or prevention of diseases caused by an inactivating mutation or deletion in the SMN1 gene and/or associated with loss or defect of SMN1 gene function, particularly for the treatment or prevention of spinal muscular atrophy (SMA).

30 A particular embodiment of the present invention relates to compounds of formula (I) or their pharmaceutically acceptable salts as defined above for use as therapeutically active substances, especially for use as therapeutically active substances for the treatment or prevention of diseases caused by an inactivating mutation or deletion in the SMN1 gene and/or associated with loss or defect of SMN1 gene function, particularly for the treatment or prevention of spinal muscular atrophy (SMA).

A particular embodiment of the present invention relates to compounds of formula (I) or their pharmaceutically acceptable salts as defined above for the use in the treatment or prevention of diseases caused by an inactivating mutation or deletion in the SMN1 gene and/or associated with loss or defect of SMN1 gene function, particularly for use in the treatment or prevention of spinal muscular atrophy (SMA).

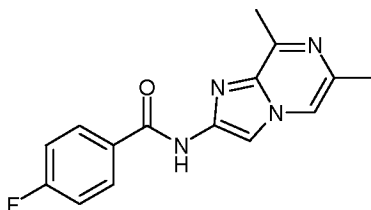
A particular embodiment of the present invention relates to a method for the treatment or prevention of diseases caused by an inactivating mutation or deletion in the SMN1 gene and/or associated with loss or defect of SMN1 gene function, particularly for the treatment or prevention of spinal muscular atrophy (SMA), which method comprises administering compounds of formula (I) or their pharmaceutically acceptable salts as defined above to a subject.

A particular embodiment of the present invention relates to the use of compounds of formula (I) or their pharmaceutically acceptable salts as defined above for the treatment or prevention of diseases caused by an inactivating mutation or deletion in the SMN1 gene and/or associated with loss or defect of SMN1 gene function, particularly for the treatment or prevention of spinal muscular atrophy (SMA).

A particular embodiment of the present invention relates to the use of compounds of formula (I) or their pharmaceutically acceptable salts as defined above for the preparation of medicaments for the treatment or prevention of diseases caused by an inactivating mutation or deletion in the SMN1 gene and/or associated with loss or defect of SMN1 gene function, particularly for the treatment or prevention of spinal muscular atrophy (SMA). Such medicaments comprise compounds of formula (I) or their pharmaceutically acceptable salts as defined above.

Examples

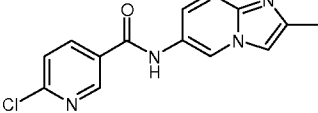
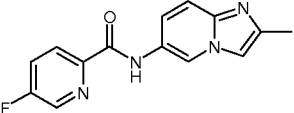
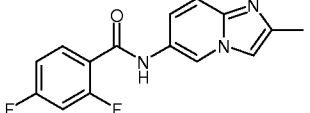
The invention will be more fully understood by reference to the following examples. They should however not be construed as limiting the scope of the invention.

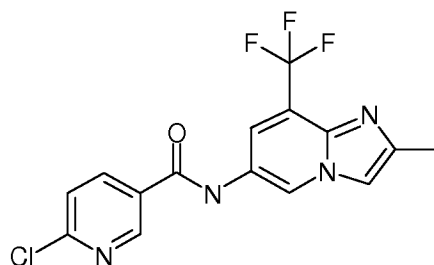
Preparation of intermediates**Example A.1****Preparation of N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-fluorobenzamide**

- 5 To a mixture of 6,8-dimethylimidazo[1,2-a]pyrazin-2-amine trihydrochloride (Example B.1) (134 mg, 494 μ mol) and N-Ethyldiisopropylamine (320 mg, 420 μ l, 2.47 mmol) in dioxane (2.0 ml) was added dropwise a solution of 4-fluorobenzoyl chloride (80 mg, 60.3 μ l, 494 μ mol) in dioxane (0.5 ml) at room temperature. The mixture was stirred for 1 hour. The solvent was removed in vacuo. The solid was taken in water and the suspension was stirred for 15 minutes.
- 10 The solid was filtered and dried to provide 125 mg (89 %) of the title compound as an off-white solid. MS (m/e): 285.4 (M+H⁺)

In analogy to Example A.1, Examples A.2 to A.7 of the following table were prepared from the acylchloride and amine derivatives:

Example No.	Structure	Systematic Name	Starting materials
A.2		N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2,4-difluorobenzamide	6,8-dimethylimidazo[1,2-a]pyrazin-2-amine trihydrochloride (Example B.1) and 2,4-difluorobenzoyl chloride (commercial)
A.3		6-chloro-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)nicotinamide	6,8-dimethylimidazo[1,2-a]pyrazin-2-amine trihydrochloride (Example B.1) and 6-chloronicotinoyl chloride (commercial)
A.4		N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluoropicolinamide	6,8-dimethylimidazo[1,2-a]pyrazin-2-amine trihydrochloride (Example B.1) and 5-Fluoropyridine-2-carbonyl chloride (717871-83-5)

A.5		6-chloro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide	2-methylimidazo[1,2-a]pyridin-6-amine hydrobromide (commercial) and 6-chloronicotinoyl chloride (commercial)
A.6		5-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)picolinamide	2-methylimidazo[1,2-a]pyridin-6-amine hydrobromide (commercial) and 5-Fluoro-pyridine-2-carbonyl chloride (717871-83-5)
A.7		2,4-difluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)benzamide	2-methylimidazo[1,2-a]pyridin-6-amine hydrobromide (commercial) and 2,4-difluorobenzoyl chloride (commercial)

Example A.8**Preparation of 6-Chloro-N-(2-methyl-8-trifluoromethyl-imidazo[1,2-a]pyridin-6-yl)-nicotinamide**

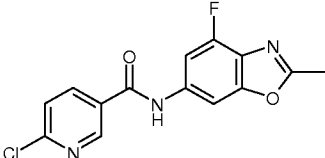
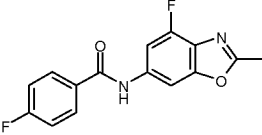
5

To a solution of 6-chloronicotinic acid (332 mg, 2.11 mmol) in DMF (4 ml) under argon at room temperature, were added HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) (1.2 g, 3.16 mmol) and N,N-diisopropylethylamine (1.4 ml, 8.42 mmol). After 5 minutes stirring, 2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-amine

10 hydrochloride (Example B.2) (530 mg, 2.11 mmol) was added. The mixture was stirred at room temperature for two days. The solvent was removed in vacuo. The residue was taken in aqueous bicarbonate. The aqueous layer was extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified with flash column chromatography on silica eluting with a gradient formed from

15 dichloromethane and methanol (0 to 5%) to provide the title compound.

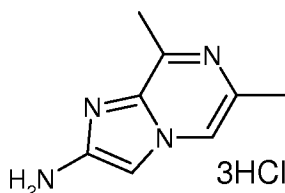
In analogy to Example A.8, Examples A.9 to A.10 of the following table were prepared from the acid and amine derivatives:

Example No.	Structure	Systematic Name	Starting materials
A.9		6-chloro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide	4-fluoro-2-methylbenzo[d]oxazol-6-amine hydrochloride (Example B.3) and 6-chloronicotinic acid (commercial)
A.10		4-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide	4-fluoro-2-methylbenzo[d]oxazol-6-amine hydrochloride (Example B.3) and 4-fluorobenzoic acid (commercial)

5

Example B.1

Preparation of 6,8-dimethylimidazo[1,2-a]pyrazin-2-amine trihydrochloride



a) step1 : Ethyl 6,8-dimethylimidazo[1,2-a]pyrazine-2-carboxylate hydrobromide

To a solution of 3,5-dimethylpyrazin-2-amine (200 mg, 1.62 mmol) in DME (6.00 ml) was added ethyl 3-bromo-2-oxopropanoate (380 mg, 245 μ l, 1.95 mmol) at 0°C. The mixture was stirred for 2 hours at room temperature. The suspension was filtered and washed with dimethoxyethane. The filtrate was taken in ethanol (4 ml) and refluxed for 1.5 hours. The reaction mixture was cooled to room temperature, filtered and washed with ethanol to provide 323 mg (66.3 %) of the title compound as a light yellow solid. MS (m/e): 220.1 (M+H+)

15

b) step 2: 6,8-dimethylimidazo[1,2-a]pyrazine-2-carboxylic acid hydrochloride

To a solution of ethyl 6,8-dimethylimidazo[1,2-a]pyrazine-2-carboxylate hydrobromide (300 mg, 0.999 mmol) in ethanol (6 ml) and water (3 ml) under nitrogen at room temperature, was added sodium hydroxide 2M (1.05 ml, 2.1 mmol). The reaction mixture was stirred at 90°C for 2 hours. The mixture was cooled to room temperature and acidified with 1 ml HCl solution (2 M). The

20

resulting suspension was cooled to 0°C, filtered, washed with cold diethyl ether and dried to provide 128 mg (56.3 %) of the title compound as a light brown solid. MS (m/e): 192.1 (M+H+)

c) step 3: tert-butyl 6,8-dimethylimidazo[1,2-a]pyrazin-2-ylcarbamate

- 5 To a suspension of 6,8-dimethylimidazo[1,2-a]pyrazine-2-carboxylic acid hydrochloride (5 g, 22.0 mmol) in tert-butanol (50.9 ml) under nitrogen at room temperature, was added triethylamine (9.17 ml, 65.9 mmol). After stirring for 10 minutes, diphenylphosphoryl azide (4.85 ml, 22.0 mmol) was added. The reaction mixture was stirred at 85°C overnight. The solvent was removed in vacuo. The residue was taken in aqueous bicarbonate. The aqueous
- 10 layer was extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The crude orange oil was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 60%) to provide 3.57 g (y: 62.0 %) of the title compound as a white foam. MS(m/e): 263.5 (M+H+)

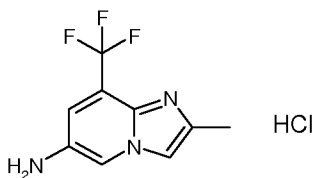
15

d) step 4: 6,8-dimethylimidazo[1,2-a]pyrazin-2-amine trihydrochloride

- To a yellow solution of tert-butyl 6,8-dimethylimidazo[1,2-a]pyrazin-2-ylcarbamate (3.57 g, 13.6 mmol) in methanol (35.7 ml) under nitrogen at room temperature, was added dropwise hydrogen chloride (34.0 ml, 136 mmol, 4M in dioxane). The reaction mixture was stirred at
- 20 room temperature overnight. The mixture was evaporated to provide 3.66 g (99 %) of the title compound as a yellow solid. MS(m/e): 163.2 (M+H+)

Example B.2

Preparation of 2-Methyl-8-trifluoromethyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride



25

a) step 1 : 6-bromo-2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridine

- In a 30ml sealed reactor, 5-bromo-3-(trifluoromethyl)pyridin-2-amine (CAS:79456-34-1) (2.5 g, 10.4 mmol) was combined with 1-chloropropan-2-one (1.04 ml, 12.4 mmol) in acetonitrile (25 ml) and heated at 130°C for 2 days. The reaction mixture was cooled to room temperature,
- 30 quenched with 100 ml of a saturated aqueous sodium bicarbonate solution. The reaction was extracted with ethylacetate and water. The organic layers were dried over sodium sulfate and

concentrated in vacuo. The crude residue was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 25%) to provide 1.2 g (y: 41.5 %) of the title compound as a pink solid.

5 b) step 2: N-(diphenylmethylene)-2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-amine

In a 250 mL pear-shaped flask, 6-bromo-2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridine (2.79 g, 10.0 mmol), rac 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (623 mg, 1.00 mmol), palladium (II) acetate (224 mg, 1.00 mmol), cesium carbonate (8.14 g, 25.0 mmol) and diphenylmethanimine (2.48 g, 2.3 ml, 13.0 mmol) were combined with THF (70 ml) to give a
10 orange suspension. The reaction mixture was heated to 70 °C and stirred for 23 h. The reaction was extracted with ethylacetate and water. The organic layers were dried over sodium sulfate and concentrated in vacuo. The crude residue purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 25%) to provide 2.33 g (y: 61.0 %) of the title compound as a yellow oil. MS(m/e): 380.5 (M+H+).

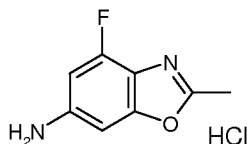
15

c) step 3 : 2-Methyl-8-trifluoromethyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride

To a solution of N-(diphenylmethylene)-2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-amine (2.3 g, 6.06 mmol) in dioxane (20 ml) was added HCl 1N (7.58 ml, 7.58 mmol). The mixture was stirred at room temperature for 30 minutes. The solvent was removed in vacuo. The
20 residue was triturated in acetonitrile. The white solid was filtered, washed with acetonitrile and dried to provide 1.08 g (71 %) of the expected compound as a white solid. MS (m/e): 216.5 (M+H+)

Example B.3

25 **Preparation of 4-fluoro-2-methylbenzo[d]oxazol-6-amine hydrochloride**



a) step 1 : 6-Bromo-4-fluoro-2-methyl-benzooxazole

To a solution of 4'-bromo-2',6'-difluoroacetanilide (4.0 g, 15.6 mmol, CAS: 658072-14-1) in N-methyl-2-pyrrolidinone (25 ml) was added cesium carbonate (10.3 g, 31.6 mmol) and the
30 mixture heated to 150°C for 1 h. The reaction was then diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and

concentrated in vacuo. The crude residue was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (20% to 50%) to provide 1.5 g (42 %) of the title compound as a light brown solid. MS (m/e): 273.1 (M+H+MeCN).

