SUBSTITUTED BICYCLIC IMIDAZOLE DERIVATIVES AS GAMMA SECRETASE MODULATORS

Field of the Invention

The present invention is concerned with novel substituted bicyclic imidazole derivatives useful as Gamma Secretase Modulators (GSM). The invention further relates to processes for preparing such novel compounds, pharmaceutical compositions comprising said novel compound as an active ingredient as well as the use of said compounds as a medicament.

Background of the invention

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder marked by loss of memory, cognition, and behavioral stability. AD afflicts 6-10 % of the population over age 65 and up to 50 % over age 85. It is the leading cause of dementia and the third leading cause of death after cardiovascular disease and cancer. There is currently no effective treatment for AD. The total net cost related to AD in the U.S. exceeds $100 billion annually.

AD does not have a simple etiology, however, it has been associated with certain risk factors including (1) age, (2) family history and (3) head trauma; other factors include environmental toxins and low levels of education. Specific neuropathological lesions in the limbic and cerebral cortices include intracellular neurofibrillary tangles consisting of hyperphosphorylated tau protein and the extracellular deposition of fibrillar aggregates of amyloid beta peptides (amyloid plaques). The major component of amyloid plaques are the amyloid beta (A-beta, Abeta or Aß) peptides of various lengths. A variant thereof, which is the Aß1-42-peptide (Abeta-42), is believed to be the major causative agent for amyloid formation. Another variant is the Aß1-40-peptide (Abeta-40). Amyloid beta is the proteolytic product of a precursor protein, beta amyloid precursor protein (beta-APP or APP).

Familial, early onset autosomal dominant forms of AD have been linked to missense mutations in the β-amyloid precursor protein (β-APP or APP) and in the presenilin proteins 1 and 2. In some patients, late onset forms of AD have been correlated with a specific allele of the apolipoprotein E (ApoE) gene, and, more recently, the finding of a mutation in alpha2-macroglobulin, which may be linked to at least 30 % of the AD population. Despite this heterogeneity, all forms of AD exhibit similar pathological findings. Genetic analysis has provided the best clues for a logical

therapeutic approach to AD. All mutations, found to date, affect the quantitative or qualitative production of the amyloidogenic peptides known as Abeta-peptides (Aβ), specifically Aβ42, and have given strong support to the "amyloid cascade hypothesis" of AD (Tanzi and Bertram, 2005, Cell 120, 545). The likely link between Aβ peptide generation and AD pathology emphasizes the need for a better understanding of the mechanisms of Aβ production and strongly warrants a therapeutic approach at modulating Aβ levels.

The release of Aβ peptides is modulated by at least two proteolytic activities referred to as β- and γ-secretase cleaving at the *N*-terminus (Met-Asp bond) and the C-terminus (residues 37-42) of the Aβ peptide, respectively. In the secretory pathway, there is evidence that β-secretase cleaves first, leading to the secretion of s-APPβ (sβ) and the retention of a 11 kDa membrane-bound carboxy terminal fragment (CTF). The latter is believed to give rise to Aβ peptides following cleavage by γ-secretase. The amount of the longer isoform, Aß42, is selectively increased in patients carrying certain mutations in a particular protein (presenilin), and these mutations have been correlated with early-onset familial Alzheimer´s disease. Therefore, Aß42 is believed by many researchers to be the main culprit of the pathogenesis of Alzheimer´s disease.

It has now become clear that the γ-secretase activity cannot be ascribed to a single particular protein, but is in fact associated with an assembly of different proteins.

The gamma (γ)-secretase activity resides within a multiprotein complex containing at least four components: the presenilin (PS) heterodimer, nicastrin, aph-1 and pen-2. The PS heterodimer consists of the amino- and carboxyterminal PS fragments generated by endoproteolysis of the precursor protein. The two aspartates of the catalytic site are at the interface of this heterodimer. It has recently been suggested that nicastrin serves as a gamma-secretase-substrate receptor. The functions of the other members of gamma-secretase are unknown, but they are all required for activity (Steiner, 2004. Curr. Alzheimer Research 1(3): 175-181).

Thus, although the molecular mechanism of the second cleavage-step has remained elusive until now, the γ-secretase-complex has become one of the prime targets in the search for compounds for the treatment of Alzheimer´s disease.

Various strategies have been proposed for targeting gamma-secretase in Alzheimer's disease, ranging from targeting the catalytic site directly, developing substrate-specific inhibitors and modulators of gamma-secretase activity (Marjaux et al., 2004. Drug Discovery Today: Therapeutic Strategies, Volume 1, 1-6). Accordingly, a variety of compounds were described that have secretases as targets (Larner, 2004.

Secretases as therapeutics targets in Alzheimer's disease: patents 2000 – 2004. Expert Opin. Ther. Patents 14, 1403-1420).

Indeed, this finding was recently supported by biochemical studies in which an effect of certain NSAIDs on γ-secretase was shown (Weggen et al (2001) Nature 414, 6860, 212 and WO 01/78721 and US 2002/0128319; Morihàra et al (2002) J. Neurochem. 83, 1009; Eriksen (2003) J. Clin. Invest. 112 , 440). Potential limitations for the use of NSAIDs to prevent or treat AD are their inhibition activity of COX enzymes, which can lead to unwanted side effects, and their low CNS penetration (Peretto et al., 2005, J. Med. Chem. 48, 5705-5720).

WO-2006/135667 relates amongst others to imidazopyridine compounds which inhibit the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I.

US 2008/0280948 A1 relates to aminophenyl derivatives which are modulators for amyloid beta.

WO-2008/137139 relates to heterocyclic derivatives and their use as gamma secretase modulators.

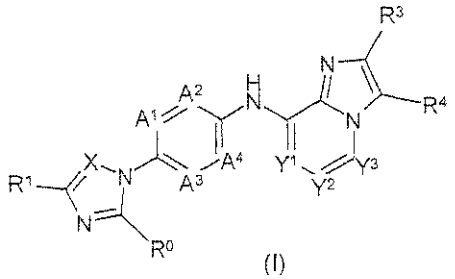
WO-2004/110350 relates to aryl compounds and their use in modulating Aβ.

There is a strong need for novel compounds which modulate γ-secretase activity thereby opening new avenues for the treatment of Alzheimer's disease. It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative. It is accordingly an object of the present invention to provide such novel compounds.

Summary

It has been found that the compounds of the present disclosure are useful as gamma secretase modulators. The compounds according to the disclosure and the pharmaceutically acceptable compositions thereof, may be useful in the treatment or prevention of Alzheimer's disease.

The present disclosure in a first aspect concerns novel compounds of Formula (I):



(I)

and stereoisomeric forms thereof, wherein

R^0 is hydrogen, halo or C_{1-4}alkyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

X is CR^7 or N; wherein R^7 is hydrogen or halo;

A^1 is CR^2 or N;

A^2 is CR^8 or N;

A^3 and A^4 each independently are CH or N;

provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^8 is hydrogen or halo;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, morpholinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, Ar, C_{1-6}alkyloxy, cycloC_{3-7}alkyloxy, and cycloC_{3-7}alkyl; carboxyl; C_{2-4}alkenyl; NR^5R^6-carbonyl; cycloC_{3-7}alkyl; Ar; tetrahydropyranyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; or Ar-O-CH_2-;
wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, and NR^5R^6; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

each R^5 independently is hydrogen, C_{1-4}alkyl, C_{1-6}alkylcarbonyl, or C_{1-4}alkyloxy$(CH_2CH_2O)_n$-CH_2-carbonyl;

n is an integer selected from 1, 2, 3, 4, 5 or 6.

each R^6 independently is hydrogen or C_{1-4}alkyl;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-4}alkyloxy; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, NR^5R^6, C_{1-4}alkyloxy, hydroxyl, and formylamino;

Y^1 is CH or N;

Y^2 is CR^9 or N;

Y^3 is CH or N;
provided that only one of Y^1, Y^2 and Y^3 may represent N;
R^9 is hydrogen; halo; C_{1-4}alkyloxy; cyano; cycloC_{3-7}alkyl; tetrahydropyranyl; C_{2-4}alkenyl; phenyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and C_{1-4}alkyloxy;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present disclosure also concerns methods for the preparation of compounds of Formula (I) and pharmaceutical compositions comprising them.

In a second aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined above.

In a third aspect, there is provided a compound as defined above for use as a medicament.

The present compounds surprisingly were found to modulate the γ-secretase activity in vitro and in vivo, and are therefore useful in the treatment or prevention of Alzheimer's disease (AD), traumatic brain injury, mild cognitive impairment (MCI), senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid, preferably Alzheimer's disease and other disorders with Beta-amyloid pathology (eg glaucoma).

In a fourth aspect, there is provided a compound as defined above for the treatment or prevention of a disease or condition selected from Alzheimer's disease, traumatic brain injury, mild cognitive impairment, senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid.

In a fifth aspect, there is provided the use of a compound as defined above for the manufacture of a medicament for the modulation of gamma-secretase activity.

In view of the aforementioned pharmacology of the compounds of Formula (I), it follows that they are suitable for use as a medicament.

More especially the compounds are suitable in the treatment or prevention of Alzheimer's disease, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome.

The present disclosure also concerns to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the manufacture of a medicament for the modulation of γ-secretase activity.

Use of a compound of Formula (I) for the modulation of γ-secretase activity resulting in a decrease in the relative amount of Aß42-peptides produced are preferred.

One advantage of the compounds or a part of the compounds of the present disclosure may lie in their enhanced CNS-penetration.

The present disclosure will now be further described. In the following passages, different aspects of the disclosure are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be

combined with any other feature or features indicated as being preferred or advantageous.

Detailed description

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.

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 each individually selected from the indicated groups, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent. Thereby, one, two, three or four substituents are preferred. In particular one, two or three subsitutents are preferred. More in particular one substituent is preferred.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, iodo unless otherwise is indicated.

The term "C_{1-6}alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 6. C_{1-6}alkyl groups comprise from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, more preferably from 1 to 3 carbon atoms, still more preferably 1 to 2 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_{1-6}alkyl includes all linear, or branched alkyl groups with between 1 and 6 carbon atoms, and thus includes such as for example methyl, ethyl, *n*-propyl, *i*-propyl, 2-methyl-ethyl, butyl and its isomers (e.g. *n*-butyl, *iso*butyl and *tert*-butyl); pentyl and its isomers, hexyl and its isomers, and the like.

The term "C_{1-4}alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 4. C_{1-4}alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_{1-4}alkyl includes all linear, or branched alkyl groups with

between 1 and 4 carbon atoms, and thus includes such as for example methyl, ethyl, *n*-propyl, *i*-propyl, 2-methyl-ethyl, butyl and its isomers (e.g. *n*-butyl, *iso*butyl and *tert*-butyl); and the like.

In the framework of this application, C_{2-4}alkenyl is a straight or branched hydrocarbon radical having from 2 to 4 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, 1-propen-2-yl and the like.

The term "C_{1-6}alkyloxy" as a group or part of a group refers to a radical having the Formula R^b-O- wherein R^b is C_{1-6}alkyl. Non-limiting examples of suitable alkyloxy include methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, *sec*-butyloxy, *tert*-butyloxy, pentyloxy, and hexyloxy.

The term "C_{1-4}alkyloxy" as a group or part of a group refers to a radical having the Formula R^c-O- wherein R^c is C_{1-4}alkyl. Non-limiting examples of suitable alkyloxy include methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, *sec*-butyloxy and *tert*-butyloxy.

The term "cycloC_{3-7}alkyl" alone or in combination, refers to a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms. Non-limiting examples of suitable cycloC_{3-7}alkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "cycloC_{3-7}alkyloxy" alone or in combination, refers to a saturated cycloC_{3-7}alkyl-O-, wherein cycloC_{3-7}alkyl is as defined above. Non-limiting examples of suitable cycloC_{3-7}alkyl include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy.

The chemical names of the compounds of the present invention were generated according to the nomenclature rules agreed upon by the Chemical Abstracts Service (CAS). In case of tautomeric forms, the name of the depicted tautomeric form of the structure was generated. However it should be clear that the other non-depicted tautomeric form is also included within the scope of the present invention.

When any variable occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of Formula (I) and their pharmaceutically acceptable addition salts and stereoisomeric forms may contain one or more centers of chirality and exist as stereoisomeric forms.

The term "stereoisomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise

mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereoisomeric forms of the compounds of Formula (I) are embraced within the scope of this invention.

When a specific stereoisomeric form is indicated, this means that said form is substantially free, *i.e.* associated with less than 50 %, preferably less than 20 %, more preferably less than 10 %, even more preferably less than 5 %, further preferably less than 2 % and most preferably less than 1 % of the other isomer(s).

When a specific regioisomeric form is indicated, this means that said form is substantially free, *i.e.* associated with less than 50 %, preferably less than 20 %, more preferably less than 10 %, even more preferably less than 5 %, further preferably less than 2 % and most preferably less than 1 % of the other isomer(s).

For therapeutic use, salts of the compounds of Formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove or hereinafter are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of Formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of Formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for

example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-*n*-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term solvate comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form, as well as the salts thereof. Examples of such forms are e.g. hydrates, alcoholates and the like.

The compounds of Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from one another following art-known resolution procedures. An manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

In the framework of this application, a compound according to the invention is inherently intended to comprise all isotopic combinations of its chemical elements. In the framework of this application, a chemical element, in particular when mentioned in relation to a compound according to formula (I), comprises all isotopes and isotopic mixtures of this element. For example, when hydrogen is mentioned, it is understood to refer to ^{1}H, ^{2}H, ^{3}H and mixtures thereof.

A compound according to the invention therefore inherently comprises a compound with one or more isotopes of one or more element, and mixtures thereof, including a radioactive compound, also called radiolabelled compound, wherein one or more non-radioactive atoms has been replaced by one of its radioactive isotopes. By the term "radiolabelled compound" is meant any compound according to formula (I), or a pharmaceutically acceptable salt thereof, which contains at least one radioactive atom.

For example, a compound can be labelled with positron or with gamma emitting radioactive isotopes. For radioligand-binding techniques, the ^{3}H-atom or the ^{125}I-atom is the atom of choice to be replaced. For imaging, the most commonly used positron emitting (PET) radioactive isotopes are ^{11}C, ^{18}F, ^{15}O and ^{13}N, all of which are accelerator produced and have half-lives of 20, 100, 2 and 10 minutes respectively. Since the half-lives of these radioactive isotopes are so short, it is only feasible to use them at institutions which have an accelerator on site for their production, thus limiting their use. The most widely used of these are ^{18}F, ^{99m}Tc, ^{201}Tl and ^{123}I. The handling of these radioactive isotopes, their production, isolation and incorporation in a molecule are known to the skilled person.

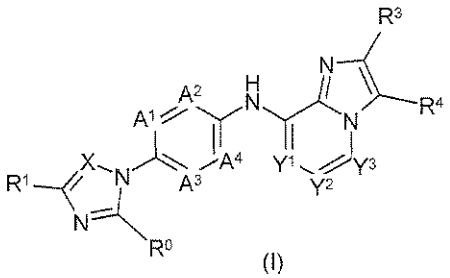
In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. In particular, the radioactive isotope is selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br.

As used in the specification and the appended claims, the singular forms "a", "an," and "the" also include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

The terms described above and others used in the specification are well understood to those in the art.

Preferred features of the compounds of this invention are now set forth.

In an embodiment, the present invention concerns novel compounds of Formula (I):



(I)

and stereoisomeric forms thereof, wherein

R^0 is hydrogen, halo or C_{1-4}alkyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

X is CR^7 or N; wherein R^7 is hydrogen or halo;

A^1 is CR^2 or N;

A^2 is CR^8 or N;

A^3 and A^4 each independently are CH or N;

provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^8 is hydrogen or halo;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, morpholinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, Ar, C_{1-6}alkyloxy, cycloC_{3-7}alkyloxy, and cycloC_{3-7}alkyl; carboxyl; C_{2-4}alkenyl; NR^5R^6-carbonyl; cycloC_{3-7}alkyl; Ar; tetrahydropyranyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; or Ar-O-CH_2-;

wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, and NR^5R^6; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

each R^5 independently is hydrogen, C_{1-4}alkyl, C_{1-6}alkylcarbonyl, or C_{1-4}alkyloxy$(CH_2CH_2O)_n$-CH_2-carbonyl;

n is an integer selected from 1, 2, 3, 4, 5 or 6.

each R^6 independently is hydrogen or C_{1-4}alkyl;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-4}alkyloxy; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, NR^5R^6, C_{1-4}alkyloxy, hydroxyl, and formylamino;

Y^1 is CH or N;

Y^2 is CR^9 or N;

Y^3 is CH or N;

provided that only one of Y^1, Y^2 and Y^3 may represent N;

R^9 is hydrogen; halo; C_{1-4}alkyloxy; cyano; cycloC_{3-7}alkyl; tetrahydropyranyl; C_{2-4}alkenyl; phenyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl optionally substituted

with one or more substituents each independently selected from the group consisting of halo and C_{1-4}alkyloxy;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereoisomeric forms thereof, wherein one or more, preferably all, of the following restrictions apply:

(a) R^0 is hydrogen or C_{1-4}alkyl;

(b) R^1 is hydrogen or C_{1-4}alkyl;

(c) X is CH or N;

(d) R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, morpholinyl, piperidinyl, tetrahydropyranyl, Ar, C_{1-6}alkyloxy, and cycloC_{3-7}alkyl; carboxyl; C_{2-4}alkenyl; NR^5R^6-carbonyl; cycloC_{3-7}alkyl; Ar; tetrahydropyranyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; or Ar-O-CH_2-;

wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from the group consisting of halo and NR^5R^6; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl;

(e) n is 2;

(f) R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-4}alkyloxy; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of NR^5R^6, C_{1-4}alkyloxy, hydroxyl, and formylamino;

(g) Y^1 is CH or N;

Y^2 is CR^9;

Y^3 is CH or N;

provided that only one of Y^1 and Y^3 may represent N;

(h) R^9 is hydrogen; halo; tetrahydropyranyl; C_{2-4}alkenyl; phenyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from halo;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereoisomeric forms thereof, wherein one or more, preferably all, of the following restrictions apply:

(a) R^0 is hydrogen or methyl;

(b) R^1 is hydrogen, methyl or ethyl;

(c) X is CH or N;

(d) A^1 is CR^2 or N;

(e) A^2 is CR^8 or N;

(f) A^3 and A^4 each independently are CH or N;

provided that no more than two of A^1, A^2, A^3 and A^4 are N;

(g) R^2 is hydrogen, fluoro or methoxy;

(h) R^8 is hydrogen or fluoro;

(i) R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of hydroxyl, fluoro, morpholinyl, piperidinyl, tetrahydropyranyl, Ar, isopropyloxy, and cyclohexyl; carboxyl; ethenyl; NR^5R^6-carbonyl; cyclopropyl; Ar; tetrahydropyranyl; ethylcarbonyl; C_{1-6}alkyloxycarbonyl; or Ar-O-CH_2-; wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of chloro, fluoro, methoxy, cyano, NR^5R^6, morpholinyl, isobutyl, methyl, and methyl substituted with one or more substituents each independently selected from the group consisting of fluoro and NR^5R^6; benzimidazolyl optionally substituted with one or more methyl groups; or pyridinyl;

(j) each R^5 independently is hydrogen, methyl, ethyl, methylcarbonyl, ethylcarbonyl, or methoxy$(CH_2CH_2O)_n$-CH_2-carbonyl;

(k) n is 2;

(l) each R^6 independently is hydrogen, methyl, or ethyl;

(m) R^4 is hydrogen; cyano; bromo; chloro; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of fluoro and phenyl; phenylcarbonyl optionally substituted with one or more fluoro atoms; methoxy; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of NR^5R^6, methoxy, hydroxyl, and formylamino;

(n) Y^1 is CH or N;

Y^2 is CR^9;

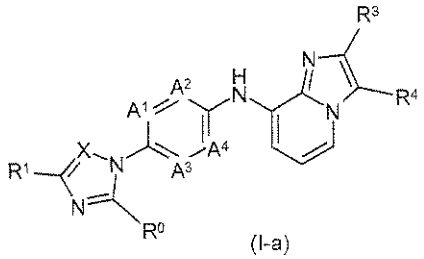
Y^3 is CH or N;

provided that only one of Y^1 and Y^3 may represent N;

(o) R^9 is hydrogen; fluoro; chloro; bromo; tetrahydropyranyl; 2-methyl-1-propen-3-yl; phenyl optionally substituted with one or more methoxy groups; or C_{1-4}alkyl optionally substituted with one or more fluoro atoms;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention relates to compounds according to any of the other embodiments or any combination of the other embodiments wherein the compounds of Formula (I) are restricted to the compounds of Formula (I-a)

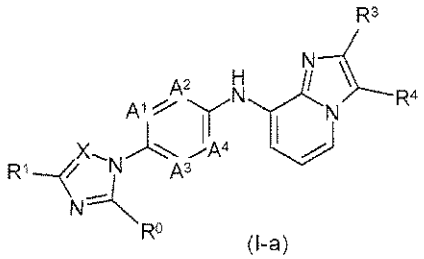


(I-a)

including any stereochemically isomeric form thereof,

and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention relates to novel compounds wherein Formula (I) is restricted to Formula (I-a):



(I-a)

and stereoisomeric forms thereof, wherein

R^0 is hydrogen or C_{1-4}alkyl; preferably hydrogen, methyl or ethyl; more preferably hydrogen or methyl; even more preferably hydrogen;

R^1 is hydrogen, C_{1-4}alkyl or halo; preferably hydrogen or C_{1-4}alkyl; more preferably hydrogen or methyl; even more preferably methyl;

X is CR^7 or N; wherein R^7 is hydrogen or halo; preferably X is CH or N;

A^1 is CR^2 or N;

A^2, A^3 and A^4 each independently are CH or N; provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, morpholinyl, piperidinyl,

pyrrolidinyl, Ar, C_{1-6}alkyloxy, cycloC_{3-7}alkyloxy, and cycloC_{3-7}alkyl; cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;
preferably R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of morpholinyl, piperidinyl, Ar, C_{1-6}alkyloxy, and cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;
more preferably R^3 is C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from Ar; tetrahydropyranyl; or Ar;
even more preferably R^3 is methyl substituted with one or more substituents each independently selected from Ar; or Ar;
each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;
preferably each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, methoxy, cyano, NR^5R^6, CF_3, morpholinyl, and C_{1-4}alkyl; 1-methyl-benzimidazolyl; or pyridinyl;
wherein each R^5 independently is hydrogen or C_{1-4}alkyl; preferably C_{1-4}alkyl; more preferably ethyl;
wherein each R^6 independently is hydrogen or C_{1-4}alkyl; preferably C_{1-4}alkyl; more preferably ethyl;
R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;
preferably R^4 is hydrogen; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy;
more preferably R^4 is hydrogen; or C_{1-6}alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereoisomeric forms thereof, wherein

R^0 is hydrogen or C_{1-4}alkyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

X is CR^7 or N; wherein R^7 is hydrogen or halo;

A^1 is CR^2 or N;

A^2, A^3 and A^4 each independently are CH or N; provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one substituent selected from the group consisting of morpholinyl, piperidinyl, Ar, C_{1-6}alkyloxy, and cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;

wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl;

wherein each R^5 independently is C_{1-4}alkyl;

wherein each R^6 independently is C_{1-4}alkyl;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereoisomeric forms thereof, wherein

R^0 is hydrogen or C_{1-4}alkyl;

R^1 is hydrogen or C_{1-4}alkyl;

X is CH or N;

A^1 is CR^2 or N;

A^2, A^3 and A^4 each independently are CH or N; provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one substituent selected from the group consisting of morpholinyl, piperidinyl, Ar, C_{1-6}alkyloxy, and cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;
wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl;
wherein each R^5 independently is C_{1-4}alkyl;
wherein each R^6 independently is C_{1-4}alkyl;
R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; or C_{1-6}alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

In another embodiment, the invention relates to compounds of Formula (I) and stereoisomeric forms thereof, wherein
R^0 is hydrogen or methyl;
R^1 is hydrogen, methyl, ethyl or bromo;
X is CR^7 or N; wherein R^7 is hydrogen or chloro;
A^1 is CR^2 or N;
A^2, A^3 and A^4 each independently are CH or N; provided that no more than two of A^1, A^2, A^3 and A^4 are N;
R^2 is hydrogen, fluoro, or methoxy;
R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one substituent selected from the group consisting of morpholinyl, piperidinyl, Ar, isopropyloxy, cyclopentyl, and cyclohexyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;
wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of fluoro, chloro, methoxy, cyano, NR^5R^6, morpholinyl, methyl, isobutyl, and trifluoromethyl; benzimidazolyl optionally substituted with one methyl; or pyridinyl;
wherein R^5 is ethyl;
wherein R^6 is ethyl;
R^4 is hydrogen; cyano; chloro; iodo; bromo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of fluoro and

phenyl; phenylcarbonyl optionally substituted with one or more fluoro atoms; C_{1-6}alkyl optionally substituted with one or more methoxy groups; or trifluoromethyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

In another embodiment, the invention relates to compounds of Formula (I) and stereoisomeric forms thereof, wherein
R^0 is hydrogen or methyl;
R^1 is hydrogen, methyl or ethyl;
X is CH or N;
A^1 is CR^2 or N;
A^2, A^3 and A^4 each independently are CH or N; provided that no more than two of A^1, A^2, A^3 and A^4 are N;
R^2 is hydrogen, fluoro or methoxy;
R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one substituent selected from the group consisting of morpholinyl, piperidinyl, Ar, isopropyloxy, and cyclohexyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;
wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of fluoro, chloro, methoxy, cyano, NR^5R^6, morpholinyl, methyl, isobutyl, and trifluoromethyl; benzimidazolyl optionally substituted with one or more methyl groups; or pyridinyl;
wherein R^5 is ethyl;
wherein R^6 is ethyl;
R^4 is hydrogen; cyano; chloro; iodo; bromo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of fluoro and phenyl; phenylcarbonyl optionally substituted with one or more fluoro atoms; or C_{1-6}alkyl;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention provides compounds according to any of the other embodiments wherein
R^0 is hydrogen or C_{1-4}alkyl;
R^1 is hydrogen, C_{1-4}alkyl or halo;
X is CR^7 or N; wherein R^7 is hydrogen or halo;
A^1 is CR^2 or N;
A^2, A^3 and A^4 each independently are CH or N; provided that no more than two of A^1, A^2, A^3 and A^4 are N;
R^2 is hydrogen, halo or C_{1-4}alkyloxy;
R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each

independently selected from the group consisting of halo, morpholinyl, piperidinyl, pyrrolidinyl, Ar, C_{1-6}alkyloxy, cycloC_{3-7}alkyloxy, and cycloC_{3-7}alkyl; cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;

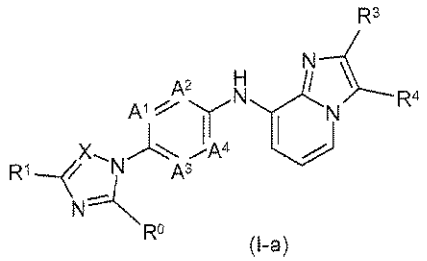
each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholino, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents selected from halo; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

wherein each R^5 independently is hydrogen or C_{1-4}alkyl;

wherein each R^6 independently is hydrogen or C_{1-4}alkyl;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl substituted with one or more substituents each independently selected from halo.

In another embodiment, the invention concerns compounds of formula (I-a)



(I-a)

and stereoisomeric forms thereof, wherein

R^0 is hydrogen or C_{1-4}alkyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

X is CR^7 or N; wherein R^7 is H or halo;

A^1 is CR^2 or N;

A^2, A^3 and A^4 each independently are CH or N; provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents selected from halo, morpholino, piperidinyl, pyrrolidinyl, Ar, C_{1-6}alkyloxy, cycloC_{3-7}alkyloxy,

or cycloC_{3-7}alkyl; cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or -CH_2-O-Ar;
wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholino, C_{1-4}alkyl, or C_{1-4}alkyl substituted with one or more substituents selected from halo; benzimidazolyl optionally substituted with C_{1-4}alkyl; or pyridinyl optionally substituted with 1 or more substituents each independently selected from halo, C_{1-4}alkyloxy, cyano, C_{1-4}alkyl, or C_{1-4}alkyl substituted with one or more substituents selected from halo;
wherein each R^5 independently is hydrogen or C_{1-4}alkyl;
wherein each R^6 independently is hydrogen or C_{1-4}alkyl;
R^4 is hydrogen; phenyl optionally substituted with halo or phenyl; carbonylphenyl optionally substituted with halo; C_{1-6}alkyl optionally substituted with C_{1-4}alkyloxy; C_{1-4}alkyl substituted with one or more substituents selected from halo; cyano; or halo;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

In another embodiment, the invention relates to compounds according to any of the other embodiments, wherein one or more, preferably all, of the following restrictions apply:
(a) R^0 is hydrogen;
(b) R^1 is C_{1-4}alkyl;
(c) X is CH or N;
(d) A^1 is CR^2;
(e) A^2 is N;
(f) A^3 and A^4 are CH;
(g) R^2 is C_{1-4}alkyloxy;
(i) R^3 is Ar; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from halo;
(j) each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from halo;
(k) R^4 is hydrogen or C_{1-6}alkyl;
(l) Y^1 is CH;
(m) Y^2 is CH;
(n) Y^3 is CH.

In another embodiment, the invention relates to compounds according to any of the other embodiments, wherein one or more, preferably all, of the following restrictions apply:

(a) R^1 is methyl;
(b) R^2 is methoxy;
(c) R^3 is Ar; or C_{1-6}alkyl substituted with one or more fluoro atoms;
(d) each Ar independently is phenyl substituted with one or more chloro atoms;
(e) R^4 is hydrogen or methyl.

In another embodiment, the invention relates to compounds according to any of the other embodiments, or any combination of the other embodiments wherein R^3 is C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from halo.

In a next embodiment, the invention relates to compounds according to any of the preceding embodiments, wherein
R^3 is phenyl;
R^4 is methyl.

In an embodiment, the invention relates to compounds according to any of the preceding embodiments, wherein
R^3 is phenyl substituted in a meta position and optionally further substituted in other positions;
R^4 is hydrogen or methyl.

In an embodiment, the invention relates to compounds according to any of the preceding embodiments, wherein
R^3 is phenyl substituted in an ortho position and optionally further substituted in other positions;
R^4 is hydrogen or methyl.

In a further embodiment, the invention relates to compounds according to any of the preceding embodiments, wherein
R^3 is methyl substituted with one or more phenyl groups, wherein phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;
R^4 is hydrogen.

In an embodiment, the present invention provides compounds according to any of the preceding embodiments, wherein R^2 represents C_{1-4}alkyloxy, preferably methoxy.

In an embodiment, the present invention provides compounds according to any of the preceding embodiments, wherein C_{1-6}alkyl is selected from the group comprising methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl and *tert*-butyl.

In an embodiment, the present invention provides compounds according to any of the preceding embodiments, wherein C_{1-4}alkyl is selected from the group comprising methyl, ethyl and *n*-propyl.

In another embodiment, the present invention relates to compounds according to any of the preceding embodiments, wherein
X is N.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein Y^1 is CH or N; Y^2 is CR^4; and Y^3 is CH or N; provided that only one of Y^1 and Y^3 may represent N;.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein Y^1 is CH; Y^2 is CR^4; and Y^3 is CH.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein Y^1 is CH; Y^2 is CH; and Y^3 is CH.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein Y^1 is N; Y^2 is CR^4; and Y^3 is CH.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein Y^1 is CH; Y^2 is N; and Y^3 is CH.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein Y^1 is CH; Y^2 is CR^4; and Y^3 is N.

In a next embodiment, the present invention relates to compound according to any of the preceding embodiments, wherein
A^1 represents CR^2;
A^2, A^3 and A^4 represents CH.

In an embodiment, the present invention relates to compounds according to any of the preceding embodiments or any combination of the preceding embodiments wherein the compounds are restricted to the compounds of formula (I-a).

In an embodiment the compound of Formula (I) is selected from the group comprising:
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,

3-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(2,4-dimethoxyphenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
4-[8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridin-2-yl]benzonitrile,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(2-methoxyphenyl)-imidazo[1,2-a]pyridin-8-amine,
2-[4-(diethylamino)phenyl]-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-methyl-2-phenyl-imidazo[1,2-a]pyridin-8-amine,
N-[4-(2,4-dimethyl-1H-imidazol-1-yl)-3-methoxyphenyl]-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(2-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-[(4-fluorophenyl)methyl]-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine .2HCl .2H_2O,
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-propyl-imidazo[1,2-a]pyridin-8-amine .2HCl,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-methyl-2-[2-(trifluoromethyl)phenyl]-imidazo[1,2-a]pyridin-8-amine .2HCl,
2-(2-fluorophenyl)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
3-ethyl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-propyl-imidazo[1,2-a]pyridin-8-amine,
2-butyl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-propyl-imidazo[1,2-a]pyridin-8-amine,
2-(4-chlorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-phenyl-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-[4-(4-morpholinyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(3-methoxyphenyl)-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(4-methoxyphenyl)-

imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(2-pyridinyl)-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-methyl-2-[4-(2-methylpropyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(2-chlorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
3-chloro-2-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(2,4-difluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
3-ethyl-2-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(2,6-difluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
2-(2-chlorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(2,4-difluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(1-methyl-1H-benzimidazol-5-yl)-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-[4-(trifluoromethyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
3-bromo-2-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(1,1-dimethylethyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(3-pyridinyl)-imidazo[1,2-a]pyridin-8-amine,
2-(3-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(3-chlorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,

N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2,3-diphenyl-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(3-methoxyphenyl)-3-methyl-imidazo[1,2-a]pyridin-8-amine,
N-[4-(1H-imidazol-1-yl)-3-methoxyphenyl]-2-(3-methoxyphenyl)-3-methyl-imidazo[1,2-a]pyridin-8-amine,
2-[(4-fluorophenoxy)methyl]-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(tetrahydro-2H-pyran-4-yl)-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(4-pyridinyl)-imidazo-[1,2-a]pyridin-8-amine,
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyrazin-8-amine,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-6-(trifluoromethyl)-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester .HCl,
N-[3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]-2-[2-methyl-5-(trifluoromethyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
3-[8-[[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]amino]imidazo[1,2-a]pyridin-2-yl]-4-methyl-benzonitrile,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-6-(trifluoromethyl)-imidazo[1,2-a]pyridine-2-carboxylic acid,
2-[(4-fluorophenoxy)methyl]-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-6-(trifluoromethyl)-imidazo[1,2-a]pyridin-8-amine,
8-[[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]amino]-6-(trifluoromethyl)-imidazo[1,2-a]pyridine-2-methanol,
6-bromo-2-(4-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyrazin-8-amine,
2-(4-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyrazin-8-amine,
2-(4-fluoro-2-methylphenyl)-*N*-[3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-ethenyl-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-6-(trifluoromethyl)-imidazo[1,2-a]pyridin-8-amine,
2-ethyl-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-6-(trifluoromethyl)-imidazo[1,2-a]pyridin-8-amine,
2-(2-chlorophenyl)-*N*-[2-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-3-methyl-

imidazo[1,2-a]pyridin-8-amine,
2-[(4-fluorophenyl)methyl]-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-6-(trifluoromethyl)-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-6-(trifluoromethyl)-imidazo[1,2-b]pyridazin-8-amine,
2-(4-fluorophenyl)-8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridine-3-methanol,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-2-(tetrahydro-2H-pyran-4-yl)-imidazo[1,2-a]pyridin-8-amine .1.1 HCl .1.5 H_2O,
2-(4-fluorophenyl)-8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridine-3-methanamine,
N-[[2-(4-fluorophenyl)-8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]imidazo[1,2-a]pyridin-3-yl]methyl]-formamide,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-alpha,alpha-dimethyl-6-(trifluoromethyl)-imidazo[1,2-a]pyridine-2-methanol,
2-(4-fluorophenyl)-3-(methoxymethyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
8-[[3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]amino]-6-(trifluoromethyl)-imidazo[1,2-*a*]pyridine-2-carboxylic acid ethyl ester,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(tetrahydro-2H-pyran-4-yl)-imidazo[1,2-a]pyridin-8-amine .1HCl .0.4 H_2O,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-6-(trifluoromethyl)-imidazo[1,2-b]pyridazin-8-amine,
6-chloro-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-imidazo[1,2-b]pyridazin-8-amine,
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-3-(3-methoxypropyl)-imidazo[1,2-a]pyridin-8-amine .1HCl,
2-cyclopropyl-*N*-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-cyclopropyl-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-cyclopropyl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(tetrahydro-2H-pyran-4-yl)-6-(trifluoromethyl)-imidazo[1,2-b]pyridazin-8-amine,

6-chloro-*N*-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(tetrahydro-2H-pyran-4-yl)-imidazo[1,2-a]pyridin-8-amine,
6-fluoro-*N*-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(tetrahydro-2H-pyran-4-yl)-imidazo[1,2-a]pyridin-8-amine .1.8HCl .0.9H_2O,
2-(4-fluorophenyl)-3-(2-methoxyethyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluorophenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyrazin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridin-8-amine,
6-chloro-2-(5-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-b]pyridazin-8-amine,
6-chloro-2-(5-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-b]pyridazin-8-amine,
6-chloro-*N*-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(5-fluoro-2-methylphenyl)-imidazo[1,2-b]pyridazin-8-amine,
3-[8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]imidazo[1,2-a]pyridin-2-yl]-4-methyl-benzonitrile,
N-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-3-methyl-2-[2-(trifluoromethyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-[(tetrahydro-2H-pyran-4-yl)methyl]-imidazo[1,2-a]pyridin-8-amine .1.7HCl .0.25H_2O,
2-(4-fluorophenyl)-3-methoxy-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[[2-(2-chlorophenyl)-8-[[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]imidazo[1,2-a]pyridin-3-yl]methyl]-*N*-methyl-acetamide,
2-(2-chlorophenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
2-[5-(aminomethyl)-2-methylphenyl]-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-2-[(tetrahydro-2H-pyran-4-yl)methyl]-imidazo[1,2-a]pyridin-8-amine .1.8HCl .2.1H_2O,
8-[[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]amino]-*N*,*N*-dimethyl-2-phenyl-imidazo[1,2-a]pyridine-3-methanamine,
2-(2-chlorophenyl)-8-[[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]amino]-*N*,*N*-dimethyl-imidazo[1,2-a]pyridine-3-methanamine,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-(methoxymethyl)-2-phenyl-

imidazo[1,2-a]pyridin-8-amine,
2-(2-chlorophenyl)-*N*-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-3-(methoxymethyl)-imidazo[1,2-a]pyridin-8-amine,
N-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-2-methyl-imidazo[1,2-a]pyridin-8-amine,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-imidazo[1,2-a]pyridin-8-amine,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(tetrahydro-2H-pyran-4-yl)-6-(trifluoromethyl)-imidazo[1,2-b]pyridazin-8-amine,
6-fluoro-*N*-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(4-fluoro-2-methylphenyl)-imidazo[1,2-a]pyridin-8-amine,
N-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-2-(tetrahydro-2H-pyran-4-yl)-imidazo[1,2-a]pyridin-8-amine
2-(5-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-b]pyridazin-8-amine,
2-(5-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-b]pyridazin-8-amine,
2-(2-chlorophenyl)-3-(methoxymethyl)-*N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-imidazo[1,2-a]pyridin-8-amine,
N-[[3-[8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]imidazo[1,2-a]pyridin-2-yl]-4-methylphenyl]methyl]-propanamide,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(5-fluoro-2-methylphenyl)-imidazo[1,2-b]pyridazin-8-amine,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-alpha,alpha-dimethyl-imidazo[1,2-a]pyridine-2-methanol,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-imidazo[1,2-b]pyridazin-8-amine,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-*N*,*N*-dimethyl-imidazo[1,2-a]pyridine-2-carboxamide,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(4-fluorophenyl)-3-methoxy-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-6-(2-methoxyphenyl)-2-methyl-imidazo[1,2-b]pyridazin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-6-(1-methylethyl)-imidazo[1,2-b]pyridazin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl-6-(tetrahydro-2H-pyran-4-yl)-imidazo[1,2-b]pyridazin-8-amine,