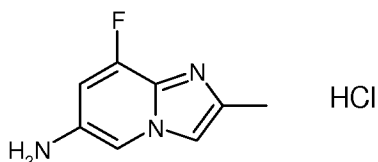
5 b) step 2 : 4-fluoro-2-methylbenzo[d]oxazol-6-amine hydrochloride

In analogy to the procedure described for the synthesis of example B.2 (steps: 2-3), the title compound was prepared from 6-Bromo-4-fluoro-2-methyl-benzooxazole. MS (m/e): 216.5 (M+H+).

10

Example B.4

Preparation of 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride

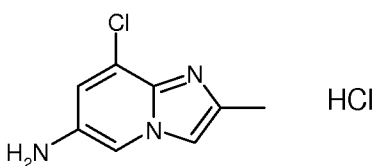


In analogy to the procedure described for the synthesis of example B.2 (steps: 1-3), the title compound was prepared from 5-bromo-3-fluoro-pyridin-2-ylamine (CAS: 748812-37-5). MS (m/e): 166.2 (M+H+).

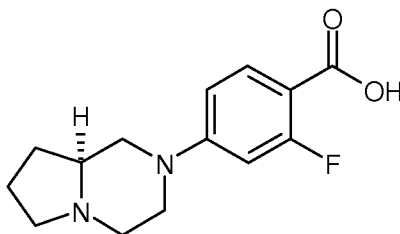
15

Example B.5

Preparation of 8-chloro-2-methylimidazo[1,2-a]pyridin-6-amine hydrochloride



20 In analogy to the procedure described for the synthesis of example B.2 (steps: 1-3), the title compound was prepared from 5-bromo-3-chloro-pyridin-2-ylamine (CAS: 38185-55-6). MS (m/e): 182.1 (M+H+).

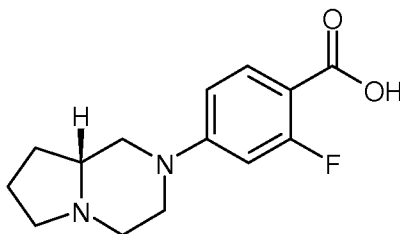
Example C.1**Preparation of (S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoic acid**a) step1 : (S)-methyl 2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoate

- 5 Toluene (1.5 ml) was added to a mixture of methyl 4-bromo-2-fluorobenzoate (200 mg, 832 μmol) and (S)-octahydropyrrolo[1,2-a]pyrazine (130 mg, 999 μmol). The mixture was stirred until complete dissolution. Then cesium carbonate (407 mg, 1.25 mmol) was added. Then $\text{Pd}_2(\text{dba})_3$ (22.9 mg, 25.0 μmol) and BINAP (46.7 mg, 74.9 μmol) were added. The reaction mixture was stirred vigorously for 24 hours at 110°C. The reaction mixture was cooled to room
- 10 temperature. Water and ethylacetate were added. The layers were separated. The aqueous layer was extracted twice with ethylacetate. The combined organic layers were washed with water, dried over sodium sulfate, filtered and evaporated. The crude orange oil was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 80%) to provide 121 mg (y: 52.2 %) of the title compound as a yellow oil
- 15 MS (m/e): 279.5 (M+H+)

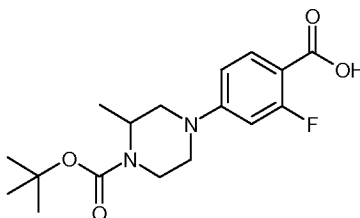
b) step 2: (S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoic acid

- To a solution of (S)-methyl 2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoate (100 mg, 359 μmol) in tetrahydrofuran (513 μl), methanol (256 μl) and water (256 μl) was added
- 20 lithium hydroxide monohydrate (45.2 mg, 1.08 mmol). The mixture was stirred at room temperature for 6 hours. The mixture was evaporated. HCl 2N was added dropwise to pH 3-4. Dichloromethane was added and the aqueous layer was extracted 3 times with dichloromethane. NaOH 5N was added to the aqueous phase to reach pH 6. The solution was evaporated. The residue was suspended in dichloromethane and methanol, filtered and evaporated to provide 82
- 25 mg (86.4 %) of the title compound as colorless oil. MS (m/e): 265.5 (M+H+)

-45-

Example C.2**Preparation of (R)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoic acid**

In analogy to the procedure described for the synthesis of example C.1 (steps: 1-2), the title compound was prepared from 4-bromo-2-fluorobenzoate and (R)-octahydropyrrolo[1,2-a]pyrazine.

Example C.3**Preparation of rac-4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid**

a) step1 : rac-tert-butyl 4-(4-(ethoxycarbonyl)-3-fluorophenyl)-2-methylpiperazine-1-carboxylate

A solution of ethyl 2,4-difluorobenzoate (200 mg, 1.07 mmol) and 2-methylpiperazine (538 mg, 5.37 mmol) in DMA (2 ml) was heated to 100°C in a microwave reactor for 15 minutes.

Ethyl acetate and water was added. The layers were separated and the aqueous layer was

extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and evaporated. A solution of this crude material and triethylamine (131 mg, 180 µl, 1.29 mmol) in dichloromethane (2.00 ml) was cooled to 0°C. Di-tert-butyl dicarbonate (352 mg, 1.61 mmol) in dichloromethane (0.5 ml) was added dropwise. The mixture was stirred at room temperature overnight. Water was added. The layers were separated. The aqueous layer was

extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified with flash column chromatography on silica gel (Eluent: Heptane/ethyl acetate 0 to 20) to provide 155 mg (34 %) of the title compound as a light yellow oil.

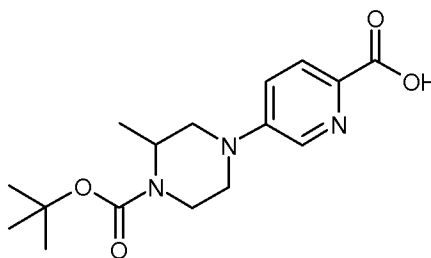
b) step 2: rac-4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid

In analogy to the procedure described for the synthesis of example C.1 (step: 2), the title compound was prepared from rac-tert-butyl 4-(4-(ethoxycarbonyl)-3-fluorophenyl)-2-methylpiperazine-1-carboxylate

5

Example C.4

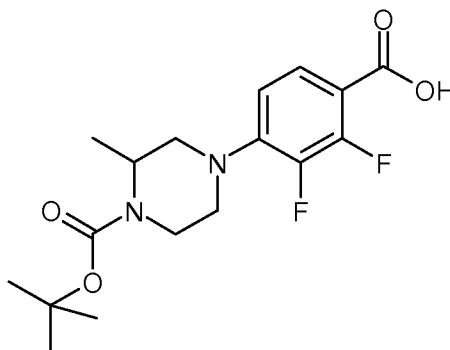
Preparation of rac-4-(6-Carboxy-pyridin-3-yl)-2-methyl-piperazine-1 carboxylic acid tert-butyl ester



- 10 A solution of 5-fluoropicolinic acid (0.47g, 3.33 mmol) and 2-methylpiperazine N1 Boc (1.00 g, 5.00 mmol) in DMA (2.00 ml) was heated to 160°C in a microwave reactor for 1 hour. The solvent was evaporated under high vacuum. The residue was taken in water and acidified to pH 3. The aqueous phase was extracted 3 times with ethyl acetate, dried and concentrated. The crude product was purified with flash column chromatography on silica gel (Eluent: Heptane/ethyl acetate 0 to 20) to provide 1.17 g (100 %) of the title compound.
- 15

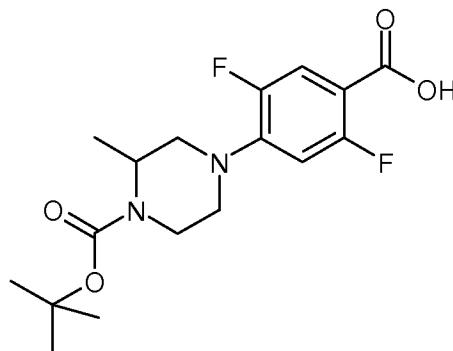
Example C.5

Preparation of rac-4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2,3-difluorobenzoic acid



20

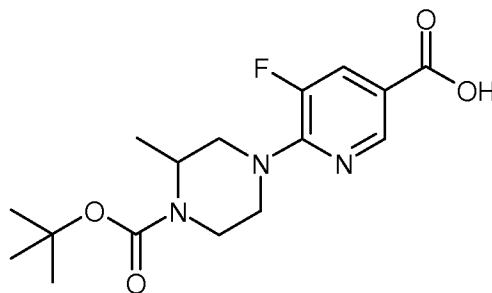
In analogy to the procedure described for the synthesis of example C.3 (steps: 1-2), the title compound was prepared from 2,3,4-trifluoro-benzoic acid ethyl ester and rac-2-methylpiperazine.

Example C.6**Preparation of rac-4-(4-Carboxy-2,5-difluoro-phenyl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester**

5

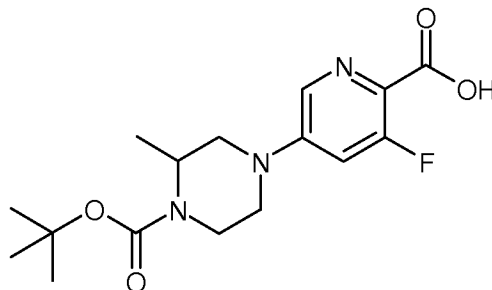
In analogy to the procedure described for the synthesis of example C.3 (steps: 1-2), the title compound was prepared from 2,4,5-Trifluoro-benzoic acid methyl ester and rac-2-methylpiperazine.

10

Example C.7**Preparation of rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-5-fluoronicotinic acid**

15

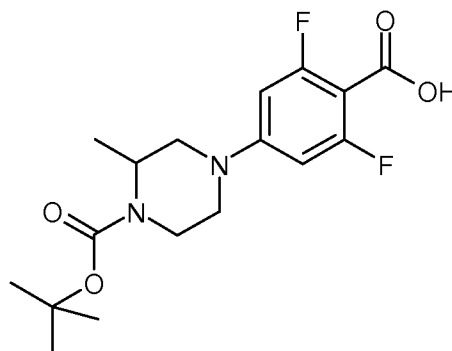
In analogy to the procedure described for the synthesis of example C.3 (steps: 1-2), the title compound was prepared from 6-Chloro-5-fluoro-nicotinic acid methyl ester and rac-2-methylpiperazine.

Example C.8**Preparation of rac-5-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-3-fluoropyridine-2-carboxylic acid**

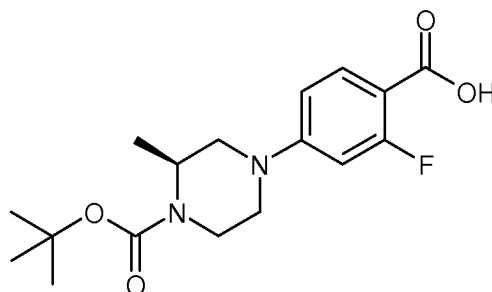
- 5 In analogy to the procedure described for the synthesis of example C.3 (steps: 1-2), the title compound was prepared from 3,5-Difluoro-pyridine-2-carboxylic acid methyl ester and rac-2-methylpiperazine.

Example C.9

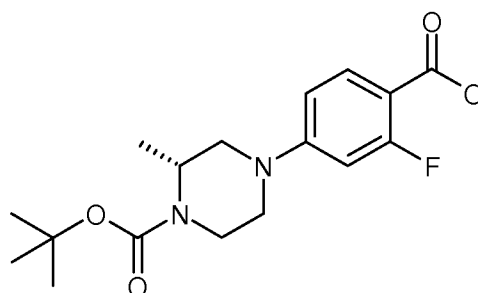
10 **Preparation of rac-4-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-2,6-difluorobenzoic acid**



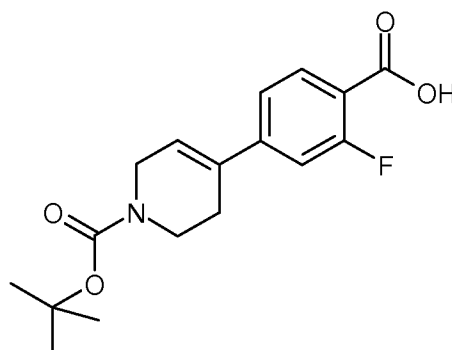
- In analogy to the procedure described for the synthesis of example C.3 (steps: 1-2), the title compound was prepared from 2,4,6-Trifluoro-benzoic acid methyl ester and rac-2-methylpiperazine.
- 15

Example C.10**Preparation of (S)-4-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid**

In analogy to the procedure described for the synthesis of example C.1 (steps: 1-2), the title compound was prepared from methyl 4-bromo-2-fluorobenzoate and (S)-tert-butyl 2-methylpiperazine-1-carboxylate.

Example C.11**Preparation of (R)-4-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid**

In analogy to the procedure described for the synthesis of example C.1 (steps: 1-2), the title compound was prepared from methyl 4-bromo-2-fluorobenzoate and (R)-tert-butyl 2-methylpiperazine-1-carboxylate.

Example C.12**Preparation of 4-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-fluorobenzoic acid**

a) step1 : tert-butyl 4-(3-fluoro-4-(methoxycarbonyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate

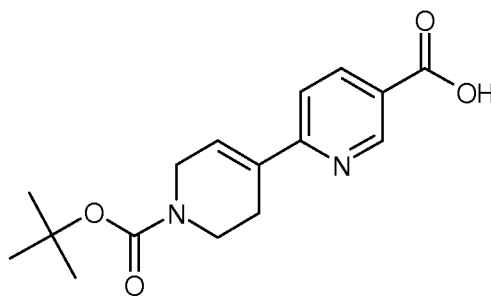
To a solution of methyl 4-bromo-2-fluorobenzoate (94 mg, 395 μ mol) in Dioxane (2 ml) were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (179.3 mg, 580 μ mol), tetrakis-(triphenylphosphine)palladium (22.8 mg, 19.8 μ mol, Eq: 0.05) and tripotassium phosphate (170.1 mg, 801 μ mol). Under an inert atmosphere, the mixture was heated at 100°C for 18h. The reaction was filtered and the filtrate was concentrated in vacuo. The resulting brown oil was purified by flash column chromatography on silica (Eluent: Heptane/ethyl acetate 0 to 20) to provide 121 mg (91 %) of the title compound as a light yellow oil. MS (m/e): 280.4 (M+H-56)

b) step 2: 4-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-fluorobenzoic acid

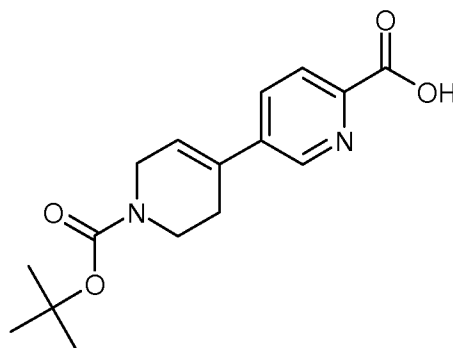
In analogy to the procedure described for the synthesis of example C.1 (step: 2), the title compound was prepared from tert-butyl 4-(3-fluoro-4-(methoxycarbonyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate

Example C.13

Preparation of 6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)nicotinic acid



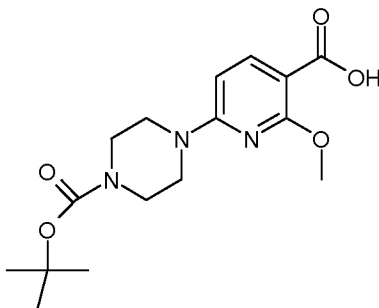
To a solution of 6-chloronicotinic acid (200 mg, 1.26 mmol) in dry DMF (2.5 ml) under nitrogen at room temperature, were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (466 mg, 1.51 mmol), tetrakis(triphenylphosphine)palladium (0) (147 mg, 126 μ mol) and potassium carbonate anhydrous (521 mg, 3.77 mmol). The reaction mixture was degassed with nitrogen for 10 minutes. The mixture was then stirred at 125°C in microwave for 45 min. The mixture was diluted with DMF. Water was added to the suspension and the mixture was cooled to 0°C. HCl 1N was slowly added, until pH 3-4. The suspension was filtered and the solid was washed with water and then ethyl acetate to provide 158 mg (41.3 %) of the title compound as a white solid. MS (m/e): 305.5 (M+H+)

Example C.14**Preparation of 5-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)picolinic acid**a) step1: methyl 5-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)picolinate

- 5 To a solution of methyl 5-bromopicolinate (205 mg, 930 μmol) in DMF (2 ml) under nitrogen at room temperature, was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (300 mg, 970 μmol), followed by sodium carbonate 2M aq. (650 μl , 1.3 mmol). The reaction mixture was degased with argon for 10 minutes. Finally, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (30.5 mg, 41.7 μmol) was added and the mixture was then stirred at 60°C in microwave for 10 minutes, and then 70°C for 70 minutes. Ethyl acetate and water were added to the reaction mixture. Both layers were separated and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude brown oil was purified with flash column chromatography on silica (Eluent: Heptane/ethyl acetate 0 to 20) to provide 202 mg (68 %) of the title compound as a white solid. MS (m/e): 319.5 (M+H-56)

b) step 2: 4-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-fluorobenzoic acid

- 20 In analogy to the procedure described for the synthesis of example C.1 (step: 2), the title compound was prepared from methyl 5-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)picolinate.

Example C.15**Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-methoxynicotinic acid**a) Step 1: tert-butyl 4-(6-fluoro-5-(methoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate

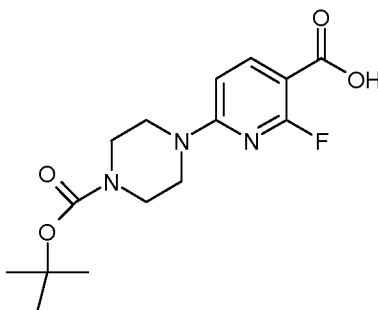
- 5 To an ice-cold solution of methyl 2,6-difluoronicotinate (2.0 g, 11.6 mmol, CAS 11767-02-0) and triethylamine (1.6 ml, 11.6 mmol) in DMF (10 ml) was added dropwise a solution of tert-butyl piperazine-1-carboxylate (2.2 g, 11.6 mmol) in DMF (5 ml). The reaction was stirred for 0.5h at 0°C after which time it was diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified with flash
10 column chromatography on silica (Eluent: Heptane/ethyl acetate 10 to 20%) to provide 2.7 g (68 %) of the title compound as a white solid. MS (m/e): 340.2 (M+H).

b) Step 2: tert-butyl 4-(6-methoxy-5-(methoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate

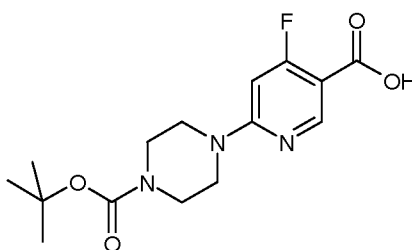
- To a solution of tert-butyl 4-(6-fluoro-5-(methoxycarbonyl)pyridin-2-yl)piperazine-1-
15 carboxylate (0.40 g, 1.2 mmol) in methanol (5 ml) was added potassium tert-butoxide (0.13 g, 1.2 mmol) and the mixture heated to reflux. After 4 h the reaction was diluted with dichloromethane, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide 0.4 g (92 %) of the title compound as a white solid. MS (m/e): 352.4 (M+H).

c) Step 3: 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-methoxynicotinic acid

- To a solution of tert-butyl 4-(6-methoxy-5-(methoxycarbonyl)pyridin-2-yl)piperazine-1-
carboxylate (0.38 g, 1.1 mmol) in methanol (5 ml) was added 6 N sodium hydroxide (0.36 ml, 2.2 mmol) and the reaction heated to 80°C for 16h. The reaction was concentrated to dryness, 5% aqueous citric acid was added and the resulting precipitate isolated by filtration, affording
25 0.31 g (86 %) of the title compound as a white solid. MS (m/e): 338.3 (M+H).

Example C.16**Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-fluoronicotinic acid**

To a suspension of tert-butyl 4-(6-fluoro-5-(methoxycarbonyl)pyridin-2-yl)piperazine-1-carboxylate (0.1 g, 0.3 mmol)-Example C.15 (step 1) in tert-butanol (2 ml) was added 6 N sodium hydroxide (0.1 ml, 0.6 mmol) and the mixture heated to 100°C for 3h. The reaction was concentrated to dryness, 5% aqueous citric acid was added and the resulting precipitate isolated by filtration, affording 0.08 g (87 %) of the title compound as a white solid. MS (m/e): 326.4 (M+H).

Example C.17**Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-fluoronicotinic acid**a) Step 1: tert-butyl 4-(4-fluoropyridin-2-yl)piperazine-1-carboxylate

In analogy to the procedure described for the synthesis of example C.1 (step 1), the title compound was prepared from 2-chloro-4-fluoropyridine and (tert-butyl piperazine-1-carboxylate. MS (m/e): 282.5 (M+H).

b) Step 2: tert-butyl 4-(4-fluoro-5-iodopyridin-2-yl)piperazine-1-carboxylate

To a solution of tert-butyl 4-(4-fluoropyridin-2-yl)piperazine-1-carboxylate (67 mg, 0.2 mmol) in DMF (0.5 ml) was added N-iodo-succinamide (82 mg, 0.4 mmol) and the mixture stirred for 24h. The reaction was then diluted with water, extracted with ethyl acetate, the organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified with flash column chromatography on silica (Eluent: Heptane/ethyl acetate 0 to

30%) to provide 73 mg (75 %) of the title compound as a light yellow solid. MS (m/e): 408.5 (M+H).

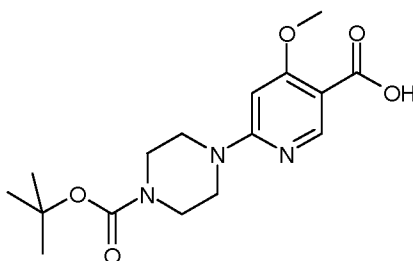
c) Step 3: 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-fluoronicotinic acid

- 5 To an ice-cold suspension of tert-butyl 4-(4-fluoro-5-iodopyridin-2-yl)piperazine-1-carboxylate (63 mg, 0.2 mmol) in tetrahydrofuran (0.2 ml) under argon was added isopropylmagnesium chloride lithium chloride complex (0.13 ml, 1.3 M in THF, 0.2 mmol). The mixture was allowed to come to ambient temperature and stirred for 45 minutes before carbon dioxide gas was bubbled into the reaction. After 1h the mixture was diluted with water, extracted with ethyl
- 10 acetate, the aqueous layer was then acidified with 5% aqueous citric acid solution and re-extracted with ethyl acetate. The ethyl acetate was then washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide 29 mg (58 %) of the title compound as an off-white foam. MS (m/e): 326.5 (M+H).

15

Example C.18

Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxynicotinic acid

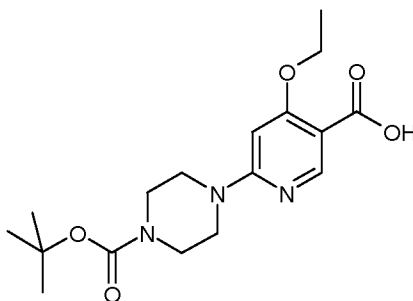


In analogy to the procedure described for the synthesis of example C.17 (steps: 1-3), the title compound was prepared from 2-chloro-4-methoxypyridine. MS (m/e): 338.6 (M+H).

20

Example C.19

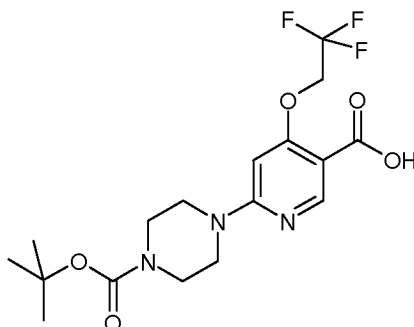
Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-ethoxynicotinic acid



In analogy to the procedure described for the synthesis of example C.17 (steps: 1-3), the title compound was prepared from 2-chloro-4-ethoxypyridine. MS (m/e): 352.5 (M+H).

Example C.20

5 Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinic acid



a) Step 1: 2-chloro-4-(2,2,2-trifluoroethoxy)pyridine

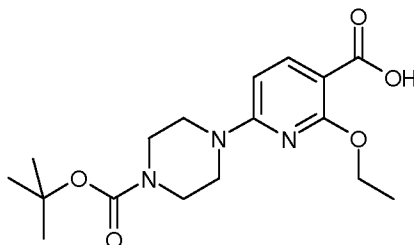
To a solution of 2-chloro-4-nitropyridine (0.5 g, 3.2 mmol) in tetrahydrofuran (20 ml) was added
10 2,2,2-trifluoroethanol (0.25 ml, 3.5 mmol) and potassium tert-butoxide (0.4 g, 3.5 mmol). The reaction mixture was stirred at 60°C overnight in a sealed vessel. The reaction was concentrated to dryness, the residue re-dissolved in ethyl acetate, washed with sodium hydrogen carbonate, brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified
15 with flash column chromatography on silica (Eluent: Heptane/ethyl acetate 0 to 30%) to provide 0.6 g (91 %) of the title compound as a colourless liquid. MS (m/e): 212.2 (M+H).

b) 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinic acid

In analogy to the procedure described for the synthesis of example C.17 (steps: 1-3), the title compound was prepared from 2-chloro-4-(2,2,2-trifluoroethoxy)pyridine. MS (m/e): 406.6
20 (M+H).