8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridine-2-carboxylic acid 1-methylethyl ester,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridine-2-carboxylic acid 1,1-dimethylethyl ester .1.5 HCl,
1-[8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]imidazo[1,2-a]pyridin-2-yl]-1-propanone .H_2O .3HCl,
6-fluoro-*N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-2-(2-methylpropyl)-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluorophenyl)-3-methoxy-*N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-imidazo[1,2-a]pyridin-8-amine,
2-[2-(2-methoxyethoxy)ethoxy]-*N*-[[3-[8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]imidazo[1,2-a]pyridin-2-yl]-4-methylphenyl]methyl]-acetamide .3H_2O .1.7HCl,
6-chloro-2-(2-chlorophenyl)-*N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-imidazo[1,2-b]pyridazin-8-amine,
2-(2-chlorophenyl)-*N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-6-(1-methylethenyl)-imidazo[1,2-b]pyridazin-8-amine,
2-(2-chlorophenyl)-*N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-6-(1-methylethyl)-imidazo[1,2-b]pyridazin-8-amine,
2-(1-chloro-2,2,2-trifluoroethyl)-*N*-[6-methoxy-5-(4-methyl-1*H*-imidazol-1-yl)-2-pyridinyl]-imidazo[1,2-*a*]pyridin-8-amine,
2-(2-chlorophenyl)-*N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
2-(2-chlorophenyl)-*N*-[6-methoxy-5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-alpha-(trifluoromethyl)-imidazo[1,2-a]pyridine-2-methanol,
N-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-2-(2,2,2-trifluoroethyl)-imidazo[1,2-*a*]pyridin-8-amine,
N-[6-methoxy-5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-2-(2,2,2-trifluoroethyl)-imidazo[1,2-*a*]pyridin-8-amine
2-(3-methoxyphenyl)-*N*-[3-methoxy-4-(1H-1,2,4-triazol-1-yl)phenyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine,
2-(3-methoxyphenyl)-3-methyl-*N*-[5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-imidazo[1,2-a]pyridin-8-amine,
2-butyl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]- imidazo[1,2-a]-pyridin-8-amine .2 HCl,

2-butyl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]- imidazo[1,2-a]-pyridin-8-amine ,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-[(1-methylethoxy)methyl]-imidazo[1,2-a]pyridin-8-amine .2 HCl,
2-(4-fluorophenyl)-3-iodo-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[4-(4-ethyl-1H-imidazol-1-yl)-3-methoxyphenyl]-2-(3-methoxyphenyl)-3-methyl-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-2-(3-methoxyphenyl)-3-methyl-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-methyl- imidazo[1,2-a]-pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(1-piperidinylmethyl)-imidazo[1,2-a]pyridin-8-amine,
2-(3-methoxyphenyl)-3-methyl-*N*-[2-(4-methyl-1H-imidazol-1-yl)-5-pyrimidinyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(4-morpholinylmethyl)-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(3-methoxyphenyl)-3-methyl-*N*-[4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(3-methoxyphenyl)-3-methyl-*N*-[4-(2-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-[3-(trifluoromethyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
3-hexyl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]-pyridin-8-amine,
N-[3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-(3-methoxyphenyl)-3-methyl-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluorophenyl)-8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridine-3-carbonitrile,
3-[1,1'-biphenyl]-2-yl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-

imidazo[1,2-a]pyridin-8-amine,
3-chloro-2-(cyclohexylmethyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
(4-fluorophenyl)[8-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-imidazo[1,2-a]pyridin-3-yl]-methanone,
3-[1,1'-biphenyl]-3-yl-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-methyl-*N*-[4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-*a*]pyridin-8-amine,
2-(2-methylphenyl)-*N*-[4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-*a*]-pyridin-8-amine,
N-[3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-2-(2-methylphenyl)-imidazo[1,2-*a*]pyridin-8-amine,
2-(5-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-*a*]pyridin-8-amine,
N-[4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-2-[2-methyl-5-(trifluoromethyl)-phenyl]-imidazo[1,2-*a*]pyridin-8-amine,
2-(2-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-2-methyl-imidazo[1,2-a]-pyridin-8-amine,
2-(2-methylphenyl)-*N*-[6-(3-methyl-1H-1,2,4-triazol-1-yl)-3-pyridinyl]-imidazo-[1,2-a]pyridin-8-amine,
2,3-dimethyl-*N*-[4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(2-chlorophenyl)-3-methyl-*N*-[5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-methoxy-4-(1H-1,2,4-triazol-1-yl)phenyl]-2-methyl-imidazo[1,2-a]pyridin-8-amine,
2-butyl-*N*-[4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-a]pyridin-8-amine .2HCl,
2-(2-chlorophenyl)-3-methyl-*N*-[6-(3-methyl-1H-1,2,4-triazol-1-yl)-3-pyridinyl]-imidazo[1,2-a]pyridin-8-amine,
N-[5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-2-[2-methyl-5-(trifluoromethyl)-phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(2-methylphenyl)-*N*-[5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-imidazo-[1,2-a]pyridin-8-amine,

2-(5-fluoro-2-methylphenyl)-*N*-[6-(3-methyl-1H-1,2,4-triazol-1-yl)-3-pyridinyl]-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluoro-2-methylphenyl)-*N*-[6-(3-methyl-1*H*-1,2,4-triazol-1-yl)-3-pyridinyl]-imidazo[1,2-*a*]pyridin-8-amine,
N-[6-(3-methyl-1H-1,2,4-triazol-1-yl)-3-pyridinyl]-2-[2-methyl-5-(trifluoromethyl)-phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]-2-[2-methyl-5-(trifluoromethyl)-phenyl]-imidazo[1,2-a]pyridin-8-amine,
N-[3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-2-[2-methyl-5-(trifluoromethyl)phenyl]-imidazo[1,2-a]pyridin-8-amine,
2-(4-fluoro-2-methylphenyl)-*N*-[3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-*a*]pyridin-8-amine, 2-(4-fluoro-2-methylphenyl)-*N*-[4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-*a*]pyridin-8-amine, 2-(4-fluoro-2-methylphenyl)-*N*-[3-fluoro-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-imidazo[1,2-*a*]pyridin-8-amine, and *N*-[3-fluoro-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]-2-(5-methoxy-2-methylphenyl)-imidazo[1,2-*a*]pyridin-8-amine,
including any stereochemically isomeric form thereof,
and the pharmaceutically acceptable addition salts and the solvates thereof.

In an embodiment the compound of Formula (I) is 2-(2-chlorophenyl)-*N*-[6-methoxy-5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine, including any stereochemically isomeric form thereof, and the pharmaceutically acceptable addition salts and the solvates thereof.

In an embodiment the compound of Formula (I) is *N*-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-2-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridin-8-amine, including any stereochemically isomeric form thereof, and the pharmaceutically acceptable addition salts and the solvates thereof.

In an embodiment the compound of Formula (I) is *N*-[6-methoxy-5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-2-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridin-8-amine, including any stereochemically isomeric form thereof, and the pharmaceutically acceptable addition salts and the solvates thereof.

The present invention also encompasses processes for the preparation of compounds of Formula (I) and subgroups thereof. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in

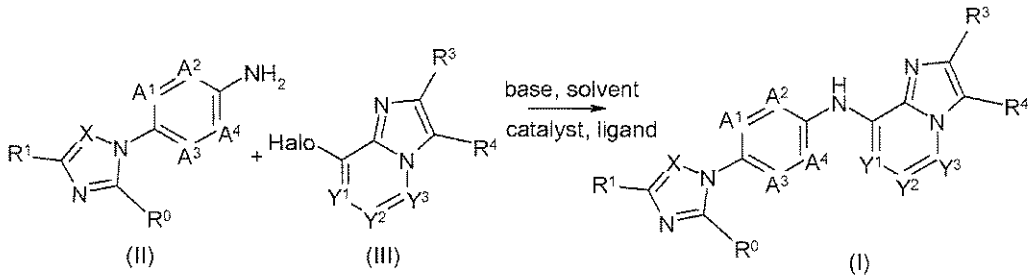
accordance with standard practice, for example, see T. W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1999.

The compounds of Formula (I) and the subgroups thereof can be prepared by a succession of steps as described hereunder. They are generally prepared from starting materials which are either commercially available or prepared by standard means obvious to those skilled in the art. The compounds of the present invention can be also prepared using standard synthetic processes commonly used by those skilled in the art of organic chemistry.

The general preparation of some typical examples is shown below:

Experimental procedure 1

In general, compounds of formula (I), can be prepared as set out below in Scheme 1 wherein halo is defined as Br, Cl or I, and wherein all other variables are defined as hereabove:

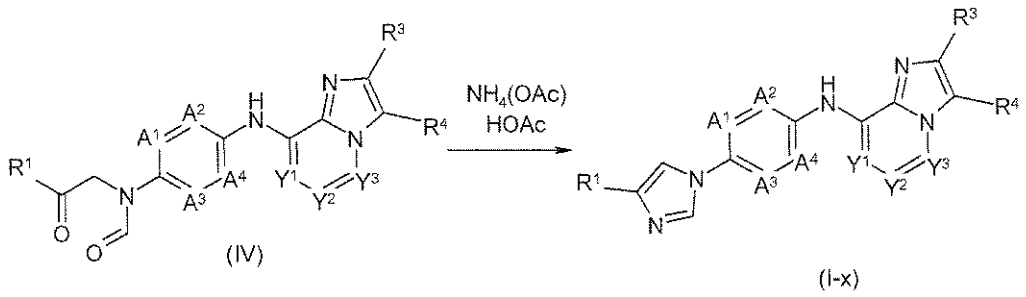


Scheme 1

Compounds of formula (I) can be prepared via a coupling reaction between an intermediate of formula (II) and formula (III). This reaction may be performed in the presence of a suitable base such as, for example, Cs_2CO_3 or sodium *tert*-butoxide. The reaction can be performed in a reaction-inert solvent such as, for example, toluene, *N*,*N*-dimethylformamide (DMF), *tert*-butanol or dioxane. The reaction typically is performed in the presence of a catalyst system comprising a suitable catalyst such as palladium(II) acetate ($Pd(OAc)_2$) or tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) and a ligand such as (9,9-dimethyl-9H-xanthene-4,5-diyl)bis[diphenylphosphine] (Xantphos), [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine] (BINAP), or dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]-phosphine (X-phos). Preferably this reaction is carried out under an inert atmosphere, such as a nitrogen or an argon atmosphere. Reaction rate and yield may be enhanced by microwave assisted heating. For compounds of formula (I), where Y^1 = N, no catalyst may be required, and couplings can also be performed under acidic conditions, for example using HCl or methanesulfonic acid in an alcoholic solvent such as 2-propanol.

Experimental procedure 2

Compounds of formula (I) wherein X represents CH and wherein R^0 represents H, hereby named compounds of formula (I-x), can also be prepared via a condensation reaction of intermediate (IV) with an ammonia source such as, for example, ammonium acetate ($NH_4(OAc)$) to yield compounds of formula (I-x).

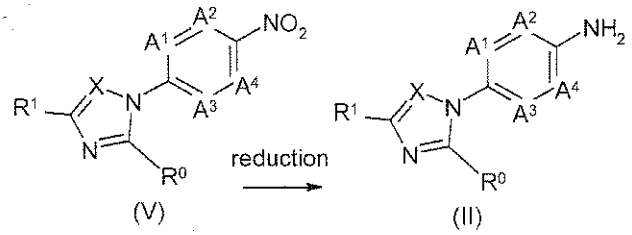


Scheme 2

Compounds of formula (I) or formula (I-x) wherein R^4 represents hydrogen, can be further derivatized towards other R^4 groups via electrophilic aromatic substitution reactions, such as halogenation (such as, for example, chlorination or bromination). The obtained compounds (I) or (I-x) wherein R^4 represents halo can be further derivatized to other R^4 groups. Both R^3 and R^4 groups containing suitable functional groups such as, for example, halo, (protected) amines, alcohols or ketones, can be used to incorporate further substitution patterns in compounds of formula (I) or formula (I-x).

Experimental procedure 3

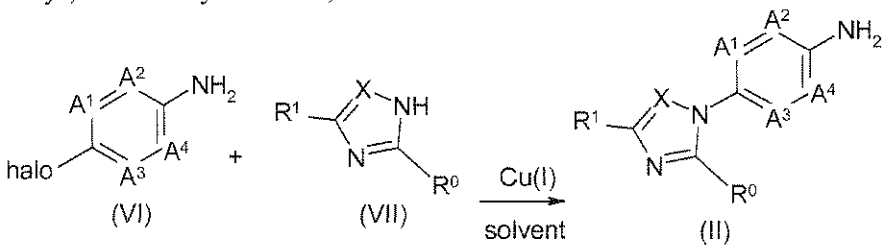
An intermediate of formula (II) can be prepared by reduction of an intermediate of formula (V) as is shown in Scheme 3, wherein all variables are as defined before. The reduction of (V) to (II) can be conducted by a conventional method such as, for example, a reductive hydrogenation or reduction with a metal or a metal salt and an acid [for example a metal such as iron or a metal salt such as $SnCl_2$ and acid such as an inorganic acid (hydrochloric acid, sulfuric acid or the like) or an organic acid (acetic acid or the like)], or other well-known methods for converting a nitro-group to the corresponding amine.



Scheme 3

Experimental procedure 4

An intermediate of formula (II) can also be prepared by a copper catalysed reaction of an intermediate of formula (VI) with an optionally substituted imidazole or triazole of formula (VII), according to Scheme 4. In Scheme 4, halo is defined as Br or I and all other variables are defined as mentioned hereabove. The reaction may be performed under a protecting atmosphere such as, for example, a N_2 atmosphere. Stirring, elevated temperatures (for example between 70-200 °C) and/or pressure may enhance the rate of the reaction. The reaction typically is performed in an organic solvent such as, for example, dimethylsulfoxide (DMSO) or DMF. The reaction may performed in the presence of a base such as, for example K_2CO_3, Cs_2CO_3 or triethylamine (Et_3N). The reaction may be performed in the presence of a ligand such as *N,N'*-dimethylethylenediamine or 1,10-phenanthroline. Typical copper catalysts that can be used in this reaction in catalytic or stoichiometric amounts, are copper salts such as, for example, copper(I)oxide, copper(I)iodide or copper(I)bromide. The amino-group in intermediate (VI) can be protected before reaction (and deprotected after reaction) via the use of a suitable amino-protecting group in accordance with standard practice, for example, see T. W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1999.

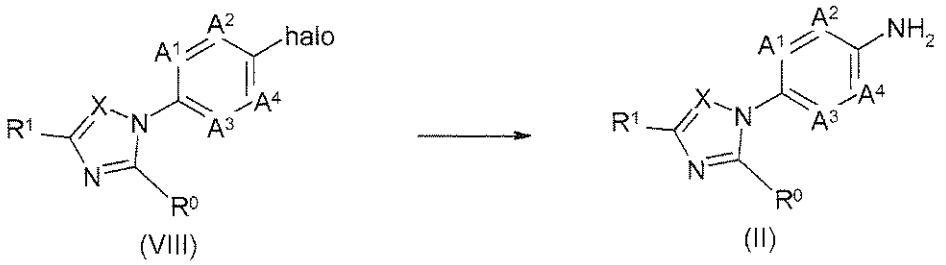


Scheme 4

Intermediates according to formula (VI) or (VII) are commercially available or can be prepared by those skilled in the art.

Experimental procedure 5

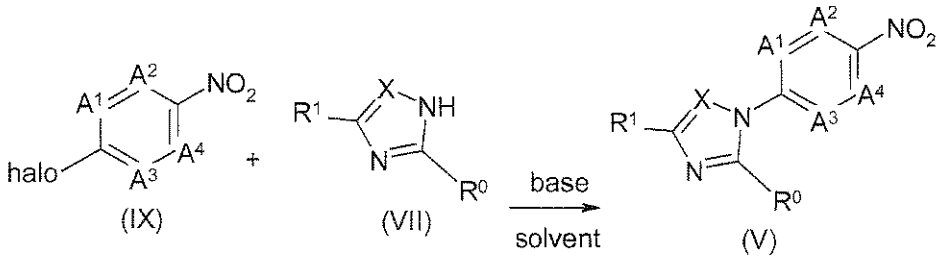
Alternatively, an intermediate of formula (II) can also be prepared by conversion of the halo-substitutent in an intermediate of formula (VIII), wherein halo is defined as Br or I, and wherein all other variables are defined as mentioned hereabove, into an amino-group or a masked amino functionality, which can subsequently be converted into an amino-group, according to Scheme 5.



Scheme 5

Experimental procedure 6

An intermediate of formula (V) can be prepared via a nucleophilic aromatic substitution of an intermediate (IX) with an optionally substituted imidazole or triazole of formula (VII) according to Scheme 6, wherein halo is defined as F, Cl, or Br and wherein all other variables are defined as mentioned hereabove. The reaction may be performed under a protecting atmosphere such as, for example, N_2 atmosphere. Stirring, elevated temperatures (for example between 70-170 °C) and/or increased pressure may enhance the rate of the reaction. The reaction typically may be performed in an organic solvent such as, for example, DMSO, DMF or *N*-methylpyrrolidinone (NMP) in the presence of a base such as, for example, K_2CO_3, Cs_2CO_3, or Et_3N.



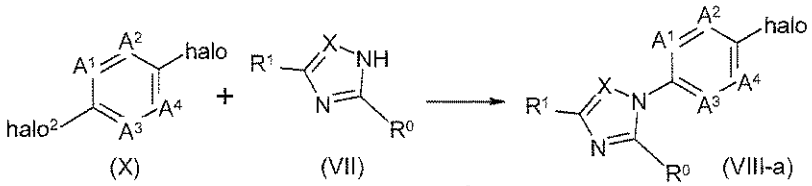
Scheme 6

Intermediates of formula (IX) and formula (VII) are commercially available or can be prepared by those skilled in the art.