Example C.21

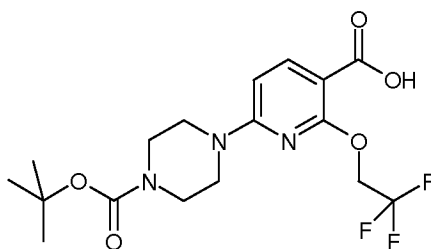
Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-ethoxynicotinic acid



-56-

In analogy to the procedure described for the synthesis of example C.15 (steps: 1-3), except that ethanol is used in place of methanol as solvent in step 2, afforded the title compound. MS (m/e): 352.5 (M+H).

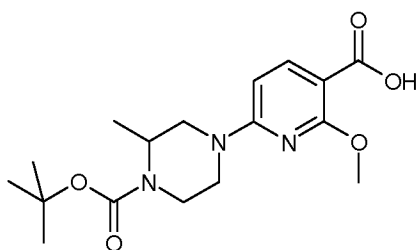
5

Example C.22**Preparation of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(2,2,2-trifluoroethoxy)nicotinic acid**

In analogy to the procedure described for the synthesis of example C.15 (steps: 1-3), except that
10 2,2,2-trifluoroethanol is used in place of methanol as solvent in step 2, afforded the title
compound. MS (m/e): 404.7 (M-H).

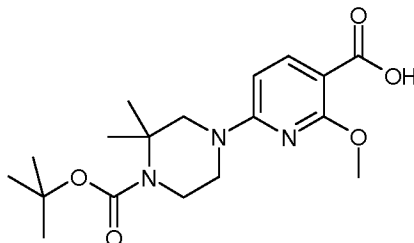
Example C.23**Preparation of rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-methoxynicotinic acid**

15



In analogy to the procedure described for the synthesis of example C.15 (steps: 1-3), the title
compound was prepared from rac-tert-butyl 2-methylpiperazine-1-carboxylate and methyl 2,6-
difluoronicotinate. MS (m/e): 350.5 (M-H).

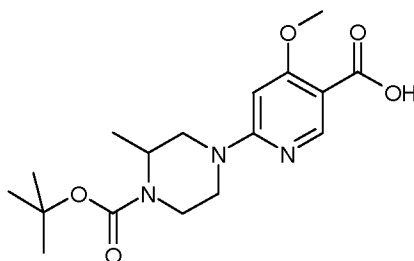
20

Example C.24**Preparation of 6-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinic acid**

- 5 In analogy to the procedure described for the synthesis of example C.15 (steps: 1-3), the title compound was prepared from 2,2-dimethyl-piperazine-1-carboxylic acid tert-butyl ester and methyl 2,6-difluoronicotinate. MS (m/e): 364.5 (M-H).

Example C.25

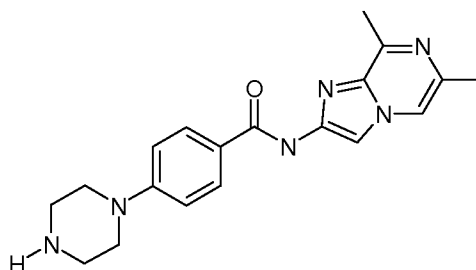
10 **Preparation of rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-4-methoxynicotinic acid**



- In analogy to the procedure described for the synthesis of example C.18 , the title compound was prepared from rac-tert-butyl 2-methylpiperazine-1-carboxylate and 2-chloro-4-methoxypyridine .
- 15 MS (m/e): 352.5 (M+H).

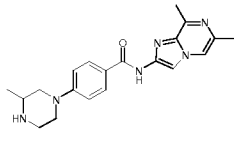
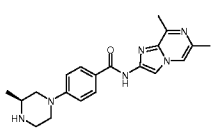
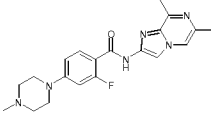
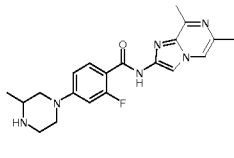
Description of examples:**Example 1**

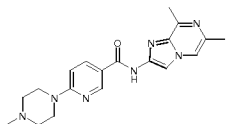
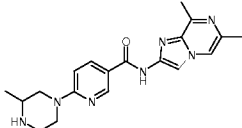
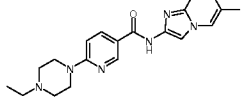
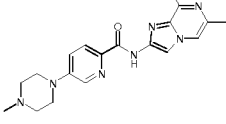
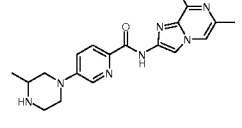
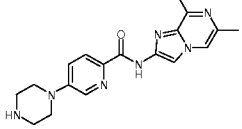
20 **Preparation of N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(piperazin-1-yl)benzamide**

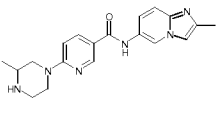
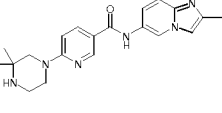
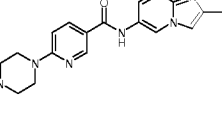
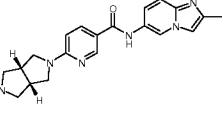
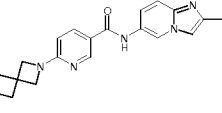


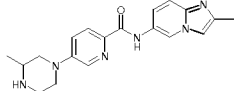
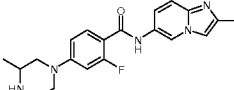
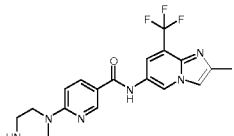
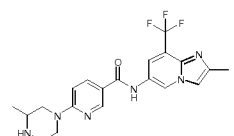
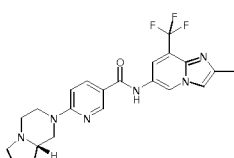
To a solution of N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-fluorobenzamide (Example A.1) (20 mg, 70.4 μ mol) in N,N-dimethylacetamide (200 μ l) under nitrogen at room temperature, was added piperazine (60.6 mg, 704 μ mol). The reaction mixture was microwaved at 160°C for 90 minutes. The mixture was cooled to room temperature. The resulting precipitate was filtered, rinsed with diethyl ether and dried to provide 4 mg (16.2 %) of the title as an off-white solid. MS (m/e): 351.4 (M+H⁺)

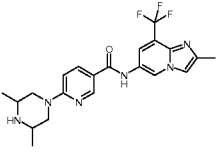
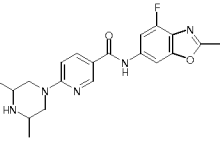
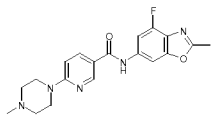
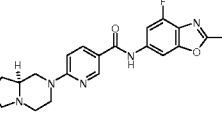
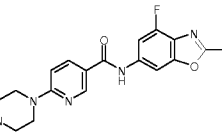
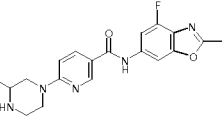
In analogy to Example 1, compounds 2 to 30 of the following table were prepared by reacting an halo-substituted amide derivative with an amino-substituted derivative at the indicated temperature:

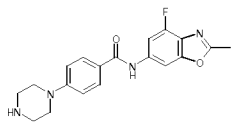
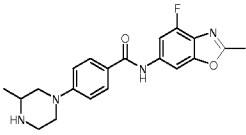
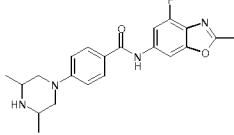
Example No.	Structure	Systematic Name	Starting materials	T (°C)	MW found (MH ⁺)
2		rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(3-methylpiperazin-1-yl)benzamide	N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-fluorobenzamide (Example A.1) and rac-2-methylpiperazine (commercial)	160	365.5
3		N-(6,8-Dimethylimidazo[1,2-a]pyrazin-2-yl)-4-((S)-3-methylpiperazin-1-yl)benzamide	N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-fluorobenzamide (Example A.1) and (S)-(+)-2-methylpiperazine (commercial)	200	365.5
4		N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(4-methylpiperazin-1-yl)benzamide	N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2,4-difluorobenzamide (Example A2) and 1-methylpiperazine (commercial)	180	383.5
5		rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide	N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2,4-difluorobenzamide (Example A2) and rac-2-methylpiperazine	180	383.5

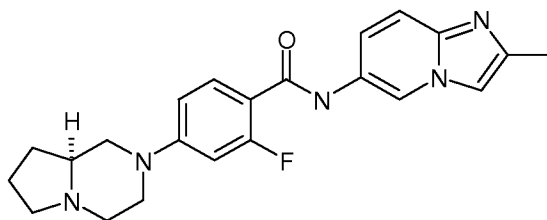
Example No.	Structure	Systematic Name	Starting materials	T (°C)	MW found (MH ⁺)
			(commercial)		
6		N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)nicotinamide	6-chloro-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)nicotinamide (Example A3) and 1-methylpiperazine (commercial)	120	366.5
7		rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(3-methylpiperazin-1-yl)nicotinamide	6-chloro-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)nicotinamide (Example A3) and rac-2-methylpiperazine (commercial)	180	366.5
8		N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-ethylpiperazin-1-yl)nicotinamide	6-chloro-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)nicotinamide (Example A3) and 1-ethylpiperazine (commercial)	130	380.5
9		N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(4-methylpiperazin-1-yl)picolinamide	N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluoropicolinamide (Example A4) and 1-methylpiperazine (commercial)	160	366.5
10		rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(3-methylpiperazin-1-yl)picolinamide	N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluoropicolinamide (Example A4) and rac-2-methylpiperazine (commercial)	160	366.5
11		N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(piperazin-1-yl)picolinamide	N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluoropicolinamide (Example A4) and piperazine (commercial)	160	352.5

Example No.	Structure	Systematic Name	Starting materials	T (°C)	MW found (MH ⁺)
12		rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide	6-chloro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide (Example A5) and rac-2-methylpiperazine (commercial)	130	351.4
13		6-(3,3-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide	6-chloro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide (Example A5) and 2,2-Dimethylpiperazine (commercial)	130	365.5
14		N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide	6-chloro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide (Example A5) and piperazine (commercial)	130	337.5
15		6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide hydrochloride	6-chloro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide (Example A5) and hexahydropyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butylester (commercial) followed by treatment with HCl	130	363.5
16		N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinamide hydrochloride	6-chloro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide (Example A5) and 2,6-Diazaspiro[3.3]heptane-2-carboxylic acid tert-butyl ester (commercial) followed by treatment	130	349.5

Example No.	Structure	Systematic Name	Starting materials	T (°C)	MW found (MH ⁺)
			with HCl		
17		rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide	5-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)picolinamide (Example A6) and rac-2-methylpiperazine (commercial)	160	351.5
18		rac-2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide	2,4-difluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)benzamide (Example A7) and rac-2-methylpiperazine (commercial)	100	368.5
19		N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide	6-Chloro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-nicotinamide (Example A8) and piperazine (commercial)	130	405.4
20		rac-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide	6-Chloro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-nicotinamide (Example A8) and rac-2-methylpiperazine (commercial)	130	419.4
21		(S)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide	6-Chloro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-nicotinamide (Example A8) and (S)-octahydropyrrolo[1,2-a]pyrazine (commercial)	130	445.7

Example No.	Structure	Systematic Name	Starting materials	T (°C)	MW found (MH ⁺)
22		6-(3,5-dimethylpiperazin-1-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide	6-Chloro-N-(2-methyl-8-trifluoromethylimidazo[1,2-a]pyridin-6-yl)-nicotinamide (Example A8) and 2,6-dimethylpiperazine	130	433.7
23		6-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide	6-chloro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide (Example A9) and 2,6-dimethylpiperazine	130	384.6
24		N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide	6-chloro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide (Example A9) and 1-methylpiperazine (commercial)	130	370.6
25		(S)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide	6-chloro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide (Example A9) and (S)-octahydropyrrolo[1,2-a]pyrazine (commercial)	130	396.6
26		N-(4-Fluoro-2-methylbenzooxazol-6-yl)-6-piperazin-1-yl-nicotinamide	6-chloro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide (Example A9) and piperazine (commercial)	130	356.6
27		rac-N-(4-Fluoro-2-methylbenzooxazol-6-yl)-6-(3-methylpiperazin-1-yl)-nicotinamide	6-chloro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide (Example A9) and rac-2-methylpiperazine	130	370.6

Example No.	Structure	Systematic Name	Starting materials	T (°C)	MW found (MH ⁺)
			(commercial)		
28		N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide	4-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide (Example A10) and piperazine (commercial)	160	355.6
29		rac-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide	4-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide (Example A10) and rac-2-methylpiperazine (commercial)	160	369.6
30		4-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide	4-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide (Example A10) and 2,6-dimethylpiperazine	160	383.7

Example 31**(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)benzamide**

5

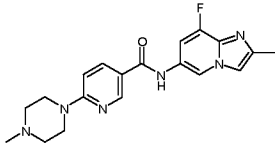
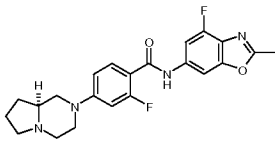
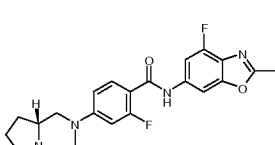
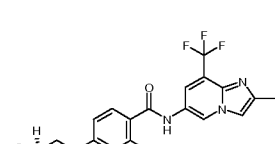
To a solution of (S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoic acid (Example C.1) (80 mg, 303 μ mol) in N,N-dimethylformamide (800 μ l) under nitrogen at room temperature, were added HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) (173 mg, 454 μ mol) and N-ethyldiisopropylamine (156 mg, 206 μ l, 1.21 mmol). After 5 minutes stirring at room temperature, 2-methylimidazo[1,2-a]pyridin-6-amine hydrobromide (commercial) (69.0 mg, 303 μ mol) was added. The mixture was shaken at 60°C

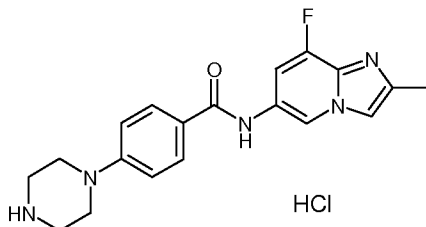
10

for 5.5 hours and then at room temperature for two days. The solvent was removed in vacuo. The residue was taken in a saturated aqueous solution of bicarbonate. Ethyl acetate was added. The resulting precipitate was filtered, rinsed with ethyl acetate and dried. The solid was stirred in ethyl acetate, filtered, rinsed with cold ethyl acetate and n-hexane and dried to provide 11 mg (9 %)

5 of the title compound as a light brown solid. MS (m/e): 394.6 (M+H)

In analogy to Example 31, compounds 32 to 35 of the following table were prepared from the acid and amine derivatives:

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
32		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide	6-(4-Methyl-piperazin-1-yl)-nicotinic acid (commercial) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4)	369.5
33		(S)-2-Fluoro-N-(4-fluoro-2-methylbenzooxazol-6-yl)-4-(S)-hexahydropyrrolo[1,2-a]pyrazin-2-yl-benzamide	(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoic acid (Example C.1) and 4-fluoro-2-methylbenzo[d]oxazol-6-amine hydrochloride (Example B.3)	413.7
34		(R)-2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide	(R)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoic acid (Example C.2) and 4-fluoro-2-methylbenzo[d]oxazol-6-amine hydrochloride (Example B.3)	413.6
35		(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)benzamide	(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoic acid (Example C.1) and 2-Methyl-8-trifluoromethyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.2)	462.5

Example 36**Preparation of N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide hydrochloride**

5 To a solution of 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzoic acid (commercial) (109 mg, 357 μ mol) in N,N-dimethylformamide (1.00 ml) under nitrogen at room temperature, were added HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) (204 mg, 536 μ mol) and N-ethyldiisopropylamine (185 mg, 243 μ l, 1.43 mmol). After 5 minutes stirring at room temperature, 8-fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride

10 (Example B.4) (72 mg, 357 μ mol) was added. The mixture was stirred at room temperature for 21 hours and then at 60°C for 2 hours. The solvent was removed in vacuo. The residue was taken in a saturated aqueous solution of bicarbonate and extracted three times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified on silica gel (Eluent: heptane/ethyl acetate 0 to 10%) to provide 78 mg of tert-

15 butyl 4-(4-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-ylcarbamoyl)phenyl)piperazine-1-carboxylate. To a suspension of this compound (40 mg, 88.2 μ mol) in methanol (400 μ l) was added HCl 4M in dioxane (221 μ l, 882 μ mol). The light yellow suspension was stirred at room temperature for 17 hours. The solid was filtered, washed with ether and hexane and dried to provide 25 mg (72.7 %) of the title compound as a light yellow solid. MS(m/e): 354.5 (M+H).

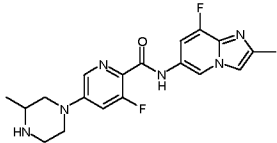
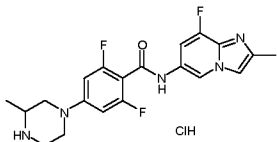
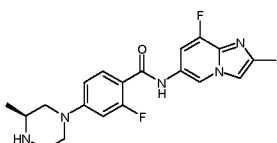
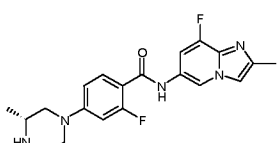
20

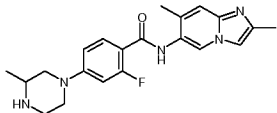
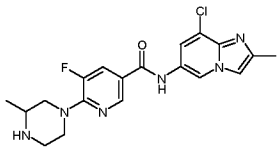
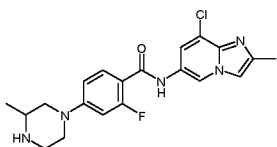
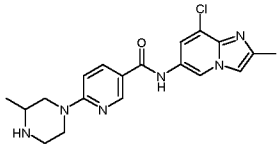
In analogy to Example 36, compounds 37 to 63 of the following table were prepared from the acid and amine derivatives followed by treatment with HCl or TFA.

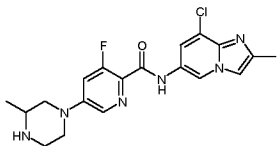
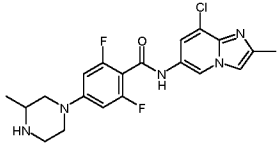
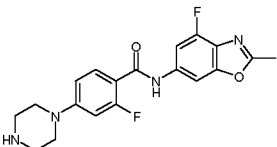
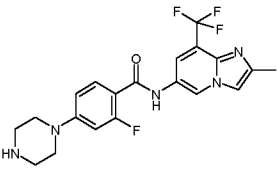
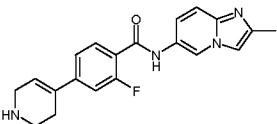
Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
37		rac-N-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride	4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid (Example C.3) and 2,8-dimethylimidazo[1,2-a]pyridin-6-amine hydrochloride (CAS:	382.6

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
			1216295-25-8) followed by treatment with HCl	
38		rac-2-fluoro-N-(2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride	4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid (Example C.3) and 2-Methyl-benzooxazol-6-ylamine (commercial) followed by treatment with HCl	369.5
39		rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride	4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid (Example C.3) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	386.6
40		2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide dihydrochloride	4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-fluorobenzoic acid (CAS: 1121596-45-9) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	372.6
41		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide dihydrochloride	4-(5-Carboxy-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (CAS: 201809-22-5) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	355.5
42		rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide dihydrochloride	rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)nicotinic acid (CAS: 904817-70-5) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example	369.6

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
			B.4) followed by treatment with HCl	
43		rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide dihydrochloride	rac-4-(6-Carboxy-pyridin-3-yl)-2-methyl-piperazine-1 carboxylic acid tert-butyl ester (Example C.4) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	369.6
44		2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide hydrochloride	4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-fluorobenzoic acid (CAS: 1121596-45-9) and 2-methylimidazo[1,2-a]pyridin-6-amine hydrobromide (commercial) followed by treatment with HCl	354.6
45		rac-2,3-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride	rac-4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2,3-difluorobenzoic acid (Example C.5) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	404.6
46		rac-2,5-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride	rac-4-(4-Carboxy-2,5-difluoro-phenyl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester (Example C.6) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	404.5
47		rac-5-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide	rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-5-fluoronicotinic acid (Example C.7) and 8-Fluoro-2-methyl-	387.5

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
		hydrochloride	imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	
48		rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide hydrochloride	rac-5-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-3-fluoropicolinic acid (Example C.8) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	387.6
49		rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride	rac-4-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-2,6-difluorobenzoic acid (Example C.9) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	404.6
50		(S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride	(S)-4-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid (Example C.10) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	386.6
51		(R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide hydrochloride	(R)-4-(4-(tertbutoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid (Example C.11) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	386.6

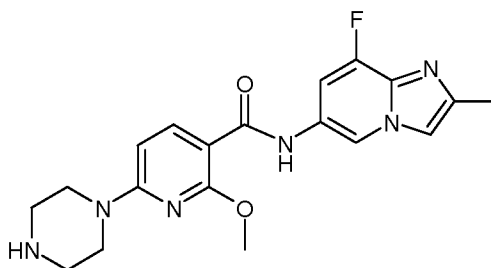
Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
52		rac-N-(2,7-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride	rac-4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid (Example C.3) and 2,7-dimethylimidazo[1,2-a]pyridin-6-amine hydrochloride (CAS: 1216109-27-1) followed by treatment with HCl	382.5
53		rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-6-(3-methylpiperazin-1-yl)nicotinamide hydrochloride	rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-5-fluoronicotinic acid (Example C.7) and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-amine hydrochloride (Example B.5) followed by treatment with HCl	403.5
54		rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide dihydrochloride	rac-4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-fluorobenzoic acid (Example C.3) and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-amine hydrochloride (Example B.5) followed by treatment with HCl	402.5
55		rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide dihydrochloride	rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)nicotinic acid (CAS: 904817-70-5) and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-amine hydrochloride (Example B.5) followed by treatment with HCl	385.6

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
56		rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide dihydrochloride	rac-5-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-3-fluoropicolinic acid (Example C.8) and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-amine hydrochloride (Example B.5) followed by treatment with HCl	403.5
57		rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2,6-difluoro-4-(3-methylpiperazin-1-yl)benzamide trihydrochloride	rac-4-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2,6-difluorobenzoic acid (Example C.9) and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-amine hydrochloride (Example B.5) followed by treatment with HCl	420.5
58		2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide	4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-fluorobenzoic acid (CAS: 1121596-45-9) and 4-fluoro-2-methylbenzo[d]oxazol-6-amine hydrochloride (Example B.3) followed by treatment with TFA	373.5
59		2-fluoro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide	4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-fluorobenzoic acid (CAS: 1121596-45-9) and 2-Methyl-8-trifluoromethylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.2) followed by treatment with TFA	422.5
60		2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-	4-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-fluorobenzoic acid (Example C.12) and 2-methylimidazo[1,2-	351.5

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
		yl)benzamide hydrochloride	a]pyridin-6-amine hydrobromide (commercial followed by treatment with HCl	
61		2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide hydrochloride	4-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-fluorobenzoic acid (Example C.12) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	369.5
62		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide dihydrochloride	6-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)nicotinic acid (Example C.13) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	352.5
63		N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)picolinamide dihydrochloride	5-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)picolinic acid (Example C.14) and 2-methylimidazo[1,2-a]pyridin-6-amine hydrobromide (commercial followed by treatment with HCl	334.5

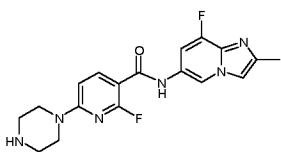
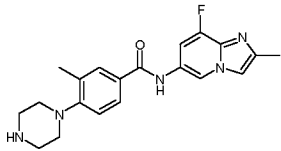
Example 64

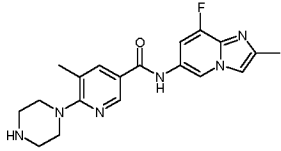
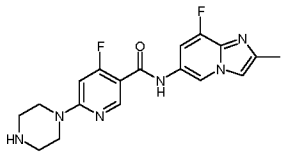
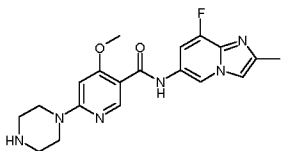
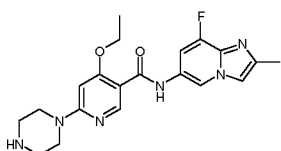
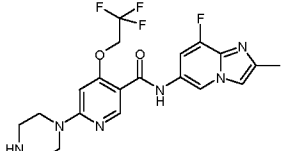
Preparation of N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(piperazin-1-yl)nicotinamide

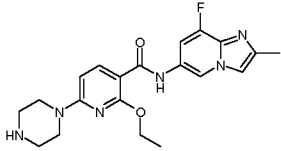
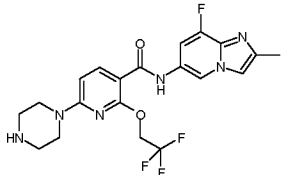
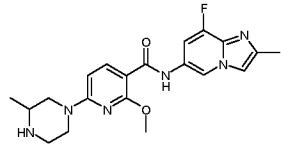
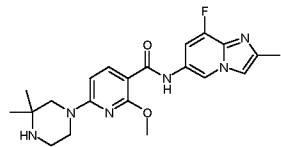
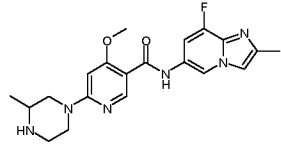


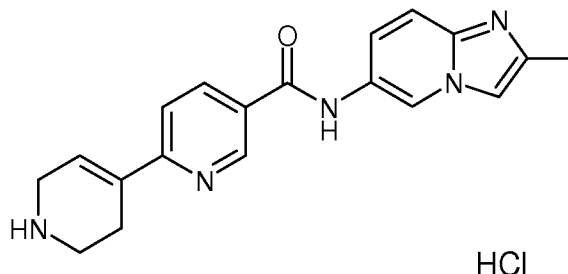
To a solution of 6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-methoxynicotinic acid (Example C.15) (100 mg, 296 μ mol) and 8-fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) (60 mg, 296 μ mol) in N,N-dimethylformamide (1.00 ml) under argon at room temperature, was added O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (114 mg, 536 μ mol) and triethylamine (124 μ l, 0.89 mmol). The mixture was stirred at 55°C for 16 hours and then at 90°C for 3 hours. The reaction was poured into water and extracted with ethyl acetate. The ethyl acetate was dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified on silica gel (Eluent: heptane/ethyl acetate 50 to 100%) to provide 76 mg of tert-butyl 4-(5-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-ylcarbamoyl)-6-methoxypyridin-2-yl)piperazine-1-carboxylate. This compound was then dissolved in 4M HCl in dioxane (2 ml) and the mixture stirred for 0.5 h. The mixture was evaporated to dryness in vacuo, the residue dissolved in saturated sodium hydrogen carbonate and repeatedly extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo, dried to provide 39 mg (63 %) of the title compound as an off-white solid. MS(m/e): 385.4 (M+H).