Experimental procedure 7

An intermediate of formula (VIII) wherein at least one of A^1 or A^3 represents N, hereby named an intermediate of formula (VIII-a), can be prepared via a nucleophilic aromatic substitution of an intermediate of formula (X), wherein at least one of A^1 or A^3 represents N, with an optionally substituted imidazole or triazole of formula (VII) according to Scheme 7, wherein $halo^2$ is defined as F,Cl or Br, wherein halo is defined as Br or I, and wherein all other substituents are defined as mentioned before. The

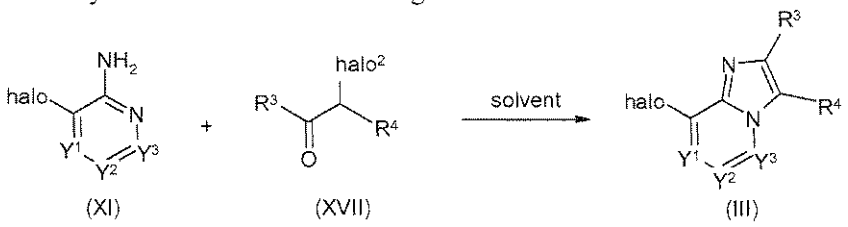
reaction may be performed under similar conditions as described for Experimental procedure 6.



Scheme 7

Experimental procedure 8

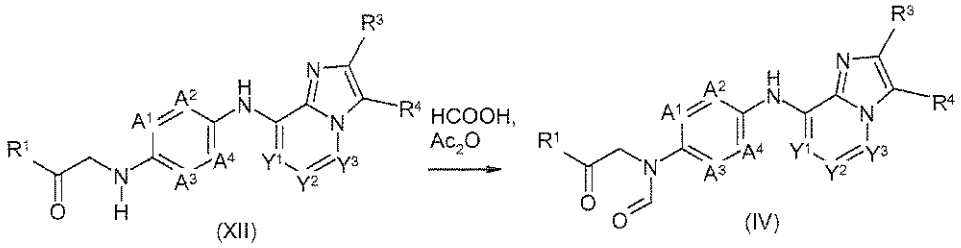
An intermediate of formula (III) can be prepared via a condensation reaction between an intermediate of formula (XI) and an intermediate of formula (XVII) as is illustrated in Scheme 8, wherein $halo^2$ is restricted to Br and Cl, and wherein all other variables are defined as hereabove. The reaction may be performed in a reaction-inert solvent such as, for example, ethanol or *n*-butanol, or by mixing the reagents without a solvent. The reaction may conveniently be carried out at elevated temperatures ranging between 50 °C and the reflux temperature of the reaction mixture. Reaction rate and yield may be enhanced by microwave assisted heating.



Scheme 8

Experimental procedure 9

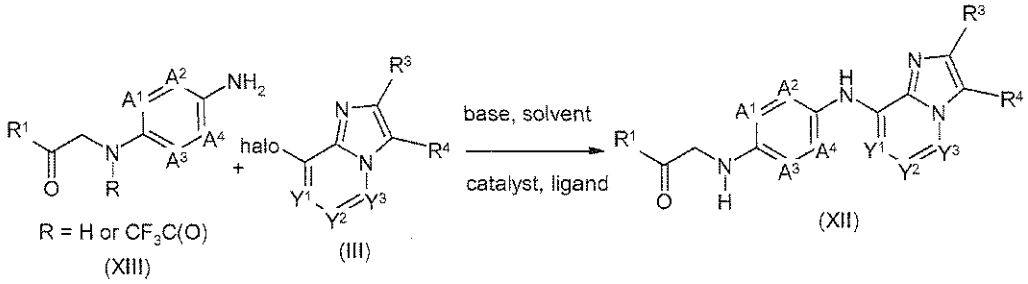
An intermediate of formula (XII) can be formylated to yield intermediate (IV) according to Scheme 9, wherein all substituents are defined as mentioned hereabove. A formylation reaction can be performed in the presence of an acid anhydride such as, for example, acetic anhydride (Ac_2O). Typically, the reaction may be performed in the presence of a solvent such as, for example, formic acid (HCOOH).



Scheme 9

Experimental procedure 10

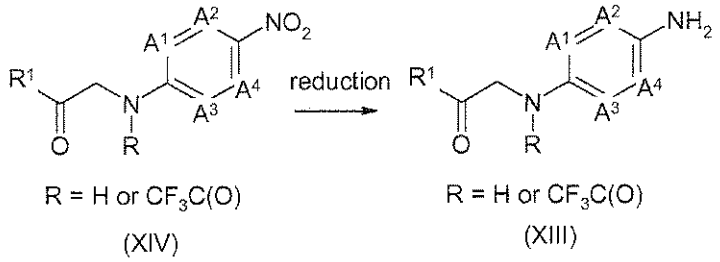
An intermediate of formula (XII) can be prepared via a coupling reaction between an intermediate of formula (XIII) and an intermediate of formula (III) under similar conditions as described for experimental procedure 1. In Scheme 10, R represents H or trifluoromethylcarbonyl ($CF_3C(O)$) and all other substituents are defined as before.



Scheme 10

Experimental procedure 11

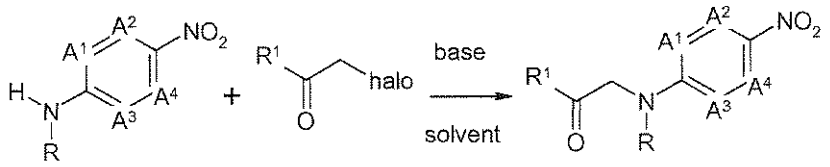
An intermediate of formula (XIII) can be prepared by reduction of an intermediate of formula (XIV) according to Scheme 11. This reaction can be performed using a conventional method such as, for example, a reductive hydrogenation or reduction with a metal or a metal salt and an acid [for example a metal such as iron, or a metal salt such as SnCl2 and acid such as an inorganic acid (hydrochloric acid, sulfuric acid or the like) or an organic acid (acetic acid or the like)], or other well-known methods for converting a nitro-group to the corresponding amine. In Scheme 11, R represents H or trifluoromethylcarbonyl ($CF_3C(O)$) and all other substituents are defined as before.



Scheme 11

Experimental procedure 12

An intermediate of formula (XIV), can be prepared via alkylation of intermediate (XVI) with an intermediate of formula (XV), wherein halo is defined as Cl or Br, in the presence of a reaction inert solvent such as, for example, DMF, and a suitable base such as, for example, Cs_2CO_3 or K_2CO_3. In Scheme 12, R represents H or trifluoromethylcarbonyl ($CF_3C(O)$) and all other substituents are defined as before.



R = H or $CF_3C(O)$ (XVI) (XV) R = H or $CF_3C(O)$ (XIV)

Scheme 12

Intermediates of formula (VI), (VII), (IX), (X), (XI), (XV), (XVI) and formula (XVII) are commercially available or can be prepared by those skilled in the art.

Where necessary or desired, any one or more of the following further steps in any order may be performed :

Compounds of Formula (I) or (III), any subgroup thereof, addition salts, solvates, and stereochemical isomeric forms thereof can be converted into further compounds according to the invention using procedures known in the art.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups. In case the functional groups of intermediate compounds were blocked by protecting groups, they can be deprotected after a reaction step.

Pharmacology

It has been found that the compounds of the present invention modulate the γ-secretase activity. The compounds according to the invention and the pharmaceutically acceptable compositions thereof are therefore useful in the treatment or prevention of Alzheimer's disease (AD), traumatic brain injury, mild cognitive impairment (MCI), senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid, preferably Alzheimer's disease.

As used herein, the term "modulation of γ-secretase activity" refers to an effect on the processing of APP by the γ-secretase-complex. Preferably it refers to an effect in which the overall rate of processing of APP remains essentially as without the application of said compounds, but in which the relative quantities of the processed products are changed, more preferably in such a way that the amount of the Aß42-peptide produced is reduced. For example a different Abeta species can be produced (e.g. Abeta-38 or other Abeta peptide species of shorter amino acid sequence instead of Abeta-42) or the relative quantities of the products are different (e.g. the ratio of Abeta-40 to Abeta-42 is changed, preferably increased).

It has been previously shown that the γ-secretase complex is also involved in the processing of the Notch-protein. Notch is a signaling protein which plays a crucial role in developmental processes (e.g. reviewed in Schweisguth F (2004) Curr. Biol. 14, R129). With respect to the use of γ-secretase modulators in therapy, it seems particularly advantageous not to interfere with the Notch-processing activity of the γ-secretase activity in order to avoid putative undesired side-effects. While γ-secretase inhibitors show side effects due to concomitant inhibition of Notch processing, γ-secretase modulators may have the advantage of selectively decreasing the production of highly aggregatable and neurotoxic forms of Aβ, i.e. Aβ42. Thus, compounds are preferred which do not show an effect on the Notch-processing activity of the γ-secretase-complex.

As used herein, the term "treatment" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting, or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

The invention relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for use as a medicament.

The invention also relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the treatment or prevention of diseases or conditions selected from Alzheimer's disease (AD), traumatic brain injury, mild cognitive impairment (MCI), senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, or Down's syndrome.

In an embodiment, said disease or condition is preferably Alzheimer's disease.

The invention also relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the treatment of said diseases.

The invention also relates to a compound according to the general formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the treatment or prevention, in particular treatment, of γ-secretase mediated diseases or conditions.

The invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the manufacture of a medicament.

The invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the manufacture of a medicament for the modulation of γ-secretase activity.

The invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

The invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the manufacture of a medicament for the treatment of any one of the disease conditions mentioned hereinbefore.

In the invention, particular preference is given to compounds of Formula (I), or any subgroup thereof with a IC_{50} value for the inhibition of the production of Aß42-peptide of less than 1000 nM, preferably less than 100 nM, more preferably less than 50 nM, even more preferably less than 20 nM as determined by a suitable assay, such as the assays used in the Examples below.

The compounds of the present invention can be administered to mammals, preferably humans for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compound of Formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from or a method of preventing warm-blooded animals, including humans, to suffer from any one of the diseases mentioned hereinbefore.

Said methods comprise the administration, i.e. the systemic or topical administration, preferably oral administration, of an effective amount of a compound of Formula (I), a stereoisomeric form thereof and a pharmaceutically acceptable addition salt or solvate thereof, to warm-blooded animals, including humans.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic daily amount would be from about 0.005 mg/kg to 50 mg/kg, in particular 0.01 mg/kg to 50 mg/kg body weight, more in particular from 0.01 mg/kg to 25 mg/kg body weight, preferably from about 0.01 mg/kg to about 15 mg/kg, more preferably

from about 0.01 mg/kg to about 10 mg/kg, even more preferably from about 0.01 mg/kg to about 1 mg/kg, most preferably from about 0.05 mg/kg to about 1 mg/kg body weight. The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutically effect will of course, vary on case-by-case basis, for example with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated.

A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the compounds according to the invention are preferably formulated prior to administration. As described herein below, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

The compounds of the present invention,that are suitable to treat or prevent Alzheimer's disease or the symptoms thereof, may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula (I) and one or more additional therapeutic agents, as well as administration of the compound of Formula (I) and each additional therapeutic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula (I) and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition.

Accordingly, the present invention further provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to Formula (I).

The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

For ease of administration, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. The compounds according to the invention, in particular the compounds according to Formula (I), a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, or any subgroup or combination thereof may be formulated into

various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of Formula (I) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch,

as a spot-on, as an ointment. Acid or base addition salts of compounds of Formula (I) due to their increased water solubility over the corresponding base or acid form, are more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Since the compounds according to the invention are potent orally administrable compounds, pharmaceutical compositions comprising said compounds for administration orally are especially advantageous.

In order to enhance the solubility and/or the stability of the compounds of Formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the compound of formula (I), and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

The following examples illustrate the present invention.

Examples

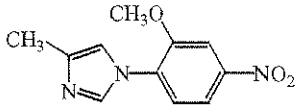
Hereinafter, the term "DCM" means dichloromethane; "MeOH" means methanol; "LCMS" means Liquid Chromatography/Mass spectrometry; "HPLC" means high-performance liquid chromatography; "r.t." means room temperature; "AcOH" means acetic acid; "m.p." means melting point; "RP" means reversed phase; "q.s." means quantum sufficit"; "BDS" means base deactivated silica; "min" means minute(s); "h" means hour(s); "I.D." means internal diameter; "EtOAc" means ethyl acetate; "Ac_2O"

means acetic anhydride; "Et_3N" means triethylamine; "BINAP" means [1,1'-binaphthalene]-2,2'-diylbis-[diphenylphosphine] (racemic); "sat." means saturated; "aq." means aqueous; "Et_2O" means diethyl ether; "EtOH" means ethanol; "eq" means equivalent; "DAPCy catalyst" means (SP-4-1)-bis(acetato-κO)bis(*N*-cyclohexyl-cyclohexanamine)palladium, also named trans-bis(dicyclohexyl-amine)palladium-diacetate; "DME" means 1,2-dimethoxyethane; "DIPE" means diisopropyl ether; "r.m." means reaction mixture(s); "DMA" means *N,N*-dimethylacetamide; "NMP" means *N*-methyl-2-pyrrolidinone, "THF" means tetrahydrofuran, "DMSO" means dimethyl sulfoxide; "w/v' means weight/volume; "DMF" means *N,N*-dimethyl formamide; "DIPEA" means diisopropylethylamine; "KO*t*Bu" means potassium tert-butoxide; "NaOMe" means sodium methoxide; "mCPBA" means meta-chloroperbenzoic acid; "PPh3" means triphenylphosphine; "HBTU" means O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate; "X-phos" means dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine; "DIBAH" means diisobutylaluminum hydride; "KOAc" means potassium acetate; and "$Pd_2(dba)_3$" means tris[μ-[(1,2-η:4,5-η)-(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one]]dipalladium.

A. Preparation of the intermediates

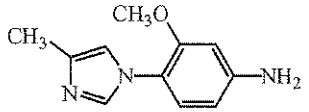
Example A1

a) Preparation of intermediate 1



A mixture of 1-chloro-2-methoxy-4-nitrobenzene (50 g, 0.26 mol), 4-methyl-1*H*-imidazole (43.77 g, 0.53 mol) and K_2CO_3 (36.84 g, 0.26 mol) in DMSO (500 ml) was reacted in an autoclave under a N_2 atmosphere for 6 h at 150 °C. This reaction was performed 3 times with 50 g of 1-chloro-2-methoxy-4-nitrobenzene. Subsequently, the three r.m. were worked up together. The mixture was poured into 6 l of ice-water. The solid was filtered off and washed with H_2O. The solid was dissolved in DCM and this solution was washed with H_2O. The separated organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified over silicagel on a glass filter (eluent: DCM/MeOH from 100/0 to 97/3). The product fractions were collected and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried in the oven. Yield: 48.54 g of **intermediate 1** (26.0 %).

b) Preparation of intermediate 2a and intermediate 2

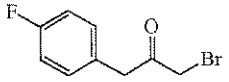


intermediate 2a: free base
intermediate 2: HCl salt (.HCl)

Intermediate 1 (13.2 g, 56.6 mmol) was dissolved in MeOH (250 ml). Pd/C (0.5 g) was added to the solution and the resulting suspension was stirred at 50 °C under H_2 (atmospheric pressure) overnight. After uptake of H_2 (1 eq), the catalyst was filtered off. The organic layer was evaporated, yielding **intermediate 2a** (free base). Intermediate 2a was dissolved in a solution of HCl/EtOH and stirred for 30 min. The solvent was removed *in vacuo*. The residue was crystallized from EtOH with petroleum ether (q.s.) to yield the desired product. Yield: 4.7 g of **intermediate 2** (41.0 %).

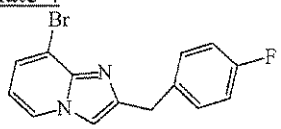
Example A2

a) Preparation of intermediate 3



A solution of bromine (10.49 g, 65.67 mmol) in AcOH (15 ml) was added to a solution of 1-(4-fluorophenyl)- 2-propanone (4.54 g, 29.85 mmol) in AcOH (10 ml) and a 48 % HBr solution (5 ml). The r.m. was stirred for 6 h at r.t. Subsequently, acetone (50 ml) was added and the mixture was stirred overnight at r.t.. The mixture was concentrated *in vacuo* and extracted with DCM. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* overnight. The residue was purified by column chromatography (eluent: EtOAc/heptane 5/95). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 5.00 g of **intermediate 3** (72.5 %).

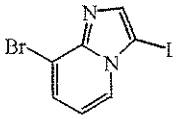
b) Preparation of intermediate 4



A mixture of 3-bromo-2-pyridinamine (3.12 g, 18.03 mmol) and intermediate 3 (5.00 g, 21.64 mmol) in 100 ml EtOH was stirred and heated overnight at 75 °C. The solvents were evaporated *in vacuo* and the residue was partitioned between DCM and a 0.5 N NaOH solution. The separated organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*, to yield 7 g of the crude product. A part of the crude product (3.5 g) was purified by reversed-phase (RP) preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH/CH_3CN]. The desired fractions were collected and worked-up. Yield: 1.70 g of **intermediate 4** (30.9 %).

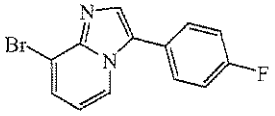
Example A3

a) Preparation of intermediate 5



1-Iodo-2,5-pyrrolidinedione (2.28 g, 10.15 mmol) was added to a solution of 8-bromo-imidazo[1,2-a]pyridine (2 g, 10.15 mmol) in CH_3CN (8 ml). The r.m. was stirred at r.t. for 30 min. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 99/1). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 2.89 g of **intermediate 5** (84.6 %).

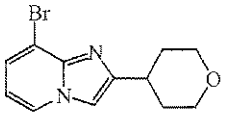
b) Preparation of intermediate 6



A mixture of intermediate 5 (0.577 g, 1.79 mmol), (4-fluorophenyl)boronic acid (275 mg, 1.97 mmol), DAPCy catalyst (52.28 mg, 0.089 mmol) and K_3PO_4 (1.14 g, 5.36 mmol) in EtOH (10 ml) was stirred at r.t. for 2 h. The solids were filtered off and the filtrate was evaporated *in vacuo*. The residue was taken up in DCM, washed with a sat. aq. $NaHCO_3$ solution, dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo* to yield a residue that was purified by flash chromatography over silicagel (eluent: DCM/MeOH (NH_3) from 100/0 to 98/2). The product fractions were combined and the solvent was evaporated *in vacuo*. Yield: 0.101 g of **intermediate 6** (19.4 %).

Example A4

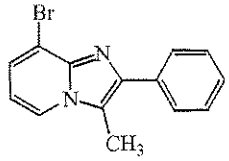
a) Preparation of intermediate 7



3-Bromo-2-pyridinamine (0.504 g, 2.9 mmol) and K_2CO_3 (0.392 g, 2.84 mmol) were added to a solution of 2-bromo-1-(tetrahydro-2*H*-pyran-4-yl)ethanone (0.784 g, 3.8 mmol) in EtOH (10 ml). The r.m. was stirred at 75 °C for 4 h. and was then cooled to r.t. Subsequently, DCM was added and the solution was washed with a sat. aq. $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography over silicagel (eluent: mixtures of hexane:EtOAc (ratios: 15:1; 10:1; 5:1; 1:1)). The desired fractions were collected and worked up. Yield 0.096 g of **intermediate 7** (12.0 %).

Example A5

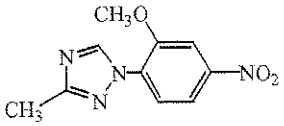
a) Preparation of intermediate 8



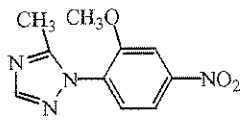
A mixture of 3-bromo-2-pyridinamine (1 g, 5.78 mmol) and 2-bromo-1-phenyl-1-propanone (1.48 g, 6.94 mmol) in EtOH (20 ml) was stirred and heated at 100 °C for 2 days. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (eluent: DCM/MeOH (NH_3) from 100/0 to 98/2). The product fractions were collected and the solvent was evaporated. The residue was purified by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH]. The product fractions were collected and worked up. Yield: 0.850 g of **intermediate 8** (51.2 %).