In analogy to Example 64, compounds 65 to 76 of the following table were prepared from the acid and amine derivatives followed by treatment with HCl

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH ⁺)
65		2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-fluoronicotinic acid (Example C.16) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	373.3
66		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-methyl-4-(piperazin-1-yl)benzamide	4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-methylbenzoic acid (CAS: 196203-51-7) and 8-Fluoro-2-methyl-imidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	368.6

67		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-methyl-6-(piperazin-1-yl)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-5-methylnicotinic acid (CAS: 1211527-14-8) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	LG
68		4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-fluoronicotinic acid (Example C.17) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	373.7
69		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(piperazin-1-yl)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxynicotinic acid (Example C.18) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	385.6
70		4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-ethoxynicotinic acid (Example C.19) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	399.6
71		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinic acid (Example C.20) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	453.6 [

72		2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-ethoxynicotinic acid (Example C.21) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	399.6
73		N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-2-(2,2,2-trifluoroethoxy)nicotinamide	6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(2,2,2-trifluoroethoxy)nicotinic acid (Example C.22) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	453.6
74		rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide	rac-6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-2-methoxynicotinic acid (Example C.23) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	399.6
75		6-(3,3-dimethylpiperazin-1-yl)-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxynicotinamide	6-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-2-methoxynicotinic acid (Example C.24) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	411.6
76		rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide	6-(4-(tert-butoxycarbonyl)-3-methylpiperazin-1-yl)-4-methoxynicotinic acid (Example C.25) and 8-Fluoro-2-methylimidazo[1,2-a]pyridin-6-ylamine hydrochloride (Example B.4) followed by treatment with HCl	399.5

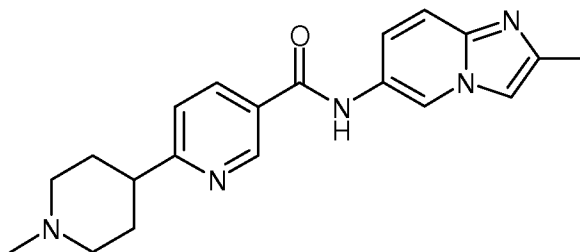
Example 77**Preparation of N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide hydrochloride**

5 a) step1 : tert-butyl 4-(5-(2-methylimidazo[1,2-a]pyridin-6-ylcarbamoyl)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate

To a solution of 6-chloro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide (Example A5) (100 mg, 349 μ mol) in a mixture of 1,2-dimethoxyethane (1.25 ml), ethanol (625 μ l) and water (1.25 ml) under nitrogen at room temperature, were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (129 mg, 419 μ mol), K₂CO₃ (122 mg, 875 μ mol) and PdCl₂(Ph₃P)₂ (25.2 mg, 35.9 μ mol, Eq: 0.103). The reaction mixture was heated in an oil bath at 100°C for 40 minutes. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and washed with brine. The aqueous phase was extracted three times with methylene chloride and the combined organic phase was dried with Na₂SO₄, filtered and concentrated to dryness to obtain 285 mg of a dark brown solid. This solid was suspended in ethyl acetate, filtered and dried to provide 86 mg (56.9 %) of the title compound as a light brown solid. MS (m/e): 434.5 (M+H⁺).

20 b) step 2 : N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide hydrochloride

To a solution of tert-butyl 4-(5-(2-methylimidazo[1,2-a]pyridin-6-ylcarbamoyl)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (20 mg, 46.1 μ mol) in methanol (200 μ l) under nitrogen at room temperature, was added dropwise hydrogen chloride (4M in dioxane) (115 μ l, 461 μ mol). The reaction mixture was stirred at room temperature overnight. The resulting precipitation was filtered, rinsed with diethyl ether and dried to provide 12.6 mg (73.8 %) of the expected compound as a grey solid. MS(m/e): 334.5 (M+H⁺).

Example 78**Preparation of N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide**

5 a) step1 : tert-butyl 4-(5-(2-methylimidazo[1,2-a]pyridin-6-ylcarbamoyl)pyridin-2-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(5-(2-methylimidazo[1,2-a]pyridin-6-ylcarbamoyl)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (Example 77, step 1) (123 mg, 284 μ mol) in methanol (7 ml) and tetrahydrofuran (3.5 ml) under nitrogen at room temperature was added palladium on
10 activated charcoal (54.3 mg, 51.0 μ mol). The reaction mixture was stirred under a hydrogen atmosphere overnight. The reaction mixture was purged with argon, filtered and the solvent was evaporated. The crude oil was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 100%) and ethyl acetate and methanol (0 to 15%) to provide 86 mg (69.6 %) of the title compound as an off-white solid. MS (m/e): 436.6
15 (M+H)

b) step2 : N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide

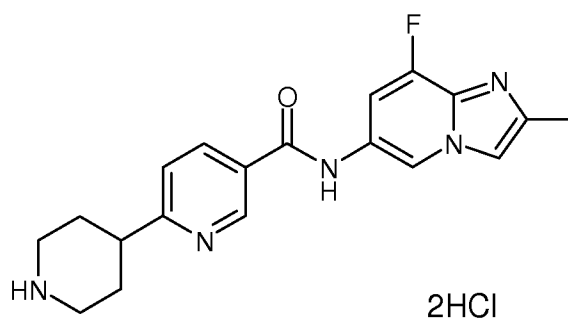
To a suspension of tert-butyl 4-(5-(2-methylimidazo[1,2-a]pyridin-6-ylcarbamoyl)pyridin-2-yl)piperidine-1-carboxylate (17 mg, 39.0 μ mol) in methanol (170 μ l) was added HCl 4M in
20 dioxane (97.6 μ l, 390 μ mol). The light yellow solution was stirred at room temperature overnight. The solvent was evaporated to provide 14 mg (87.8%) of the title compound as a grey solid. MS(m/e): 336.3 (M+H)

c) step3 : N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide

25 To a suspension of N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide (25 mg, 74.5 μ mol) in 1,2-dichloroethane (250 μ l) under nitrogen at 5-10°C, was added sodium triacetoxyborohydride (26.3 mg, 112 μ mol), followed dropwise (over 5 minutes) by formaldehyde solution (37% in water) (18.1 mg, 16.6 μ l, 224 μ mol). The temperature was kept to 5-10°C and the reaction mixture was stirred for 40 minutes. The reaction was quenched with a

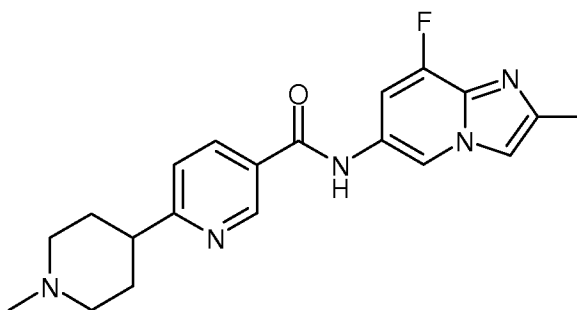
2N sodium carbonate aqueous solution. The resulting precipitation was stirred at room temperature for 30 minutes, filtered, rinsed and dried to provide 17 mg (65.3 %) of the title compound as an off-white solid. MS(m/e): 350.5 (M+H+)

5

Example 79**Preparation of N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide dihydrochloride**

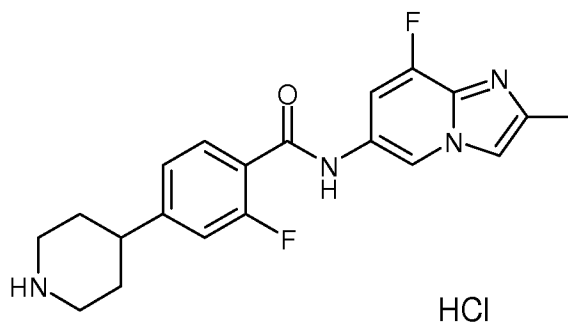
To a solution of N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide dihydrochloride (Example 62) (30 mg, 70.7 μ mol) in methanol (1.7 ml) and tetrahydrofuran (850 μ l) under nitrogen at room temperature, was added palladium on activated charcoal (20 mg, 18.8 μ mol, Eq: 0.266). The reaction mixture was stirred under a hydrogen atmosphere for 4 hours. The reaction mixture was purged with argon, filtered and the solvent was evaporated to provide 28 mg (92.9 %) of the title compound as a yellow solid. MS (m/e): 354.5 (M+H+).

15

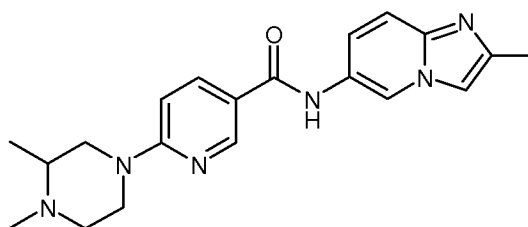
Example 80**Preparation of N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide**

20

In analogy to the procedure described for the synthesis of example 78 (steps: 3), the title compound was prepared from N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide dihydrochloride (Example 79). MS (m/e): 368.5 (M+H+).

Example 81**Preparation of 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperidin-4-yl)benzamide hydrochloride**

In analogy to the procedure described for the synthesis of example 79, the title compound was prepared from 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (Example 61). MS (m/e): 371.5 (M+H+).

Example 82**Preparation of rac-6-(3,4-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide**

In analogy to the procedure described for the synthesis of example 78 (step 3), the title compound was prepared from rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide (Example 12). MS (m/e): 365.6 (M+H+).

Biological Assays

To describe in more detail and assist in understanding the present description, the following non-limiting biological examples are offered to more fully illustrate the scope of the description and are not to be construed as specifically limiting the scope thereof. Such variations of the present description that may be now known or later developed, which would be within the purview of one skilled in the art to ascertain, are considered to fall within the scope of the present description and as hereinafter claimed. These examples illustrate the testing of certain compounds described herein in vitro and/or in vivo and demonstrate the usefulness of the

compounds for treating of SMA by enhancing the inclusion of exon 7 of SMN2 into mRNA transcribed from the SMN2 gene. Compounds of formula (I) enhance inclusion of exon 7 of SMN2 into mRNA transcribed from the SMN2 gene and increase levels of SMN protein produced from the SMN2 gene, and thus can be used to treat SMA in a human subject in need thereof. These examples further illustrate the testing of certain compounds described herein in vitro and/or in vivo and demonstrate the usefulness of the compounds for enhancing the inclusion of exon 7 of SMN1 into mRNA transcribed from the SMN1 gene. Accordingly, compounds of formula (I) also enhance the inclusion of exon 7 of SMN1 into mRNA transcribed from the SMN1 gene and increase levels of SMN protein produced from the SMN1 gene.

10

Example D.1

SMN2 minigene mRNA splicing RT-qPCR assay in cultured cells

The reverse transcription-quantitative PCR-based (RT-qPCR) assay is used to quantify the level of the full length SMN2 minigene (referred to herein by the term “FL SMN2mini”) mRNA containing SMN2 exon 7 in a HEK293H cell line stably transfected with said minigene and treated with a test compound.

15

Material	Source
HEK293H cells	Life Technologies, Inc. (formerly Invitrogen) Catalog No. 11631-017
Cells-To-Ct lysis buffer	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4399002
DMEM	Life Technologies, Inc. (formerly Invitrogen) Catalog No. 11960-044
96-well flat-bottom plates	Becton Dickinson Catalog No. 353072
RT-PCR Enzyme Mix	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4388520
RT-PCR buffer	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4388519
AgPath-ID One-Step RT-PCR kit	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4387391
Thermocycler	Life Technologies, Inc. (formerly Applied Biosystems) 7900HT

The SMN2-A minigene construct was prepared as described in International Patent Application WO2009/151546A1 page 145 paragraph [00400] to page 147 paragraph [00412] (incl. Figure 1 and Figure 3 therein).

HEK293H cells stably transfected with the SMN2-A minigene construct (10,000 cells/well) are seeded in 200 μ L of cell culture medium (DMEM plus 10% FBS, with 200 μ g/mL hygromycin) in 96-well flat-bottom plates and the plate is immediately swirled to ensure proper dispersal of cells and the formation of an even monolayer of cells. Cells are allowed to attach for 6 hours. Test compounds are serially diluted 3.16-fold in 100% DMSO to generate a 7-point concentration curve. A solution of test compound (1 μ L, 200x in DMSO) is added to each cell-containing well and the plate is incubated for 24 hours in a cell culture incubator (37°C, 5% CO₂, 100% relative humidity). 2 replicates are prepared for each test compound concentration. The cells are then lysed in the Cells-To-Ct lysis buffer and the lysate is stored at -80°C.