Example A6

a) Preparation of intermediate 9 and intermediate 10



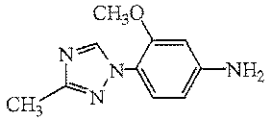
intermediate 9



intermediate 10

A mixture of 1-fluoro-2-methoxy-4-nitrobenzene (821.414 mg, 4.8 mmol), 5-methyl-1*H*-1,2,4-triazole (800 mg, 9.63 mmol), K_2CO_3 (4.8 mmol) and DMSO (8 ml) was stirred at 120 °C for 1 h. After cooling to r.t., the r.m. was poured into ice H_2O. The solid was filtered off, washed with H_2O and dried *in vacuo* at 50 °C. Yield: 0.554 g of **intermediate 9** (49 %). The aq. layer was sat. with NaCl, extracted with DCM and the organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography over silicagel (eluent: DCM). The desired fraction was collected and the solvent was evaporated *in vacuo*. Yield: 0.147 g of **intermediate 10** (13 %).

b) Preparation of intermediate 11

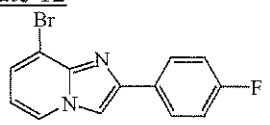


MeOH (50 ml) was added to Pd/C 10 % (150 mg) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (1 ml) and intermediate 9 (550 mg, 2.35 mmol) were added. The r.m. was stirred at 25 °C under a H_2 atmosphere until 3 eq of H_2 was absorbed. The catalyst was filtered off over diatomaceous earth. The filtrate

was evaporated and the residue was suspended in DIPE, filtered off and dried *in vacuo*. Yield : 0.350 g of **intermediate 11** (73.0 %).

Example A7

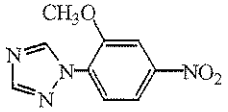
a) Preparation of intermediate 12



A mixture of 3-bromo-2-pyridinamine (50 g, 289 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (75.3 g, 346.8 mmol) in EtOH (300 ml) was heated at 75 °C for 17 h. The r.m. was cooled to r.t.. The formed precipitate was filtered off, washed with EtOH (50 ml) and dried *in vacuo*, yielding fraction 1. The corresponding filtrate was concentrated to a volume of 100 ml. EtOH (20 ml) and DIPE (100 ml) were added to the concentrate resulting in precipitation of the product. The solids were filtered off, washed with a mixture of DIPE (50 ml) and EtOH (10 ml), and dried *in vacuo*, yielding fraction 2. Fractions 1 and 2 were combined and stirred for 30 min in a sat. aq. $NaHCO_3$ solution (500 ml). This mixture was extracted with DCM (500 ml). The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated *in vacuo*. The residue was recrystallized from EtOAc. The solid was filtered off and dried *in vacuo*. Yield: 46.5 g of **intermediate 12** (55.3 %).

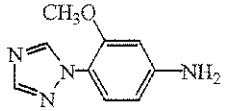
Example A8

a) Preparation of intermediate 13



A mixture of 1-fluoro-2-methoxy-4-nitrobenzene (7 g, 40 mmol), 1*H*-1, 2,4-triazole (4.28 g, 60 mmol), K_2CO_3 (8.31g, 60 mmol) and DMF (50 ml) was stirred for 1 h at 75 °C. The solvent was evaporated and the residue was taken up in EtOAc/H_2O. The aq. layer was extracted 3 times with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. Yield: 4.4 g of **intermediate 13**. The crude product was used as such in the next reaction step.

b) Preparation of intermediate 14

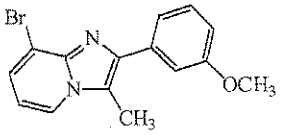


MeOH (50 ml) was added to Pd/C 10 % (300 mg) under a N_2 atmosphere. A 0.4 % thiophene solution in DIPE (2 ml) and intermediate 13 (3.13 g, 11.4 mmol) was added. The r.m. was stirred at 25 °C under a H_2 atmosphere until 3 eq of H_2 was absorbed. The

catalyst was filtered off over diatomaceous earth and the filtrate was evaporated. The residue was purified by flash chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 98/2). The desired fraction was collected and the solvent was evaporated *in vacuo*. Yield: 1.4 g of **intermediate 14** (64.8 %).

Example A9

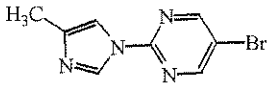
a) Preparation of intermediate 15



3-Bromo-2-pyridinamine (24.9 g, 144 mmol), 2-bromo-1-(3-methoxyphenyl)-1-propanone (42 g, 172.8 mmol) and 250 ml *n*-butanol were heated at reflux temperature for 3 nights. The mixture was separated between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 98/2. The purest fractions were concentrated under reduced pressure and the residue was crystallized from DIPE. Yield: 19 g of **intermediate 15** (41.6 %).

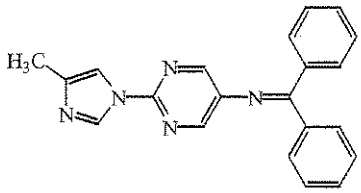
Example A10

a) Preparation of intermediate 16



A mixture of 4-bromo-2-chloropyrimidine (5 g, 25.8 mmol), 4-methyl-1*H*-imidazole (4.25 g, 51.7 mmol) and K_2CO_3 (10.72 g, 77.5 mmol) in NMP (100 ml) was heated at 85 °C overnight. The mixture was separated between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. H_2O was added to the residue and the resulting precipitate was collected by filtration and dried *in vacuo*. Yield: 4.7 g of **intermediate 16** (76 %).

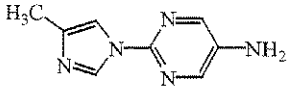
b) Preparation of intermediate 17



A mixture of 2-methyl-2-propanol, sodium salt (1.688 g, 17.6 mmol), BINAP (195 mg, 0.314 mmol), $Pd_2(dba)_3$ (287 mg, 0.314 mmol), intermediate 16 (3 g, 12.5 mmol) and benzophenone imine (2.27 g, 12.5 mmol) in toluene (40 ml; previously deoxygenated) was stirred and heated at 120°C for 4 h. The mixture was separated between DCM and

H_2O. The organic phase was separated, dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. Yield: 3.4 g of crude **intermediate 17**.

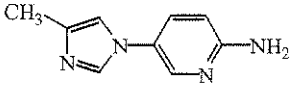
c) Preparation of intermediate 18



A 1 N aq. HCl solution (11 ml, 11 mmol) was added to a solution of intermediate 17 (3.4 g, 4.1 mmol) in THF (10 ml). The r.m. was stirred at r.t. for 2 h. The solvent was evaporated *in vacuo* and the residue was separated between DCM and H_2O, basified with an aq. NH_4OH solution to pH 10. The organic phase was separated, dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The product was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 98/2 to 95/5). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 0.36 g of **intermediate 18** (16 % over 2 steps).

Example A11

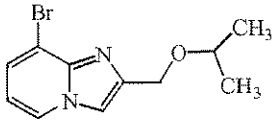
a) Preparation of intermediate 19



CuI (8.25 g, 43 mmol) was added under a N_2 flow to a solution of 5-bromo-pyridin-2-ylamine (5 g, 28.9 mmol), 4-methyl-1*H*-imidazole (5.9 g, 72 mmol), and Cs_2CO_3 (9.4 g, 28.9 mmol) in DMSO (100 ml). The r.m. was heated at 130 °C for 2 days, then cooled, and CH_3CN was added. A blue precipitate was filtered off. The filtrate was concentrated, and the residue was separated between DCM and H_2O. The organic phase was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH 98/2 to 95/5). The product fractions were collected and the solvent was evaporated. Yield: 0.628 g of **intermediate 19**. The aq. layer was concentrated to precipitate more product, which was filtered off and dried *in vacuo*. Yield: 0.16 g of **intermediate 19** (total yield 15 %).

Example A12

a) Preparation of intermediate 20

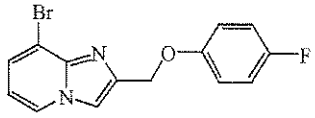


8-Bromo-2-chloromethyl-imidazo[1,2-a]pyridine hydrochloric acid salt (0.3 g, 1.06 mmol), and 2-propanol (0.122 ml g, 1.59 mmol) were dissolved in DMF (3 ml) and sodium hydride (60 % dispersion in mineral oil, 0.106 g, 2.3 mmol) was added. The r.m. was stirred at r.t. overnight. The mixture was separated between EtOAc and H_2O.

The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash column chromatography over silicagel (eluent: hexane/EtOAc from 91/9 to 83/17). The purest fractions were concentrated under reduced pressure. Yield: 0.11 g of **intermediate 20** (44 %).

Example A13

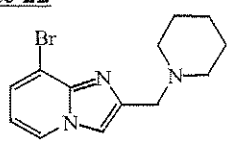
a) Preparation of intermediate 21



8-Bromo-2-chloromethyl-imidazo[1,2-a]pyridine hydrochloric acid salt (0.14 g, 0.5 mmol), 4-fluoro-phenol (0.072 g, 0.64 mmol), and Cs_2CO_3 (0.419 g, 1.29 mmol) in DMF (1.3 ml) were stirred at 45 °C overnight. The mixture was separated between EtOAc and H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: hexane/EtOAc from 100/1 to 83/17). The purest fractions were concentrated under reduced pressure. Yield: 0.111 g of **intermediate 21** (69 %).

Example A14

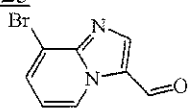
a) Preparation of intermediate 22



8-Bromo-2-chloromethyl-imidazo[1,2-a]pyridine hydrochloric acid salt (0. 4 g, 1.42 mmol), piperidine (0.14 ml, 1.56 mmol), and diisopropylethylamine (0.367 ml, 2.13 mmol) in DMA (5 ml) were stirred at 50 °C overnight. The mixture was separated between EtOAc and a sat. aq. $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 95/5 to 91/9). The purest fractions were concentrated under reduced pressure. Yield: 0.136 g of **intermediate 22** (33 %).

Example A15

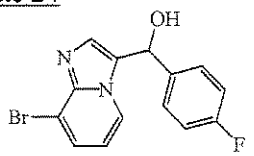
a) Preparation of intermediate 23



Phosphoroxychloride (0.59 ml, 6.34 mmol) was added to DMF (7 ml) at 0 °C and the mixture was stirred for 0.5 h at this temperature. 8-Bromo-imidazo[1,2-a]pyridine (0.5 g, 2.53 mmol) was added at 0 °C, and the r.m. was stirred at r.t. overnight. The r.m. was

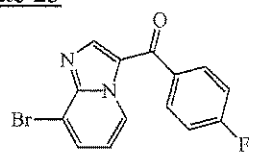
poured into an ice-cooled aq. Na_2CO_3 solution and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was triturated with DIPE. The solid was collected and air dried. Yield: 0.45 g of **intermediate 23** (78 %).

b) Preparation of intermediate 24



A solution of 1-Bromo-4-fluoro benzene (0.5 g, 2.86 mmol) in THF (6.4 ml) was added to a suspension of magnesium (63 mg, 2.6 mmol) and ethyl magnesiumchloride (2 drops of a 1 M solution in THF) in THF (6 ml) at r.t. under a N_2 atmosphere. The mixture was heated at reflux for 10 min., then cooled to r.t. The resulting mixture was added to a solution of intermediate 23 (0.234 g, 1.04 mmol) in THF (0.9 ml), and the r.m. was stirred at r.t. overnight. The r.m. was poured in a sat. aq. NH_4Cl solution and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: EtOAc/MeOH from 83/17 to 50/50). The purest fractions were concentrated under reduced pressure. Yield: 0.07 g of **intermediate 24** (21 %).

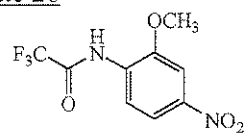
c) Preparation of intermediate 25



A solution of $Na_2Cr_2O_7$ in aq. H_2SO_4 (Jones reagent) (0.092 ml, 0.44 mmol) was added to a solution of intermediate 24 (0.07 g, 0.22 mmol) in acetone (3 ml), and the r.m. was stirred at r.t. for 15 min. Et_2O (1.5 ml) and 2-propanol (0.046 ml) were added, and the green solid was filtered off. The filtrate was separated between EtOAc and a sat. aq. $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 0.07 g of **intermediate 25** which was used as such in the next step.

Example A16

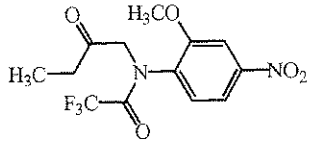
a) Preparation of intermediate 26



Trifluoroacetic acid anhydride (41.4 ml, 0.297 mol) was added dropwise to a solution of 2-methoxy-4-nitro-aniline (50 g, 0.297 mol) in pyridine (125 ml). The r.m. was

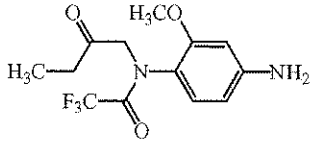
stirred at r.t. for 1 h. and then separated between DCM and ice-water. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was triturated with heptane. The solid was collected and air dried. Yield: 75 g of **intermediate 26** (95 %).

b) Preparation of intermediate 27



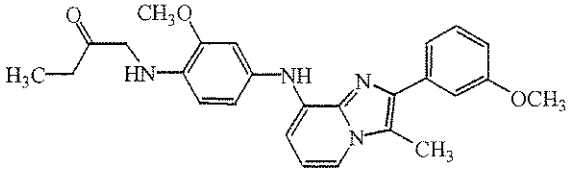
1-Bromo-butan-2-one (5 g, 31.8 mmol) was added dropwise to a suspension of intermediate 26 (4.2 g, 15.9 mmol), potassium iodide (0.264 g, 1.59 mmol) and Cs_2CO_3 (10.4 g, 31.8 mmol) in DMF (320 ml). The formed yellow precipitate was filtered off, washed with H_2O, and dried *in vacuo*. Yield: 4.2 g of **intermediate 27** (79 %).

c) Preparation of intermediate 28



MeOH (150 ml) was added to Pd/C 10 % (1 g) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (2 ml) and intermediate 27 (4 g, 12 mmol) were added. The r.m. was stirred at 25 °C under a H_2 atmosphere until 3 eq of H_2 was absorbed. The catalyst was filtered off over diatomaceous earth and the filtrate was evaporated. The residue was separated between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. Yield: 2.7 g of **intermediate 28** (74 %).

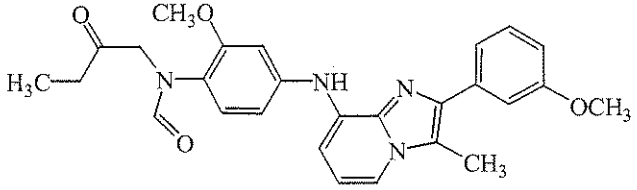
d) Preparation of intermediate 29



2-Methyl-2-propanol, sodium salt (0.99 g, 10.3 mmol), BINAP (0.12 g, 0.193 mmol), palladium(II) diacetate (29 mg, 0.13 mmol) and intermediate 28 (1.18 g, 3.87 mmol) were added to a solution of intermediate 15 (818 mg, 2.58 mmol) in toluene (15 ml) and the mixture was purged with N_2 for 5 min. The r.m. was stirred and heated at 100 °C overnight under a N_2 atmosphere. H_2O was added and the mixture was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by RP preparative HPLC [RP Shandon Hyperprep®

C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH/CH_3CN]. The product fractions were collected and worked up. Yield: 236 mg of **intermediate 29** (21 %).

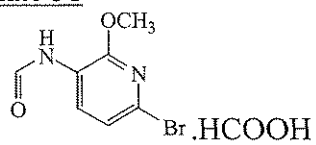
e) Preparation of intermediate 30



A mixture of formic acid (0.2 ml, 2.07 mmol) and Ac_2O (3 ml) was stirred at 0°C for 0.5 h. Subsequently, a solution of intermediate 29 (230 mg, 0.52 mmol) in DCM (6 ml) was added dropwise and the resulting r.m. was stirred at r.t. for 1h. The r.m. was neutralized to pH 7 with an aq. 1 N NaOH solution, and then extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Yield: 250 mg of **intermediate 30** which was used as such in the next step.

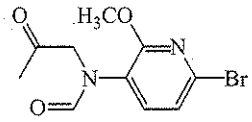
Example A17

a) Preparation of intermediate 31



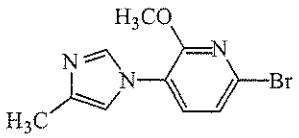
A mixture of formic acid (12.8 ml, 340 mmol) and Ac_2O (8.54 ml, (91 mmol) was stirred at r.t. for 40 min. A solution of 3-amino-6-bromo-2-methoxy-pyridine (5 g, 24.6 mmol) in THF (30 ml) was added dropwise and the resulting r.m. was stirred overnight at 60 °C. The r.m. was cooled and poured into ice-water. The precipitate was filtered off, washed (H_2O) and dried. Yield: 5.2 g of **intermediate 31** (76 %; obtained as a formic acid salt .HCOOH).

b) Preparation of intermediate 32



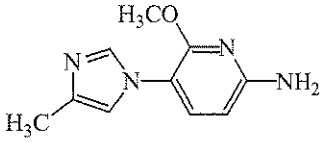
1-Chloro-propan-2-one (4.34 g, 46.9 mmol) was added dropwise to a mixture of intermediate 31 (5.2 g, 18.8 mmol), KI (0.343 g, 2.06 mmol) and Cs_2CO_3 (21.4 g, 65.9 mmol) in DMF (50 ml). The r.m. was stirred at r.t. overnight and was then poured into ice-water. The mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was suspended in DIPE. The precipitate was filtered off, washed with DIPE and dried. Yield: 4.43 g of **intermediate 32** (82 %).

c) Preparation of intermediate 33



Intermediate 32 (4.4 g, 15.3 mmol) was added to a mixture of CH_3COONH_4 (5.41 g, 70.2 mmol) in AcOH (10 ml). The r.m. was heated at reflux for 1 h. The r.m. was cooled to r.t. and poured into a mixture of ice-water and EtOAc. The mixture was basified with a 50 % w/v aq. NaOH solution to pH 9. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The solid was used as such in the next reaction step. Yield: 3.78 g of crude **intermediate 33**.

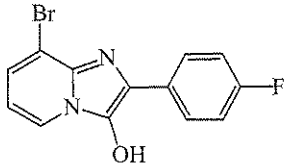
d) Preparation of intermediate 34



2-Methyl-2-propanol sodium salt (0.717 g, 7.46 mmol), BINAP (464 mg, 0.746 mmol), $Pd_2(dba)_3$ (342 mg, 0.373 mmol), intermediate 33 (1.0 g, 3.73 mmol) and benzophenone imine (0.845 g, 4.66 mmol) in toluene (20 ml; previously deoxygenated) were stirred and heated at 100 °C for 2 h under microwave conditions. The mixture was cooled, and the solvent was removed *in vacuo*. THF (50 ml) and a 1 N aq. HCl solution (50 ml) were added to the residue and the mixture was stirred at r.t. for 1 h. The r.m. was basified with a 10 % aq. Na_2CO_3 solution and extracted with EtOAc. The organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The product was purified by flash column chromatography over silica gel (eluent: DCM/MeOH from 100/0 to 95/5). The product fractions were collected and the solvent was evaporated. Yield: 0.6 g of **intermediate 34** (52 % yield over 2 reaction steps).

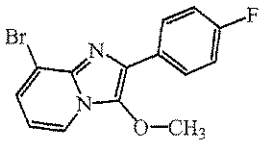
Example A18

a) Preparation of intermediate 35



BF_3 etherate (0.154 ml, 1.32 mmol) was added to a mixture of 4-fluorophenylglyoxal hydrate (4.5 g, 26.5 mmol) and 2-amino-3-bromopyridine (4.72 g, 26.5 mmol) in DCM (100 ml). The r.m. was stirred at r.t. for 6 h. The resulting precipitate was filtered off and dried *in vacuo*. Yield: 4 g of **intermediate 35** (49 %).

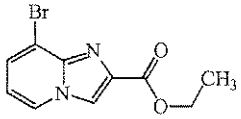
b) Preparation of intermediate 36



NaH (60 % in mineral oil, 414 mg, 10.3 mmol) was added to an ice-cooled solution of intermediate 35 (1.06 g, 3.45 mmol) in DMF (50 ml). The r.m. was stirred at 0 °C for 15 min, then CH_3I (0.258 ml, 4.14 mmol) was added and the resulting r.m. was stirred at r.t. overnight. The r.m. was quenched with H_2O, and then concentrated *in vacuo*. The residue was partitioned between DCM and H_2O, the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: *n*-heptane/EtOAc from 100/0 to 50/50). The product fractions were collected and the solvent was evaporated *in vacuo*. The residue was suspended in DIPE and dried *in vacuo*. Yield: 445 mg of **intermediate 36** (40 %).

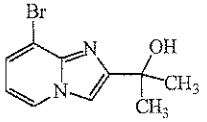
Example A19

a) Preparation of intermediate 37



2-Amino-3-bromopyridine (12.0 g, 69 mmol) and 3-bromo-pyruvic acid ethyl ester (20.0 g, 0.104 mol) were dissolved in EtOH and heated to reflux for 60 h. The solution was cooled to r.t. and the solvent was evaporated. The residue was dissolved in EtOAc and washed with sat. aq. $NaHCO_3$, H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH]. The product fractions were collected and worked up. Yield: 10 g of **intermediate 37** (50 %).

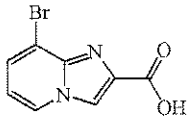
b) Preparation of intermediate 38



Intermediate 37 (350 mg, 1.3 mmol) was added to a refluxing solution of CH_3MgBr (3 M in THF, 0.91 ml, 2.73 mmol) in THF (10.5 ml), and refluxing was continued for 15 min. The solution was cooled to r.t. Then H_2O was added and the solution was stirred for 5 min. The solution was acidified with aq. 1 N HCl until pH 2. The THF was evaporated under reduced pressure. A sat. K_2CO_3 solution was added until neutral pH. The mixture was extracted twice with ether. The combined organic layers were dried

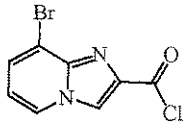
($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified via flash column chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 97.5/2.5). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 240 mg of **intermediate 38** (72 %).

c) Preparation of intermediate 39



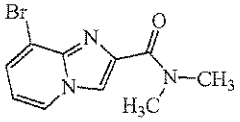
Intermediate 37 (2.02 g, 7.4 mmol) was dissolved in a mixture of dioxane/ H_2O (16 ml/4 ml) and the mixture was cooled on an ice-bath. LiOH (355 mg, 14.8 mmol) was added and the resulting mixture was stirred for 20 h at r.t. The volatiles were evaporated under reduced pressure. The mixture was cooled using an ice-bath, and was acidified with an aq. 1N HCl solution until pH 4. The precipitate was filtered off, washed with cold water (10 ml), and dried *in vacuo*. Yield 1.5 g of **intermediate 39** (88 %).

d) Preparation of intermediate 40



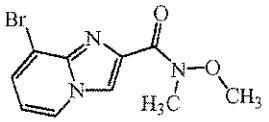
$SOCl_2$ (15 ml, 206 mmol) was added slowly to intermediate 39 (1.6 g, 6.6 mmol) while cooling on ice. The resulting solution was heated to reflux temperature for 4 h, and was then cooled to r.t. and concentrated *in vacuo*. The residue was triturated with DIPE and finally the product was dried. Yield: 1.7 g of **intermediate 40** (99 %).

e) Preparation of intermediate 41



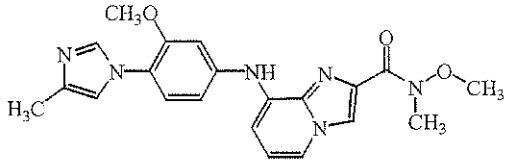
A 2 M solution of dimethylamine in THF (0.58 ml, 1.16 mmol) was added to an ice-cooled suspension of intermediate 40 (300 mg, 1.16 mmol) in THF (5 ml). The reaction vial was sealed off and stirred for 3 h at r.t. Another equivalent of dimethylamine (0.58 ml, 1.16 mmol) was added and the resulting mixture was stirred overnight. The solvent was evaporated. Yield: 151 mg of **intermediate 41** (49 %).

f) Preparation of intermediate 42



A suspension of intermediate 39 (322 mg, 1.34 mmol) and carbonyldiimidazole (238 mg, 1.47 mmol) in THF (11 ml) was stirred at r.t. for 2 h. DIPEA (0.233 ml, 1.34 mmol) was added and the resulting mixture was stirred for 30 min. at r.t. Then DMF (2 ml) was added to the suspension and the mixture was stirred for 60 h at r.t. The r.m. was cooled to 0 °C and O,N-dimethyl-hydroxylamine (143 mg, 1.47 mmol) was added. The mixture was stirred for 20 h at r.t. The solvents were evaporated under reduced pressure. The residue was dissolved in DCM and washed 3 times with H_2O. The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified via flash column chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 99/1). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 216 mg of **intermediate 42** (57 %).

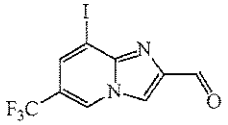
g) Preparation of intermediate 43



Intermediate 2a (80 mg, 0.396 mmol), $Pd_2(dba)_3$ (40 mg, 0.044 mmol), X-phos (42 mg, 0.088 mmol) and Cs_2CO_3 (430 mg, 1.32 mmol) were added to a solution of intermediate 42 (125 mg, 0.44 mmol) in 2-methyl-2-propanol (10 ml) under a N_2 atmosphere. The r.m. was heated at 90 °C for 22 h. Then, H_2O was added and the mixture was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 97/3). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 71 mg of **intermediate 43** (40 %).

Example A20

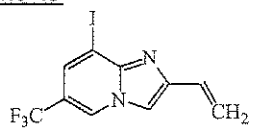
a) Preparation of intermediate 44



DIBAH (1 M in hexane, 2.6 ml, 2.6 mmol) was added to a cooled (-78 °C) solution of ethyl 8-iodo-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylate (1.0 g, 2.6 mmol) in THF (30 ml). The r.m. was stirred at -78 °C for 1 h, then another eq of DIBAH (1 M in hexane) was added and stirring was continued at -78 °C for 1 h. The r.m. was quenched with H_2O (5 ml). The mixture was partitioned between DCM and H_2O. The organic layer was separated, dried ($MgSO_4$), and filtered. MnO_2 (4,53 g, 52 mmol) was added and the r.m. was stirred at r.t. overnight. The mixture was filtered over a pad of

diatomaceous earth, and the filtrate was concentrated *in vacuo*. Yield: 0.51 g of **intermediate 44** (used as such in the next reaction step).

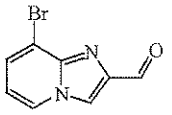
b) Preparation of intermediate 45



A solution of KO*t*Bu (0.505 g, 4.5 mmol) and methyltriphenylphosphonium bromide (1.6 g, 4.5 mmol) in Et_2O (15 ml) was stirred at 0 °C for 1 h. A solution of intermediate 44 (0.51 g, 1.5 mmol) in Et_2O (10 ml) was added at 0°C, and the r.m. was stirred for 18 h at r.t. The r.m. was filtered over diatomaceous earth and the filtrate was concentrated *in vacuo*. The residue was reacted again under the same reaction conditions and worked-up. The now obtained residue was purified by column chromatography over silicagel (eluent: DCM). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 55 mg of **intermediate 45** (11 %).

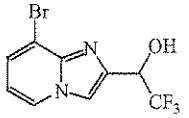
Example A21

a) Preparation of intermediate 46



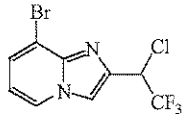
1,1,3-Trichloroacetone (11.3 mL, 88.7 mmol) in DME (10 ml) was added dropwise to a solution of 2-amino-3-bromopyridine (10.0 g, 57.8 mmol) in DME (90 ml) and heated at 40 °C overnight. The r.m. was then heated at 80 °C for 4 h, cooled to r.t., and DIPEA (10 ml, 57.8 mmol) was added. Subsequently, the r.m. was heated at 80 °C for 60 h. The mixture was cooled to r.t. and DCM and H_2O were added. The mixture was made alkaline by the addition of K_2CO_3, then filtered, and the layers were separated. The aq. layer was extracted with DCM, and the combined organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified via column chromatography over silicagel (eluent: DCM). The product fractions (a mixture of intermediate 46 and the dichloro precursor) were collected and the solvent was evaporated *in vacuo*. A suspension of $CaCO_3$ (13.1 g, 131 mmol) in H_2O (200 ml) was added to the residue, and the r.m. was heated at 90 °C for 1 h, and then overnight at r.t. The mixture was extracted with DCM. The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified via column chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 97.5/2.5). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 7.25 g of **intermediate 46** (56 %).

b) Preparation of intermediate 64



Trimethyl-trifluoromethyl-silane (8.25 ml, 55.8 mmol) was added to a degassed and ice-cooled sol. of intermediate 46 (6.1 g, 27.1 mmol) in DME (92 ml). CsF (823 mg, 5.4 mmol) was added to this mixture, and the r.m. was stirred ar r.t. for 30 min. Another eq of trimethyl-trifluoromethyl-silane was added, and the r.m. was stirred at r.t. for 1 h. The r.m. was cooled on an ice-bath, and a 1 N aq. HCl sol. (40 ml) was added and the mixture was stirred at r.t. for 5 h. Additional a 1 N aq. HCl sol. (10 ml) was added and the mixture was stirred at 45 °C overnight. The mixture was partly concentrated *in vacuo* to remove the organic solvents. H_2O was added, and the mixture was cooled and basified with a sat. aq. $NaHCO_3$ solution to pH 8. The resulting solids were filtered off, washed with H_2O and dried *in vacuo*. Yield: 5.9 g of **intermediate 64** (74 %).

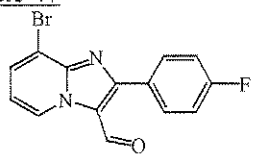
c) Preparation of intermediate 65



$SOCl_2$ (0.44 ml, 6 mmol) and pyridine (0.244 ml, 3 mmol) were added to a solution of intermediate 64 (490 mg, 1.51 mmol) in DCM (10 ml) while cooling on ice. The resulting solution was heated at 45 °C overnight, and was then cooled to r.t. and concentrated *in vacuo*. The residue was partitioned between DCM and an aq. K_2CO_3 solution. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*.Yield: 0.55 g of crude **intermediate 65** which was used as such in the next reaction step.

Example A22

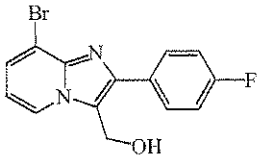
a) Preparation of intermediate 47



Phosphoroxychloride (1.25 ml, 13.7 mmol) was added to DMF (3.5 ml) at 0 °C and the mixture was stirred for 30 min at 0 °C. Intermediate 12 (1 g, 3.44 mmol) was added at 0 °C, and the r.m. was stirred at r.t. and DMF (5 ml) was added. The r.m. was stirred at r.t. overnight. The r.m. was poured on ice and the mixture was neutralized by adding $NaHCO_3$. The mixture was extracted with DCM. The organic layer was dried ($MgSO_4$),

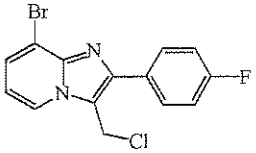
filtered and the solvent was evaporated *in vacuo*. The residue was triturated with DIPE. The solid was collected and dried. Yield: 0.625 g of **intermediate 47** (57 %).

b) Preparation of intermediate 48



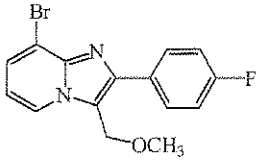
$NaBH_4$ (28 mg, 0.75 mmol) was added to a solution of intermediate 47 (200 mg, 0.63 mmol) in MeOH (5 ml) and THF (2 ml). The r.m. was stirred at r.t for 15 min and then the solvents were removed. The residue was partitioned between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. Yield: 90 mg of **intermediate 48** (45 %).

c) Preparation of intermediate 49



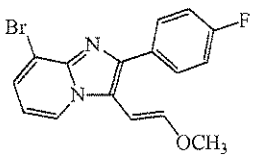
$SOCl_2$ (33 mg, 0.28 mmol) was added to intermediate 48 (90 mg, 0.28 mmol) in DCM (2 ml). The r.m. was stirred at r.t for 30 min, then an aq.sat. $NaHCO_3$ sol. was added, and the organic layer was separated. The organic layer was filtered over diatomaceous earth and the filtrate was concentrated. Yield: 90 mg of **intermediate 49** (95 %).

d) Preparation of intermediate 50



A 0.5 M NaOMe solution in MeOH (0.64 ml, 0.32 mmol) was added to a solution of intermediate 49 (90 mg, 0.265 mmol) in MeOH (2 ml). The r.m. was stirred at r.t for 30 min and then the solvents were removed *in vacuo*. The residue was partitioned between DCM and H_2O. The organic layer was filtered over diatomaceous earth and the filtrate was concentrated. The residue was triturated with DIPE and dried *in vacuo*. Yield: 60 mg of **intermediate 50** (67 %).

e) Preparation of intermediate 51

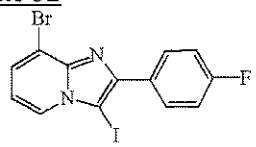


E/Z mixture

A solution of KO*t*Bu (0.87 g, 7.74 mmol) in THF (7 ml) was added to a suspension of methoxymethylenetriphenylphosphonium chloride (1.53 g, 4.47 mmol) in THF (3 ml) at -15 °C. The r.m. was stirred for 30 min. Subsequently, a solution of intermediate 47 (0.95 g, 3 mmol) in THF (3 ml) was added at 5 °C and the r.m. was stirred for 1h at r.t. The r.m. was partitioned between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography over silicagel (eluent: DCM/MeOH 99/1). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 700 mg of **intermediate 51** (68 %; E/Z mixture).

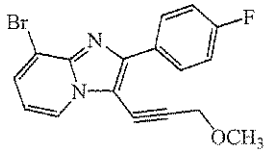
Example A23

a) Preparation of intermediate 52



1-Iodo-2,5-pyrrolidinedione (2.32 g, 10.3 mmol) was added to intermediate 12 (2 g, 6.87 mmol) in DCM (25 ml). The r.m. was stirred at r.t. for 1 h and was then washed with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was triturated with DIPE, and dried *in vacuo*. Yield: 1.2 g of **intermediate 52** (42 %).

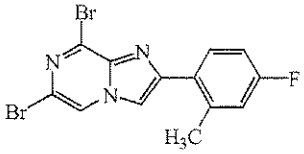
b) Preparation of intermediate 53



A mixture of intermediate 52 (600 mg, 1.44 mmol), 3-methoxy-propyne (111 mg, 1.58 mmol), $PdCl_2(PPh_3)_2$ (40 mg, 0.057 mmol), CuI (10 mg, 0.053 mmol) in Et_3N (6 ml) was stirred at 50 °C for 20 h under a N_2 atmosphere. The mixture was partitioned between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography over silicagel (eluent: DCM/MeOH 99/1). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 170 mg of **intermediate 53** (33 %).

Example A24

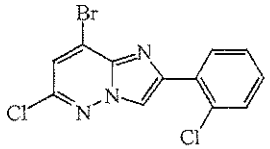
Preparation of intermediate 54



A mixture of 3,5-dibromo-pyrazin-2-ylamine (5 g, 19.8 mmol) and 2-bromo-1-(4-fluoro-2-methyl-phenyl)-ethanone (13.7 g, 59.3 mmol) was heated at 100 °C for 76 h. The solvent was removed under reduced pressure, and the residue was purified via flash column chromatography over silicagel (eluent: *n*-heptane/EtOAc 90/10). The product fractions were collected and the solvent was evaporated *in vacuo*. The residue was suspended in DIPE and dried *in vacuo*. Yield: 3.1 g of **intermediate 54** (41 %).

Example A25

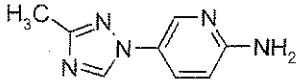
Preparation of intermediate 55



A mixture of 4-bromo-6-chloro-pyridazin-3-ylamine (5 g, 24 mmol) and 2-bromo-1-(2-chloro-phenyl)-ethanone (10 g, 43 mmol) in 2-propanol (20 ml) was heated at 100 °C overnight. The solvent was removed under reduced pressure, and the residue was triturated with DIPE. The solid was dissolved in DCM and washed with an aq. sat. $NaHCO_3$ sol. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified via flash column chromatography over silicagel (eluent: DCM/MeOH 95/5). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 3.1 g of **intermediate 55** (38 %).

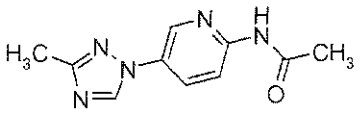
Example A26

a) Preparation of intermediate 56



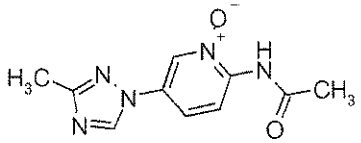
CuI (1.71 g, 8.9 mmol) and N,N'-dimethylethylenediamine (1.91 ml, 17.92 mmol) were added to a mixture of 2-amino-5-iodopyridine (5.03 g, 22.4 mmol), 3-methyl-1*H*-1,2,4-triazole (2.42 g, 29.1 mmol) and Cs_2CO_3 (14.60 g, 44.81 mmol) in DMF (40 ml). The r.m. was heated at 110 °C for 7 h., the r.m. was cooled, EtOAc was added and the mixure was washed with H_2O. The H_2O layer was extracted 5 times with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH/CH_3CN]. The product fractions were collected and the solvent was evaporated. Yield: 1.5 g of **intermediate 56** (38 %).

b) Preparation of intermediate 57



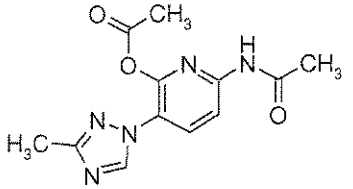
Intermediate 56 (3.3 g, 18.8 mmol) was dissolved in THF (20 ml). Et_3N (13.1 ml, 94.2 mmol) and Ac_2O (17.8 ml, 188.4 mmol) were added. The r.m. was stirred at 65 °C for 18 h. The r.m. was cooled to r.t. and concentrated *in vacuo*. The residue was suspended in DIPE. The resulting solid was filtered off, washed with DIPE, and dried. Yield: 3.25 g of **intermediate 57** (79 %).

c) Preparation of intermediate 58



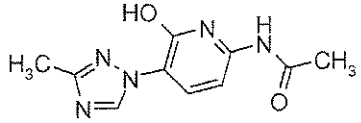
Intermediate 57 (10 g, 46.0 mmol) was dissolved in DCM (500 ml). mCPBA (14.75 g, 59.84 mmol) was added to the solution. The r.m. was stirred at r.t. for 18 h. DCM and a solution of 10 % $NaHCO_3$ in H_2O was added. The organic phase was separated, and washed 2 times with a solution of 10 % $NaHCO_3$ in H_2O. The combined aq. layers were extracted 10 x with DCM. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 10.1 g of **intermediate 58** (94 %).

d) Preparation of intermediate 59



Intermediate 58 (10.1 g, 43.3 mmol) was dissolved in Ac_2O (307 ml, 3.25 mol). The r.m. was stirred at 80 °C for 2 h. The r.m. was cooled to r.t. and concentrated *in vacuo*. The residue was suspended in DIPE. The resulting solid was filtered off. Yield: 10.5 g of crude **intermediate 59**, which was used as such in the next reaction step.