Full length SMN2-A minigene and GAPDH mRNA are quantified using the primers and probes referenced in Table 1. Primer SMN Forward A (SEQ ID NO.1) hybridizes to a nucleotide sequence in exon 7 (nucleotide 22 to nucleotide 40), primer SMN Reverse A (SEQ ID NO.2) hybridizes to a nucleotide sequence in the coding sequence of Firefly luciferase, SMN Probe A (SEQ ID NO.3) hybridizes to a nucleotide sequence in exon 7 (nucleotide 50 to nucleotide 54) and exon 8 (nucleotide 1 to nucleotide 21). The combination of these three oligonucleotides detects only SMN1 or SMN2 minigenes (RT-qPCR) and will not detect endogenous SMN1 or SMN2 genes.

Primers/Probes	Sequences	Source
SMN Forward Primer A	SEQ ID N0.1: GAAGGAAGGTGCTCACATT	PTC ¹
SMN Reverse Primer A	SEQ ID N0.2: TCTTTATGTTTTTGGCGTCTTC	PTC ¹
SMN Forward Probe A	SEQ ID N0.3: 6FAM- AAGGAGAAATGCTGGCAT AGAGCAGC-TAMRA	PTC ¹
hGAPDH Forward Probe	SEQ ID N0.4: VIC-CGCCTGGTCACCAGGGCTGCT- TAMRA	LTI ²
hGAPDH Forward Primer	SEQ ID N0.5: CAACGGATTTGGTCGTATTGG	LTI ²
hGAPDH Reverse Primer	SEQ ID N0.6: TGATGGCAACAATATCCACTTTACC	LTI ²

Table 1. ¹ Primers and probes designed by PTC Therapeutics, Inc.; ² Commercially available from Life Technologies, Inc. (formerly Invitrogen).

The SMN forward and reverse primers are used at final concentrations of 0.4 μM . The SMN probe is used at a final concentration of 0.15 μM . The GAPDH primers are used at final concentrations of 0.2 μM and the probe at 0.15 μM .

5 The SMN2-minigene GAPDH mix (15 μL total volume) is prepared by combining 7.5 μL of 2x RT-PCR buffer, 0.4 μL of 25x RT-PCR enzyme mix, 0.75 μL of 20x GAPDH primer-probe mix, 4.0075 μL of water, 2 μL of 10-fold diluted cell lysate, 0.06 μL of 100 μM SMN forward primer, 0.06 μL of 100 μM SMN reverse primer, and 0.225 μL of 100 μM SMN probe.

10 PCR is carried out at the following temperatures for the indicated time: Step 1: 48°C (15 min); Step 2: 95°C (10 min); Step 3: 95°C (15 sec); Step 4: 60°C (1 min); then repeat Steps 3 and 4 for a total of 40 cycles.

Each reaction mixture contains both SMN2-A minigene and GAPDH primers/probe sets (multiplex design), allowing simultaneous measurement of the levels of two transcripts.

15 The increase in the abundance of the FL SMN2mini mRNA relative to that in cells treated with vehicle control is determined from real-time PCR data using a modified $\Delta\Delta\text{Ct}$ method (as described in *Livak and Schmittgen, Methods, 2001, 25:402-8*). The amplification efficiency E is calculated from the slope of the amplification curve for FL SMN2mini and GAPDH individually. The abundance of FL SMN2mini and GAPDH mRNA are then calculated as $(1 + E)^{-\text{Ct}}$, where Ct is the threshold value for each amplicon. The abundance of FL SMN2mini mRNA is normalized to GAPDH mRNA abundance. The normalized FL SMN2mini mRNA abundance from test
20 compound-treated samples is then divided by normalized FL SMN2mini mRNA abundance from vehicle-treated cells to determine the level of FL SMN2mini mRNA relative to vehicle control.

Table 2 provides $\text{EC}_{1.5x}$ concentrations for production of full length SMN2 minigene mRNA that was obtained from the 7-point concentration data generated according to the above procedure for particular compounds of the present invention.

25 Particular compounds of the present invention exhibit an $\text{EC}_{1.5x}$ concentration for production of full length SMN2 minigene mRNA $\leq 1 \mu\text{M}$.

More particular compounds of the present invention exhibit an $\text{EC}_{1.5x}$ concentration for production of full length SMN2 minigene mRNA $\leq 0.1 \mu\text{M}$.

30 Most particular compounds of the present invention exhibit an $\text{EC}_{1.5x}$ concentration for production of full length SMN2 minigene mRNA $\leq 0.02 \mu\text{M}$.

Ex.	EC _{1.5x} minigene (μ M)		Ex.	EC _{1.5x} minigene (μ M)		Ex.	EC _{1.5x} minigene (μ M)
1	0.0316		11	0.2971		21	0.3856
2	0.1399		12	0.3122		22	0.2626
3	0.5522		13	1.0335		23	0.201
4	0.2323		14	0.2314		24	0.6489
5	0.0612		15	0.2539		25	0.3823
6	0.2332		16	1.0364		26	0.0445
7	0.1423		17	0.2334		27	0.0989
8	0.201		18	0.0523		28	0.2524
9	0.794		19	0.2673		29	0.2667
10	0.6652		20	0.4894		30	0.4096
31	0.1195		41			51	0.0084
32	0.0938		42	0.0544		52	0.04
33			43	0.057		53	0.2104
34	0.328		44	0.0648		54	0.0128
35	0.2022		45	0.0615		55	0.1411
36	0.0278		46	0.0887		56	0.017
37	0.028		47	0.3964		57	0.0262
38	0.4717		48	0.0164		58	0.0398
39	0.0168		49	0.0107		59	0.1089
40	0.0108		50	0.0068		60	0.0428
61	0.01		71	0.077		81	0.0374
62	0.0136		72	0.015		82	0.3714
63	0.1602		73	0.062			
64	0.0291		74	0.0161			
65	0.0762		75	0.0654			
66	0.5177		76	0.0187			
67	0.3175		77	0.0641			
68	0.0285		78	0.6222			
69	0.0308		79	0.0559			
70			80	0.1148			

Table 2. EC_{1.5x} concentrations for production of full length SMN2 minigene mRNA.

Example D.2

SMN protein assay in cultured cells

The SMN HTRF (homogeneous time resolved fluorescence) assay is used to quantify the level of SMN protein in SMA patient fibroblast cells treated with test compounds.

Material	Source
SMA Type 1 human cells	GM03813 (Coriell Institute)
Protease inhibitor cocktail	Roche Applied Science Catalog No. 11836145001
Anti-SMN d2	Blue cap Cisbio Catalog No. 63IDC002-SMN
Anti-SMN kryptate	Red cap Cisbio Catalog No. 63IDC002-SMN
SMN reconstitution buffer	Cisbio Catalog No. 63IDC002-SMN-Buffer
DMEM	Life Technologies (formerly Invitrogen) Catalog No. 11960-044
RIPA Lysis Buffer	20 mM Tris-HCl pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% Thermo Scientific NP-40 Surfact-Amps Detergent Solution (Fisher Scientific, Pittsburgh/PA), 1% Sodium deoxycholate
Diluent Buffer	20 mM Tris-HCl pH 7.5, 150 mM NaCl
Envision Plate Reader	Perkin Elmer Model # 2103

5

Cells are thawed and cultured in DMEM-10% FBS for 72 hours. Cells are trypsinized, counted and re-suspended to a concentration of 25,000 cells/mL in DMEM-10% FBS. The cell suspensions are plated at 5,000 cells per well in a 96 well microtiter plate and incubated for 3 to 5 hours. Test compounds are serially diluted 3.16-fold in 100% DMSO to generate a 7-point concentration curve. 1 μ L of test compound solution is transferred to cell-containing wells and cells are incubated for 48 hours in a cell culture incubator (37°C, 5% CO₂, 100% relative humidity). Triplicate samples are set up for each test compound concentration. After 48 hours, the supernatant is removed from the wells and 25 μ L of the RIPA lysis buffer, containing protease inhibitors, is added to the wells and incubated with shaking at room temperature for 1 hour. 25 μ L of the diluent is added and then 35 μ L of the resulting lysate is transferred to a 384-well plate, where each well contains 5 μ L of the antibody solution (1:100 dilution of anti-SMN d2 and anti-SMN kryptate in SMN reconstitution buffer). The plate is centrifuged for 1 minute to

10

15

bring the solution to the bottom of the wells, then incubated overnight at room temperature. Fluorescence for each well of the plate at 665 nm and 620 nm is measured on an EnVision multilabel plate reader (Perkin-Elmer).

5 The normalized fluorescence signal is calculated for each sample, Blank and vehicle control well by dividing the signal at 665 nm by the signal at 620 nm. Normalizing the signal accounts for possible fluorescence quenching due to the matrix effect of the lysate. The ΔF value (a measurement of SMN protein abundance as a percent value) for each sample well is calculated by subtracting the normalized average fluorescence for the Blank control wells from
10 the normalized fluorescence for each sample well, then dividing this difference by the normalized average fluorescence for the Blank control wells and multiplying the resulting value by 100. The ΔF value for each sample well represents the SMN protein abundance from test compound-treated samples. The ΔF value for each sample well is divided by the ΔF value for the vehicle control wells to calculate the fold increase in SMN protein abundance relative to the
15 vehicle control. Table 3 provides $EC_{1.5x}$ concentrations for SMN protein expression that was obtained from the 7-point concentration data generated according to the above procedure for particular compounds of the present invention.

Particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for SMN protein expression $\leq 2 \mu M$.

20 More particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for SMN protein expression $\leq 0.3 \mu M$.

Most particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for SMN protein expression $\leq 0.1 \mu M$.

25 Table 4 provides the maximum fold increase of SMN protein that was obtained from the 7-point concentration data generated according to the above procedure for particular compounds of the present invention

Particular compounds of the present invention exhibit a maximum fold increase > 1.4 .

More particular compounds of the present invention exhibit a maximum fold increase > 1.7 .

Most particular compounds of the present invention exhibit a maximum fold increase > 1.8 .

Ex.	EC _{1.5x} SMN protein (μ M)		Ex.	EC _{1.5x} SMN protein (μ M)		Ex.	EC _{1.5x} SMN protein (μ M)
1	0.7747		11	0.321		21	0.6542
2	0.2984		12	0.7037		22	0.4468
3	1.47		13	1.7564		23	0.5092
4	0.5614		14	0.7944		24	1.2616
5	0.107		15	0.281		25	0.5694
6	0.5305		16	1.1992		26	0.2853
7	0.2834		17	0.5022		27	0.3964
8	0.5175		18	0.1346		28	0.2868
9	1.527		19	1.3818		29	0.4618
10	0.329		20	0.8065		30	0.7612
31	0.2746		41	0.0508		51	0.0561
32	0.2028		42	0.1488		52	0.1518
33	0.5703		43	0.104		53	0.7455
34	0.7793		44	0.13		54	0.056
35	1.2664		45	0.5147		55	0.7112
36	0.1094		46	0.3584		56	0.07
37	0.1196		47	0.611		57	1.7363
38	0.6124		48	0.0621		58	0.1159
39	0.0147		49	0.1733		59	0.2749
40	0.0276		50	0.0344		60	0.107
61			71	0.4077		81	0.2723
62			72	0.1324		82	0.7698
63	1.0431		73	0.7589			
64	0.1192		74	0.1524			
65	0.1135		75	0.3061			
66	0.6108		76	0.1629			
67	0.866		77	0.2279			
68	0.057		78	1.013			
69	0.1645		79	0.2559			
70	0.0187		80	0.52			

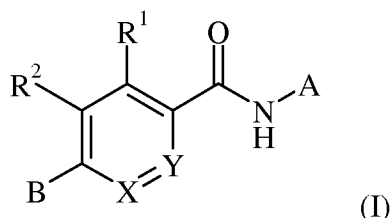
Table 3. EC_{1.5x} concentrations for SMN protein expression.

Ex.	max. fold increase		Ex.	max. fold increase		Ex.	max. fold increase
1	1.6736		11	1.7143		21	1.7755
2	1.8878		12	1.6512		22	1.7566
3	1.7558		13	1.624		23	1.6942
4	1.769		14	1.5912		24	1.756
5	1.7757		15	1.6859		25	1.6652
6	1.8047		16	1.6598		26	1.8316
7	1.7936		17	1.6966		27	1.6617
8	1.7677		18	1.7677		28	1.7291
9	1.6085		19	1.664		29	1.632
10	1.735		20	1.7789		30	1.6734
31	1.7849		41	1.7973		51	1.7266
32	1.7579		42	1.6988		52	1.8152
33	1.7541		43	1.7873		53	1.6563
34	1.6527		44	1.8243		54	1.8217
35	1.6275		45	1.6445		55	1.8752
36	1.7018		46	1.5572		56	1.7299
37	1.7758		47	1.7065		57	1.578
38	1.8706		48	1.738		58	1.7744
39	1.8791		49	1.658		59	1.7116
40	1.7607		50	1.6607		60	1.7375
61	1.7077		71	1.4815		81	1.6719
62	1.5583		72	1.7095		82	1.7306
63	1.6807		73	1.5775			
64	1.7581		74	1.709			
65	1.7675		75	1.7035			
66	1.5438		76	1.7274			
67	1.6552		77	1.6649			
68	1.6943		78	1.7897			
69	1.7612		79	1.6574			
70	1.933		80	1.5928			

Table 4. Maximum fold increase of SMN protein.