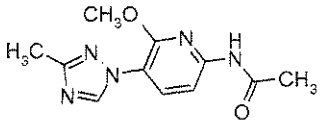
e) Preparation of intermediate 60



Intermediate 59 (2.5 g, 9.1 mmol) and K_2CO_3 (1.26 g, 9.1 mmol) were added to MeOH (30 ml). The r.m. was stirred at r.t. for 1 h. The residue was purified without

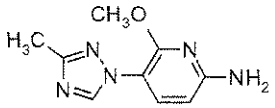
evaporation of the solvent by flash column chromatography over silica gel (eluent: DCM/MeOH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated *in vacuo*. The residue was suspended in DIPE. The solid was filtered off, washed with DIPE, and dried. Yield: 1 g of **intermediate 60** (47 %).

f) Preparation of intermediate 61



Intermediate 60 (1 g, 4.28 mmol), CH_3I (0.4 ml, 6.43 mmol) and Ag_2CO_3 (1.18 g, 4.29 mmol) were stirred in DMF (50 ml) at 60 °C for 4 h. The r.m. was cooled to r.t. and filtered over diatomaceous earth. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (eluent: DCM/EtOAc from 100/0 to 0/100). The product fractions were collected and the solvent was evaporated. Yield: 450 mg of **intermediate 61** (42 %).

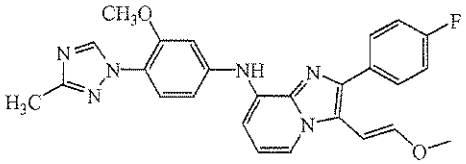
g) Preparation of intermediate 62



Intermediate 61 (1.1 g, 4.45 mmol) was dissolved in MeOH (120 ml) and a 10 % NaOH in H_2O (30 ml) was added. The r.m. was stirred at 80 °C for 3 h. The r.m. was cooled to r.t. and concentrated *in vacuo*. The residue was partitioned between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Yield: 870 mg of **intermediate 62** (95 %).

Example A27

Preparation of intermediate 63



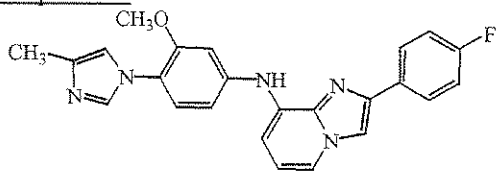
E/Z mixture

Intermediate 63 was prepared by reacting intermediates 11 and 51 in a manner identical to the procedure described for compound 181, Example B11.a.

B. Preparation of the compounds

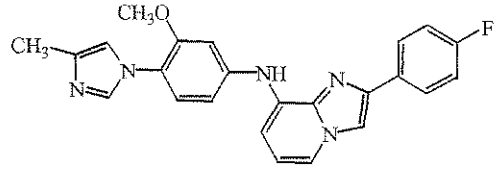
Example B1

a) Preparation of compound 1



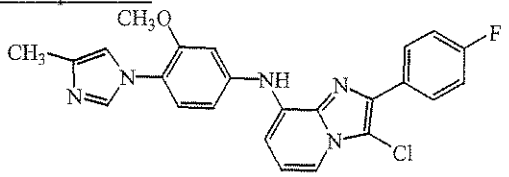
2-Methyl-2-propanol sodium salt (0.495 g, 5.15 mmol), BINAP (0.08 g, 0.13 mmol), palladium(II) diacetate (19 mg, 0.08 mmol) and intermediate 2 (0.454 g, 2.23 mmol) were added to a solution of 8-bromo-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine (0.5 g, 1.72 mmol) in toluene (20 ml) and the mixture was purged with N_2 for 5 min. The r.m. was stirred and heated at 100 °C overnight under a N_2 atmosphere. EtOAc was added, and the mixture was washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 98/2). The product fractions were collected and the solvent was evaporated *in vacuo*.The residue was crystallized form DIPE. The solid was collected and dried *in vacuo*. Yield: 0.49 g of **compound 1** (69 %).

a-1) Preparation of compound 1 (alternative procedure)



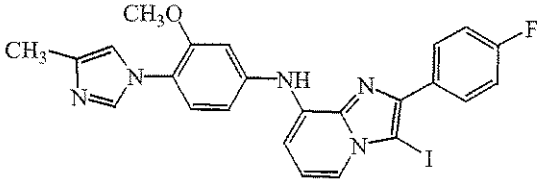
A solution of 8-bromo-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine (3.2 g, 10.99 mmol) in toluene (100 ml) heated on an oil bath of 80 °C, was purged with N_2 for 15 min. 2-Methyl-2-propanol, sodium salt (4.23g, 43.97 mmol), BINAP (0.51 g, 0.82 mmol), palladium(II) diacetate (0.12 g, 0.55 mmol) and intermediate 2 (3.16 g, 13.19 mmol) were added and purging with N_2 was continued for 5 min. The oil bath was heated to 100 °C and the r.m. was stirred for 16 h at this temperature. H_2O was added and further diluted with EtOAc (300 ml). The layers were separated. The aq. phase was extracted with EtOAc (3 x 200 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 98/2). The product fractions were collected and the solvent was evaporated *in vacuo* to yield an off-white solid. This fraction was triturated under DIPE/CH_3CN and stirred for 2 h. A white solid was collected and air dried. Yield: 3.74 g of **compound 1** (82.3 %).

b) Preparation of compound 2



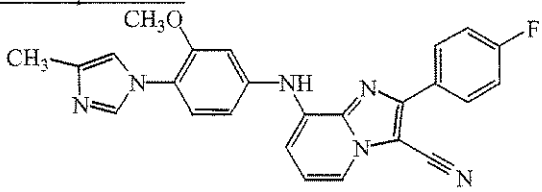
1-Chloro-2,5-pyrrolidinedione (72 mg, 0.54 mmol) was added to compound 1 (223 mg, 0.54 mmol) in DCM (25 ml) and the mixture was stirred overnight at r.t.. The r.m. was quenched with an aq. NaOH solution (10 ml; 1 M solution) and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/CH_3CN]. The product fractions were collected and worked up. Yield: 120 mg of **Compound 2** (50 %).

c) Preparation of compound 57



1-Iodo-2,5-pyrrolidinedione (3.282 g, 14.6 mmol) was added to compound 1 (5.02 g, 12.1 mmol) in a mixture of chloroform (500 ml) and acetic acid (20 ml). The r.m. was stirred at r.t. for 1h, and then a 10 % aq. Na_2SO_3 solution (50 ml) and chloroform (100 ml) were added. The layers were separated and the organic layer was washed successively with a 10 % aq. Na_2SO_3 solution (25 ml) and a 1 N aq. NaOH solution. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 99/1). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 5.76 g of **Compound 57** (88 %).

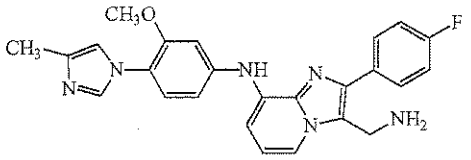
d) Preparation of compound 58



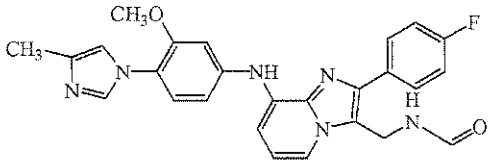
A mixture of compound 57 (500 mg, 0.927 mmol), $Pd_2(dba)_3$ (17 mg, 0.0185 mmol), 1,1'-bis(diphenylphosphino)ferrocene (20.5 mg, 0.037 mmol), zinc (7.3 mg, 0.11 mmol), $Zn(CN)_2$ in DMA (10 ml) was loaded in a microwave vial under a N_2 atmosphere. The mixture was stirred and heated at 150°C using microwave irradiation

for 1 h. The r.m. was poured into an aq. NH_4OH solution, and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH/CH_3CN]. The product fractions were collected and worked up. Yield: 275 mg of **compound 58** (68 %).

e) Preparation of compounds 122 and 100



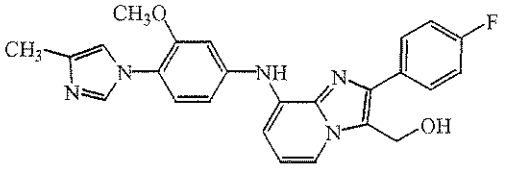
Compound 122



Compound 100

A mixture of compound 58 (150 mg, 0.34 mmol), Raney nickel (50 mg), in a 7N NH_3 solution in MeOH (40 ml) was stirred at 14 °C under H_2 (atmospheric pressure). After uptake of H_2 (2 eq), the catalyst was filtered off over diatomaceous earth and washed with DMF. The combined organic layers were evaporated. The residue was purified by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (10 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.05 % TFA solution in H_2O and 5% CH_3CN)/ CH_3CN]. The product fractions were collected and worked up. Yield: 41 mg of **compound 122** (27 %) and 11 mg of **compound 100** (7 %).

f) Preparation of compound 101

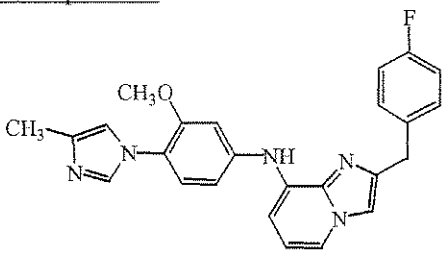


A mixture of compound 57 (1570 mg, 2.91 mmol), palladium(II) diacetate (13 mg, 0.058 mmol), 1,3-bis(diphenylphosphino)propane (48 mg, 0.116 mmol), KOAc (570 mg, 5.82 mmol) in a 1/1 mixture of THF/MeOH (20 ml) in a stainless steel autoclave was pressurized under a 30 bar CO atmosphere. The mixture was stirred and heated at 100°C for 16 h. The r.m. was cooled and concentrated *in vacuo*. The residue was partitioned between DCM and H_2O, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH 99/1). The product fractions were collected and the solvent was evaporated *in vacuo*. The residue (400 mg, 0.85 mmol) was dissolved in THF (2 ml) and added to a suspension of $LiAlH_4$ (32 mg) in THF (14 ml). The mixture was stirred for 1 h at r.t. Subsequently, H_2O (1 ml) and a 1 N aq.

NaOH (3 ml) solution were added. The resulting mixture was extracted with DCM and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH 99/1). The product fractions were collected and the solvent was evaporated *in vacuo*. The residue was suspended in DIPE and dried *in vacuo*. Yield: 46 mg of **compound 101** (12 %).

Example B2

Preparation of compound 3

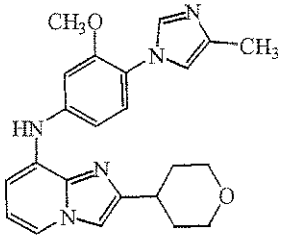


.2HCl.2H_2O

2-Methyl-2-propanol, sodium salt (384.42 mg, 4 mmol), BINAP (46.7 mg, 0.075 mmol), palladium(II) diacetate (11.33 mg, 0.05 mmol) and intermediate 2 (359.56 mg, 1.5 mmol) were added to a solution of intermediate 4 (305.15 mg, 1 mmol) in toluene (10 ml; previously deoxygenated) under a N_2 atmosphere. The r.m. was heated overnight at 100 °C. Subsequently, H_2O was added and the mixture was extracted with DCM. The organic phase was separated, dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (eluent: DCM/MeOH(NH_3) from 100/0 to 96/4).The product fractions were collected and the solvent was evaporated *in vacuo*. The residue was dissolved in Et_2O, and then 1 N HCl in Et_2O was added. The precipitate (HCl salt) was filtered off and dried. Yield: 0.145 g of **compound 3** (27.0 %; .2HCl .2H_2O).

Example B3

Preparation of compound 4

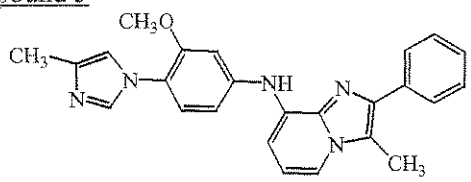


Intermediate 2 (0.106 g, 0.44 mmol), palladium(II) diacetate (0.004 g, 0.017 mmol), 2-methyl-2-propanol, sodium salt (0.131 g, 1.37 mmol) and BINAP (0.016g, 0.026 mmol) were added to a solution of intermediate 7 (0.096g, 0.34 mmol) in toluene (5 ml) under a N_2 atmosphere. N_2 gas was bubbled through the suspension and the

suspension was heated overnight at 100 °C. The r.m. was allowed to cool to r.t. and was then diluted with EtOAc and washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The product was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 100/1 to 20/1). The product fractions were collected and the solvent was evaporated *in vacuo*. The residue was recrystallized from DIPE. The product was dried *in vacuo* at r.t. Yield: 0.079 g of **compound 4** (57 %).

Example B4

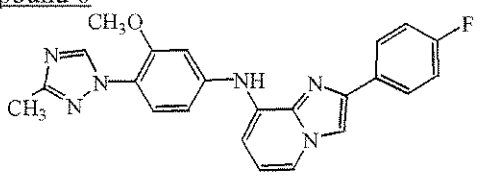
Preparation of compound 5



2-Methyl-2-propanol, sodium salt (256 mg, 2.66 mmol), BINAP (31.1 mg, 0.05 mmol), palladium(II) diacetate (7.54 mg, 0.033 mmol) and intermediate 2a (203 mg, 1 mmol) were added to a solution of intermediate 8 (191.21 mg, 0.67 mmol) in toluene (8 ml; previously deoxygenated) under a N_2 atmosphere. The r.m. was heated overnight at 100 °C. Then, H_2O was added and the mixture was extracted with DCM. The organic phase was separated, dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography over silicagel (Eluent: DCM/MeOH(NH_3) from 100/0 to 96/4). The desired fractions were collected and the solvent was evaporated *in vacuo*. The residue was crystallized from DIPE/CH_3CN. The precipitate was filtered off and dried. Yield: 0.195 g of **compound 5** (71.5 %).

Example B5

Preparation of compound 6

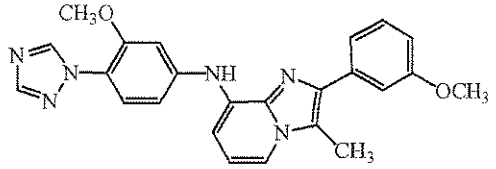


2-Methyl-2-propanol, sodium salt (276 mg, 2.78 mmol), BINAP (45 mg, 0.07 mmol), palladium(II) diacetate (10 mg, 0.046 mmol) and intermediate 11 (189 mg, 0.93 mmol) were added to a solution of intermediate 12 (270 mg, 0.93 mmol) in toluene (5 ml; previously degassed and put under N_2).The r.m. was degassed and put under a N_2 atmosphere. The r.m. was stirred overnight at 100 °C. H_2O (q.s.) was added and the mixture was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over

silicagel (eluent: DCM/MeOH 99/1). The product fractions were collected and evaporated. The residue was suspended in DIPE (q.s.) and a drop of CH_3CN. The product was filtered off and dried *in vacuo* at 50 °C. Yield: 73 mg of **compound 6**.

Example B6

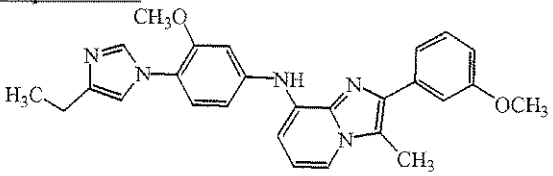
Preparation of compound 7



Intermediate 14 (190 mg, 1 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), X-Phos (105 mg, 0.22 mmol) and Cs_2CO_3 (978 mg, 3 mmol) were added to a solution of intermediate 15 (317 mg, 1 mmol) in 2-methyl-2-propanol (5 ml) under a N_2 atmosphere. The r.m. was heated at 110 °C for 20 h. H_2O was added and the mixture was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash chromatography over silicagel (eluent: DCM/ $MeOH(NH_3)$ 100/0 to 98/2). The first product fraction was collected and the solvent was evaporated: Yield: 0.038 g of **compound 7** (8.9 %). A second product fraction was collected and the solvent was evaporated, yielding 250 mg of crude compound 7. This crude fraction was further purified by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH/CH_3CN]. The product fractions were collected and worked up. Yield: 181 mg of **compound 7** (42.4 %).

Example B7

Preparation of compound 63

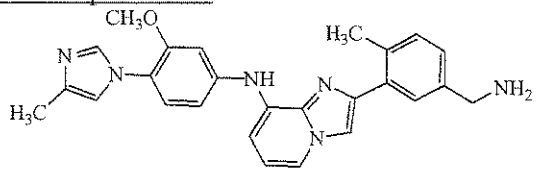


Intermediate 30 (220 mg, 0.466 mmol) was added to a mixture of $NH_4(OAc)$ (0.179 g, 2.32 mmol) in acetic acid (3 ml). The r.m. was heated at reflux for 1 h. The r.m. was neutralized to pH 7 with an aq. 1 N NaOH solution, and then extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by flash column chromatography over silicagel (eluent: DCM/$MeOH(NH_3)$ from 100/0 to 96/4). The product fractions were collected and the solvent was evaporated. The residue was purified further by RP preparative HPLC [RP Shandon Hyperprep® C18 BDS (8 µm, 250 g, I.D. 5 cm); mobile phase: a

gradient of (0.25 % NH_4HCO_3 solution in H_2O)/MeOH/CH_3CN]. The product fractions were collected and worked up. Yield: 88 mg of **compound 63** (41.7 %).