Claims

1. Compounds of formula (I)



wherein

- 5 X is N or CR³;
- Y is N or CR⁴; with the proviso that not both X and Y are N;
- A is a bicyclic 9-membered heteroaryl comprising two or three heteroatoms independently selected from N or O, wherein A can be optionally substituted with one, two or three R⁵;
- 10 B is a saturated or partially unsaturated mono- or bicyclic 4 to 9-membered heterocycloalkyl comprising one or two ring nitrogen atoms, the remaining ring atoms being carbon, wherein B can be optionally substituted with one, two or three R⁶;
- R¹ is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;
- 15 R² is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;
- R³ is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;
- R⁴ is hydrogen, halo, C₁₋₇-alkyl, C₁₋₇-haloalkyl, C₁₋₇-alkoxy or C₁₋₇-haloalkoxy;
- each R⁵ is independently selected from halo, cyano, C₁₋₇-alkyl, C₁₋₇-haloalkyl or C₃₋₇-cycloalkyl;
- 20 each R⁶ is independently selected from C₁₋₇-alkyl, or two R⁶ together form a C₂₋₇-alkylene;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein A is selected from the group of imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyridinyl, and benzo[d]oxazolyl, which can be optionally substituted with one, two or three R⁵.
- 25

3. A compound according to claim 1 or 2, wherein A is selected from the group of imidazo[1,2-a]pyrazin-2-yl substituted with two C₁₋₇-alkyl, imidazo[1,2-a]pyridin-6-yl substituted with one or two C₁₋₇-alkyl, imidazo[1,2-a]pyridin-6-yl substituted with one C₁₋₇-alkyl and one halo, imidazo[1,2-a]pyridin-6-yl substituted with one C₁₋₇-alkyl and one C₁₋₇-haloalkyl, benzo[d]oxazol-6-yl substituted with one C₁₋₇-alkyl, and benzo[d]oxazol-6-yl substituted with one C₁₋₇-alkyl and one halo.
5
4. A compound according to any one of claims 1 to 3, wherein A is selected from 2-methylbenzo[d]oxazol-6-yl, 4-fluoro-2-methylbenzo[d]oxazol-6-yl, 6,8-dimethylimidazo[1,2-a]pyrazin-2-yl, 2-methylimidazo[1,2-a]pyridin-6-yl, 2,7-dimethylimidazo[1,2-a]pyridin-6-yl, 2,8-dimethylimidazo[1,2-a]pyridin-6-yl, 2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl, 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl, and 8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl.
10
5. A compound according to any one of claims 1 to 2, wherein each R⁵ is independently selected from halo, C₁₋₇-alkyl, or C₁₋₇-haloalkyl.
- 15 6. A compound according to any one of claims 1 to 2, wherein each R⁵ is independently selected from methyl, fluoro, chloro, and trifluoromethyl.
7. A compound according to any one of claims 1 to 6, wherein B as defined herein is further characterized in that one ring nitrogen atoms is basic.
8. A compound according to any one of claims 1 to 7, wherein B is selected from 1,2,3,6-tetrahydropyridinyl, 2,6-diazaspiro[3.3]heptanyl, hexahydropyrrolo[3,4-c]pyrrolyl, hexahydropyrrolo[1,2-a]pyrazinyl, piperazinyl, and piperidinyl, wherein each can be optionally substituted with one, two or three R⁶.
20
9. A compound according to any one of claims 1 to 8, wherein B is selected from piperazin-1-yl, 3-methyl-piperazin-1-yl, and 3,3-dimethylpiperazin-1-yl.
- 25 10. A compound according to any one of claims 1 to 8, wherein each R⁶ is C₁₋₇-alkyl.
11. A compound according to any one of claims 1 to 10, wherein each R⁶ is independently selected from methyl, and ethyl.
12. A compound according to any one of claims 1 to 11, wherein X is CR³ and Y is CR⁴, or X is N and Y is CR⁴, or X is CR³ and Y is N.
- 30 13. A compound according to any one of claims 1 to 12, wherein X is CR³ and Y is CR⁴.
14. A compound according to any one of claims 1 to 13, wherein X is N and Y is CR⁴.

15. A compound according to any one of claims 1 to 14, wherein R^1 is hydrogen, halo, C_{1-7} -alkoxy or C_{1-7} -haloalkoxy.
16. A compound according to any one of claims 1 to 15, wherein R^1 is hydrogen, fluoro, methoxy, ethoxy or trifluoroethoxy.
- 5 17. A compound according to any one of claims 1 to 16, wherein R^1 is hydrogen.
18. A compound according to any one of claims 1 to 17, wherein R^2 is hydrogen, halo, or C_{1-7} -alkyl.
19. A compound according to any one of claims 1 to 18, wherein R^2 is hydrogen, fluoro or methyl.
- 10 20. A compound according to any one of claims 1 to 19, wherein R^2 is hydrogen.
21. A compound according to any one of claims 1 to 20, wherein R^3 is hydrogen or fluoro.
22. A compound according to any one of claims 1 to 21, wherein R^3 is hydrogen.
23. A compound according to any one of claims 1 to 22, wherein R^4 is hydrogen, halo or C_{1-7} -alkoxy.
- 15 24. A compound according to any one of claims 1 to 23, wherein R^4 is hydrogen, fluoro, methoxy, ethoxy or trifluoroethoxy.
25. A compound according to any one of claims 1 to 24, wherein R^4 is hydrogen or fluoro.
26. A compound according to any one of claims 1 to 25, wherein R^4 is hydrogen, halo or C_{1-7} -alkoxy.
- 20 27. A compound according to any one of claims 1 to 26, selected from the group consisting of:
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(piperazin-1-yl)benzamide;
rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-4-(3-methylpiperazin-1-yl)benzamide;
N-(6,8-Dimethyl-imidazo[1,2-a]pyrazin-2-yl)-4-((S)-3-methyl-piperazin-1-yl)-benzamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(4-methylpiperazin-1-yl)benzamide;
25 rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
30 N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-6-(4-ethylpiperazin-1-yl)nicotinamide;

- N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(4-methylpiperazin-1-yl)picolinamide;
rac-N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
N-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-(piperazin-1-yl)picolinamide;
rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
5 6-(3,3-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
6-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;
N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinamide;
10 rac-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
rac-2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
15 rac-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
(S)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
6-(3,5-dimethylpiperazin-1-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)nicotinamide;
20 6-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)nicotinamide;
N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
(S)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide;
25 N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-piperazin-1-yl-nicotinamide;
rac-N-(4-Fluoro-2-methyl-benzooxazol-6-yl)-6-(3-methyl-piperazin-1-yl)-nicotinamide;
N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;
rac-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
4-(3,5-dimethylpiperazin-1-yl)-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)benzamide;
30 (S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(4-methylpiperazin-1-yl)nicotinamide;
(S)-2-Fluoro-N-(4-fluoro-2-methyl-benzooxazol-6-yl)-4-(S)-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl-benzamide;
35 (R)-2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide;
(S)-2-fluoro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
rac-N-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
rac-2-fluoro-N-(2-methylbenzo[d]oxazol-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
5 rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
10 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
rac-2,3-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
15 rac-2,5-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
rac-5-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
20 rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
(S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
25 (R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
rac-N-(2,7-dimethylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
30 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-6-(3-methylpiperazin-1-yl)nicotinamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(3-methylpiperazin-1-yl)nicotinamide;
35 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide;
rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2,6-difluoro-4-(3-methylpiperazin-1-

yl)benzamide;

2-fluoro-N-(4-fluoro-2-methylbenzo[d]oxazol-6-yl)-4-(piperazin-1-yl)benzamide;

2-fluoro-N-(2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;

5 2-fluoro-N-(2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;

2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;

10 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;

N-(2-methylimidazo[1,2-a]pyridin-6-yl)-5-(1,2,3,6-tetrahydropyridin-4-yl)picolinamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(piperazin-1-yl)nicotinamide;

2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

15 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-methyl-4-(piperazin-1-yl)benzamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-methyl-6-(piperazin-1-yl)nicotinamide;

4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(piperazin-1-yl)nicotinamide;

20 4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-4-(2,2,2-trifluoroethoxy)nicotinamide;

2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;

25 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)-2-(2,2,2-trifluoroethoxy)nicotinamide;

rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;

6-(3,3-dimethylpiperazin-1-yl)-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxynicotinamide;

30 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;

N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;

N-(2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;

N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperidin-4-yl)nicotinamide;

35 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1-methylpiperidin-4-yl)nicotinamide;

2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperidin-4-yl)benzamide;

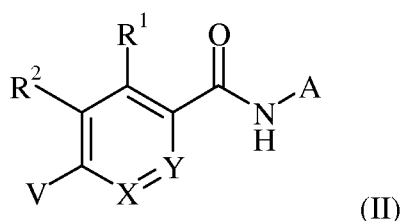
rac-6-(3,4-dimethylpiperazin-1-yl)-N-(2-methylimidazo[1,2-a]pyridin-6-yl)nicotinamide;

and pharmaceutically acceptable salts thereof.

28. A compound according to any one of claims 1 to 27, selected from the group consisting of:
 rac-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(piperazin-1-yl)benzamide;
 5 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 rac-3-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-5-(3-methylpiperazin-1-yl)picolinamide;
 rac-2,6-difluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 10 (S)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 (R)-2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(3-methylpiperazin-1-yl)benzamide;
 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoro-4-(3-methylpiperazin-1-yl)benzamide;
 15 rac-N-(8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoro-5-(3-methylpiperazin-1-yl)picolinamide;
 2-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide;
 20 N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(1,2,3,6-tetrahydropyridin-4-yl)nicotinamide;
 4-fluoro-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 4-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 2-ethoxy-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-6-(piperazin-1-yl)nicotinamide;
 25 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
 rac-N-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-4-methoxy-6-(3-methylpiperazin-1-yl)nicotinamide;
 and pharmaceutically acceptable salts thereof.

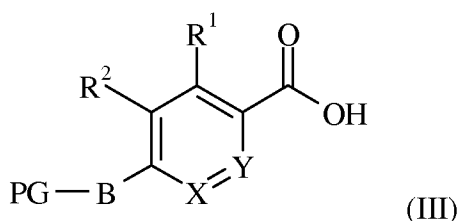
29. A process for the preparation of compounds of formula (I) according to any of claims 1 - 28, comprising:

- a) the Buchwald-Hartwig amination reaction of a compound of formula (II)



with a compound of formula B-H, in the presence of a catalyst and a ligand and a base and a solvent, wherein the hydrogen H of the compound of formula B-H is bound to a ring nitrogen atom of B, V is chloro or bromo, and A, B, X, Y, R¹, and R² are as defined in any of claims 1-28; or

- 5 b) a nucleophilic aromatic substitution reaction between a compound of formula (II) with a compound of formula B-H by heating in a solvent, wherein the hydrogen H of the compound of formula B-H is bound to a ring nitrogen atom of B, V is fluoro if X is CR³ or V is chloro if X is N, and A, B, X, Y, R¹, R² and R³ are as defined in any of claims 1-28; or
- 10 c) the Suzuki coupling reaction of a compound of formula (II) with a compound of formula PG-B-pinB in the presence of a base and a catalyst, followed by removal of PG, wherein pinB is pinacolboranyl which is bound to a ring carbon atom of B, PG is an amino-protecting group, V is fluoro or chloro, and wherein A, B, X, Y, R¹, and R² are as defined in any of claims 1-28; or
- 15 d) the amidation reaction of a compound of formula (III)



with a compound of formula A-NH₂ in the presence of a tertiary amine and a coupling reagent, optionally followed by the removal of PG, wherein PG is an optional amino-protecting group, and wherein A, B, X, Y, R¹, and R² are as defined in any of claims 1-28.

- 20 in any of claims 1-28.
30. Compounds of formula (I) according to any of claims 1 - 28, obtainable by a process of claim 29.
31. Pharmaceutical compositions comprising compounds of formula (I) according to any of claims 1 - 28 or their pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients.
- 25 32. Compounds of formula (I) according to any of claims 1 - 28 or their pharmaceutically acceptable salts above for use as therapeutically active substances.

33. Compounds of formula (I) according to any of claims 1 - 28 or their pharmaceutically acceptable salts for the use in the treatment or prevention of spinal muscular atrophy (SMA).
- 5 34. A method for the treatment or prevention of spinal muscular atrophy (SMA), which method comprises administering compounds of formula (I) according to any of claims 1 - 28 or their pharmaceutically acceptable salts as defined above to a subject.
35. The use of compounds of formula (I) according to any of claims 1 - 28 or their pharmaceutically acceptable salts for the treatment or prevention of spinal muscular atrophy (SMA).
- 10 36. The use of compounds of formula (I) according to any of claims 1 - 28 or their pharmaceutically acceptable salts for the preparation of medicaments for the treatment or prevention of spinal muscular atrophy (SMA).
37. The invention as described hereinbefore.