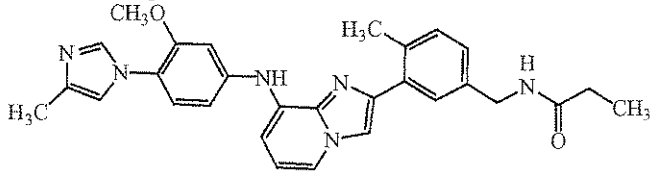
Example B8

a) Preparation of compound 107



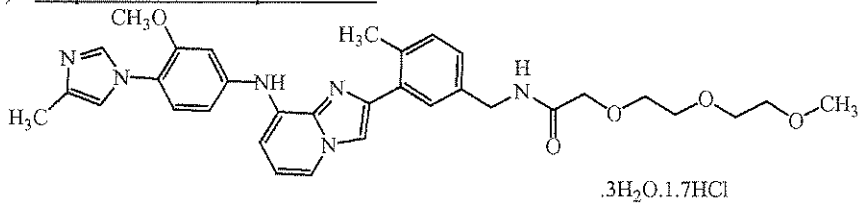
A mixture of compound 105 (prepared analogously to compound 7, Example B6) (432 mg, 0.99 mmol), Raney nickel (200 mg), in a 7 N NH_3 solution in MeOH (100 ml) was stirred at 14 °C under H_2 (atmospheric pressure). After uptake of H_2 (2 eq), the catalyst was filtered off over diatomaceous earth and washed with MeOH. The combined organic layers were concentrated *in vacuo*. The residue was partitioned between DCM and H_2O and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography over silicagel (eluent: DCM/MeOH(NH_3) 100/0 to 90/10). The product fractions were collected and the solvent was evaporated *in vacuo*. Yield: 350 mg of **compound 107** (80 %).

b) Preparation of compound 111



n-Propionylchloride (3.8 µl, 0.043 mmol) was added to an ice-cooled mixture of compound 107 (20 mg, 0.046 mmol) and Et_3N (13 µl, 0.091 mmol) in DCM (1 ml). The r.m. was stirred at r.t. for 24 h. The solvent was evaporated and the residue was partitioned between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by flash column chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 93/7). The product fractions were collected and the solvent was evaporated. Yield: 10 mg of **compound 111** (44 %).

c) Preparation of compound 114

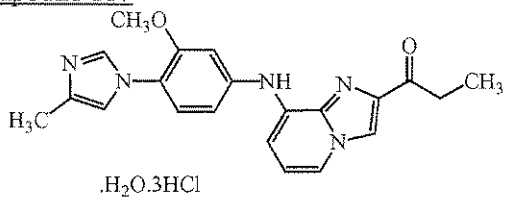


.3H2O.1.7HCl

HBTU (107 mg, 0.28 mmol) was added to a solution of [2-(2-methoxy-ethoxy)-ethoxy]-acetic acid (40 µl, 0.26 mmol) and DIPEA (57 µL, 0.32 mmol) in DMF (1 ml). After stirring for 10 min at r.t., compound 107 (95 mg, 0.22 mmol) was added to the mixture and the r.m. was stirred at r.t. for 2 h. The solvent was evaporated and the residue was dissolved in DCM. The organic layer was washed with H_2O and with a sat. aq. Na_2CO_3 solution, was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by flash column chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 98/2). The product fractions were collected and the solvent was evaporated. The resulting oil was dissolved in CH_3CN and converted into the HCl salt by adding a 6 N HCl solution in 2-propanol. The precipitate was filtered off and dried *in vacuo*. Yield: 36 mg of **compound 114** (23 %; .3H_2O .1.7HCl).

Example B9

Preparation of compound 117



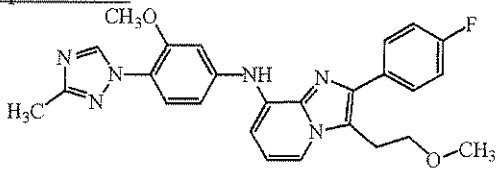
.H_2O.3HCl

A 1 M solution of CH_3CH_2MgBr in THF (0.49 ml, 0.49 mmol) was added to an ice-cooled solution of intermediate 43 (50 mg, 0.12 mmol) in THF (1 ml) under N_2 atmosphere. The r.m. was warmed up to r.t. and stirred for 2 h, then cooled again to 0 °C and more CH_3CH_2MgBr (0.25 ml, 0.25 mmol) was added. The solution was warmed up to r.t., stirred for 2 h, cooled again to 0 °C, and again CH_3CH_2MgBr (0.25 ml, 0.25 mmol) was added. The r.m. was warmed up to r.t. and stirred for 2 h. H_2O was added and the solution was acidified until pH 3 using an aq. 1 N HCl solution. The solution was stirred for 45 min and was basified using $NaHCO_3$. The volatiles were evaporated. The product was extracted 3 x with DCM. The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by RP preparative HPLC [RP Vydac Denali C18 (10 µm, 250 g, I.D. 5 cm); mobile phase: a gradient of (0.25 % NH_4HCO_3 solution in H_2O)/CH_3CN]. The product fractions were collected and worked up. The resulting oil was dissolved in CH_3CN and

a 6 N HCl solution in 2-propanol was added. The precipitate was filtered off and dried *in vacuo*. Yield: 15 mg of **compound 117** (32 %; .H_2O.3HCl).

Example B10

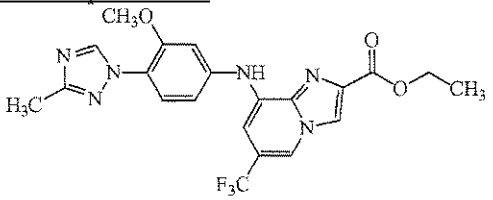
Preparation of compound 127



A mixture of intermediate 63 (350 mg, 0.74 mmol) and Raney nickel (50 mg), in THF (40 ml) was stirred at r.t. under H_2 (atmospheric pressure). After uptake of H_2 (1 eq), the catalyst was filtered off over diatomaceous earth. The solvent was evaporated and the residue was partitioned between DCM and H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 99/1). The product fractions were collected and the solvent was evaporated. The residue was triturated with DIPE and a drop of CH_3CN. The product was then dried *in vacuo*. Yield: 26 mg of **compound 127** (7 %).

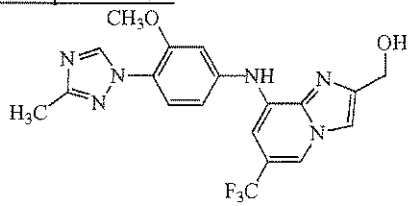
Example B11

a) Preparation of compound 181



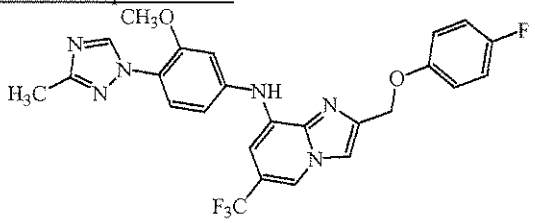
Intermediate 11 (408 mg, 2 mmol), $Pd_2(dba)_3$ (184 mg, 0.2 mmol), X-phos (0.21 g, 0.0.44 mmol) and Cs_2CO_3 (1.95 g, 6 mmol) were added to a solution of ethyl 8-iodo-6-(trifluoromethyl)imidazo[1,2-a]pyridine-2-carboxylate (0.768 g, 2 mmol) in 2-methyl-2-propanol (10 ml) under a N_2 atmosphere. The r.m. was heated at 100 °C for 2 h. Then, H_2O was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 97/3). The product fraction was collected and the solvent was evaporated: Yield: 0.509 g of **compound 181** (55 %).

b) Preparation of compound 152



A solution of compound 181 (0.509 g, 1.1 mmol) in THF (3.3 ml) was added dropwise to a suspension of $LiAlH_4$ (84 mg, 2.2 mmol) in THF (10 ml). The r.m. was stirred at r.t for 1 h and was then diluted with EtOAc. The organic layer was washed with a 3 N aq. NaOH solution, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The product was purified by flash column chromatography over silicagel (eluent: DCM/MeOH from 50/1 to 10/1). The product fractions were collected and the solvent was evaporated. Yield: 377 mg of **compound 152** (82 %).

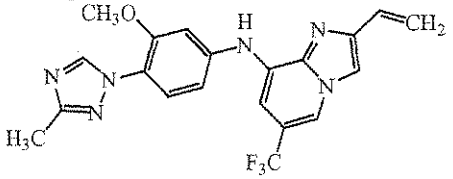
c) Preparation of compound 147



Diisopropyl azodicarboxylate (0.12 ml, 0.62 mmol) was added to a solution of PPh_3 (0.167 g, 0.64 mmol) in THF (40 ml) at 0 °C. The mixture was stirred for 30 min. Subsequently, compound 152 (0.172 g, 0.41 mmol) and 4-fluorophenol (46 mg, 0.41 mmol) were added. The r.m. was stirred at r.t. for 2 h and was then partitioned between DCM and an aq. 1 N NaOH solution. The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by RP preparative HPLC [RP Luna C18, mobile phase: gradient of (25 mM aq. NH_4HCO_3 solution)/(1/1 CH_3CN/MeOH) from 47/53 to 18/82)]. The product fractions were collected and worked up. Yield: 46 mg of **compound 147** (22 %).

Example B12

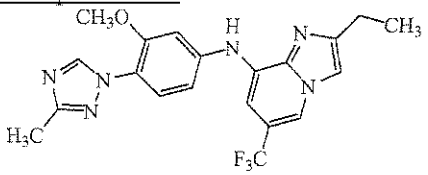
a) Preparation of compound 154



Intermediate 11 (38 mg, 0.15 mmol), $Pd_2(dba)_3$ (14 mg, 0.015 mmol), X-phos (14 mg, 0.015 mmol) and Cs_2CO_3 (145 mg, 0.44 mmol) were added to a solution of

intermediate 45 (50 mg, 0.15 mmol) in 2-methyl-2-propanol (5 ml) under a N_2 atmosphere. The r.m. was heated at 100 °C for 18 h. Then, H_2O was added and the mixture was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash chromatography over silicagel (eluent: Et_2O/heptane from 1/1 to 2/1). The product fraction was collected and the solvent was evaporated. Yield: 0.034 g of **compound 154** (54 %).

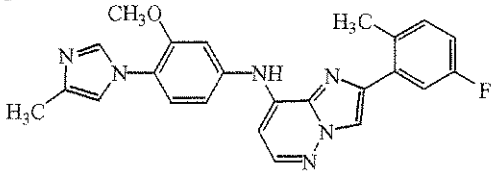
b) Preparation of compound 153



THF (40 ml) was added to Pd/C (10%, 30 mg) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (1 ml) and compound 154 (30 mg, 0.072 mmol) were added. The r.m. was stirred at 25 °C under a H_2 atmosphere until 1 eq of H_2 was absorbed. The catalyst was filtered off over diatomaceous earth. The filtrate was evaporated and the residue was purified by flash chromatography over silicagel (eluent: eluent: Et_2O/heptane from 1/1 to 1/0). The product fraction was collected and the solvent was evaporated. Yield: 0.027 g of **compound 153** (88 %).

Example B13

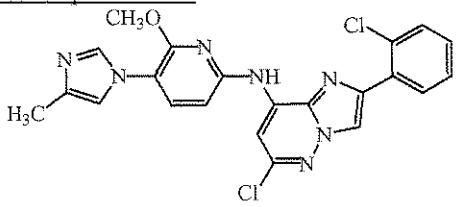
Preparation of compound 159



A 1/1 mixture of THF and MeOH (100 ml) was added to Pd/C (10 %, 500 mg) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (1 ml), compound 157 (prepared according to example B6, 141 mg, 0.3 mmol), and KOAc (36 mg, 0.36 mmol) were added, and the r.m. was stirred at 25 °C under a H_2 atmosphere until 1 eq of H_2 was absorbed. The catalyst was filtered off over diatomaceous earth. The filtrate was evaporated and the residue was partitioned between DCM and a sat. aq. $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 0.103 g of **compound 159** (79 %).

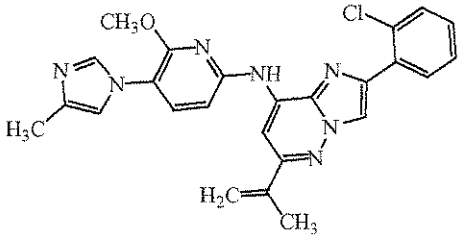
Example B14

a) Preparation of compound 174



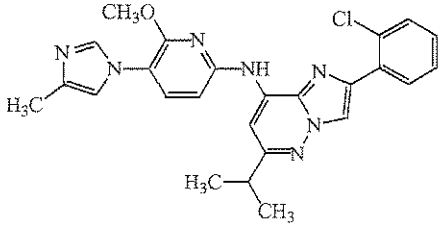
Intermediate 34 (1.22 g, 6 mmol), $Pd_2(dba)_3$ (640 mg, 0.0.7 mmol), X-phos (670 mg, 1.4 mmol) and Cs_2CO_3 (6.87 g, 21 mmol) were added to a solution of intermediate 55 (2.74 g, 6 mmol) in 2-methyl-2-propanol (50 ml) under a N_2 atmosphere. The r.m. was heated at 100 °C for 16 h. Then, H_2O was added and the mixture was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 97/3). The product fraction was collected and the solvent was evaporated: Yield: 1.2 g of **compound 174** (34 %).

b) Preparation of compound 171



2-Isopropenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (132 mg, 0.79 mmol) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol) were added to a mixture of compound 174 (306 mg, 0.66 mmol) in dioxane (10 ml) and an aq. sat. $NaHCO_3$ solution (5 ml). The r.m. was heated under microwave conditions at 160 °C for 10 min. The r.m. was cooled and filtered over diatomaceous earth, using EtOAc as eluent. The filtrate was evaporated and the residue was purified by flash chromatography over silicagel (eluent: DCM/MeOH(NH_3) from 100/0 to 97/3). Yield: 0.25 g of **compound 171** (81 %).

c) Preparation of compound 163

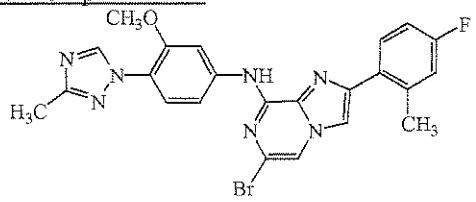


Compound 171 (120 mg, 0.25 mmol) was added to a mixture of MeOH (40 ml) and Pt/C (5 %, 50 mg) under a N_2 atmosphere. The r.m. was stirred at 25 °C under a H_2

atmosphere until 1 eq of H_2 was absorbed. The mixture was filtered over diatomaceous earth. The filtrate was evaporated and the residue was purified by flash chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 95/5). The product fraction was collected and the solvent was evaporated. Yield: 0.055 g of **compound 163** (46 %).

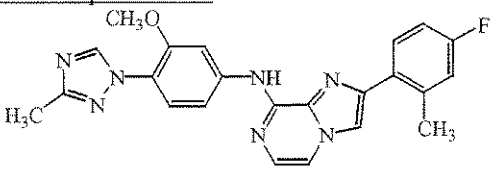
Example B15

a) Preparation of compound 177



A solution of intermediate 11 (318 mg, 1.56 mmol), intermediate 54 (400 mg, 1.04 mmol) and DIPEA (269 mg, 2.08 mmol) in CH_3CN (5 ml) was heated under microwave conditions first for 3 h at 160 °C, and then for 2 h at 170 °C. The r.m. was cooled and the resulting precipitate was filtered off, washed with CH_3CN and DIPE, and dried. The precipitate was purified further by flash chromatography over silicagel (eluent: DCM/MeOH from 100/0 to 97/3). The product fraction was collected and the solvent was evaporated: Yield: 0.044 g of **compound 177** (8 %).

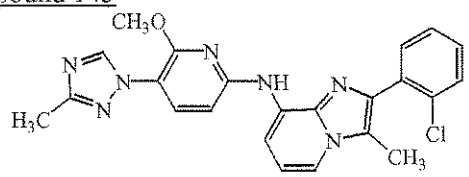
b) Preparation of compound 176



MeOH (40 ml) was added to Pd/C (10%, 50 mg) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (1 ml) was added and the mixture was stirred at 25 °C under a H_2 atmosphere for 30 min. Compound 177 (100 mg, 0.2 mmol) and KOAc (39 mg, 0.39 mmol) were added and the r.m. was stirred at 25 °C under a H_2 atmosphere until 1 eq of H_2 was absorbed. The catalyst was filtered off over diatomaceous earth. The filtrate was evaporated and the residue was purified by flash chromatography over silicagel (eluent: eluent: DCM/MeOH from 100/0 to 95/5). The product fraction was collected and the solvent was evaporated. The residue was triturated with DIPE and dried *in vacuo*. Yield: 0.065 g of **compound 176** (77 %).

Example B16

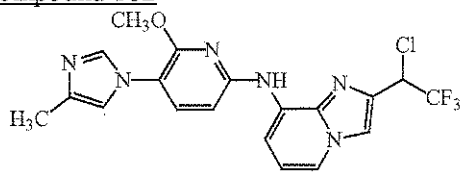
Preparation of compound 145



Intermediate 62 (160 mg, 0.78 mmol), $Pd_2(dba)_3$ (71 mg, 0.078 mmol), X-phos (74 mg, 0.156 mmol) and Cs_2CO_3 (762 mg, 2.34 mmol) were added to a solution of 8-bromo-2-(2-chloro-phenyl)-3-methyl-imidazo[1,2a]pyridine (prepared according to synthesis protocol described in example A9; 301 mg, 0.94 mmol) in 2-methyl-2-propanol (20 ml) under a N_2 atmosphere. The r.m. was heated at 100 °C for 16 h. Then, the r.m. was cooled to r.t., H_2O was added and the mixture was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (eluent: DCM/MeOH from 100/0 to 95/5). The product fractions were collected and concentrated *in vacuo*. The residue was triturated with DIPE. The solid was collected and dried *in vacuo*. Yield: 0.210 g of **compound 145** (60 %).

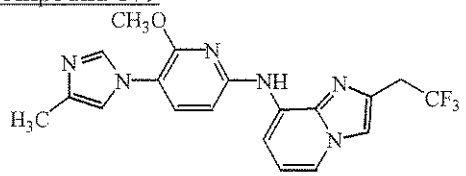
Example B17

a) Preparation of compound 182



Intermediate 34 (195 mg, 0.96 mmol), $Pd_2(dba)_3$ (88 mg, 0.096 mmol), X-Phos (100 mg, 0.211 mmol) and Cs_2CO_3 (935 mg, 2.87 mmol) were added to a solution of intermediate 65 (300 mg, 0.96 mmol) in 2-methyl-2-propanol (23 ml) under a N_2 atmosphere. The r.m. was heated at 110 °C overnight. H_2O was added and the mixture was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash chromatography over silicagel (eluent: DCM/ MeOH(NH_3) 100/0 to 97/3). The product fractions were collected and the solvent was evaporated: Yield: 0.020 g of **compound 182** (5 %).

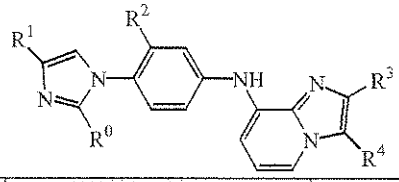
b) Preparation of compound 179

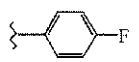
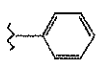
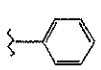
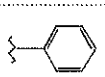
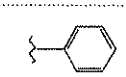


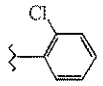
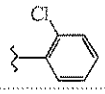
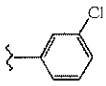
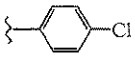
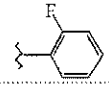
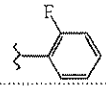
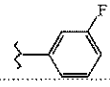
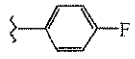
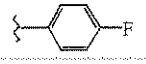
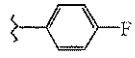
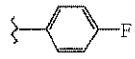
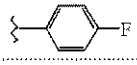
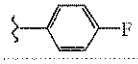
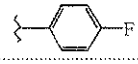
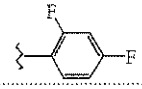
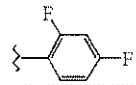
MeOH (30 ml) was added to Pd/C 10 % (20 mg) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (0,1 ml) and compound 182 (20 mg, 0.046 mmol) were added. The r.m. was stirred at 25 °C under a H_2 atmosphere until 1 eq of H_2 was absorbed. The catalyst was filtered off over diatomaceous earth. The filtrate was evaporated and the residue was purified by flash column chromatography over silica gel (eluent: DCM/MeOH from 100/0 to 97/3). The product fractions were collected and concentrated *in vacuo*. The residue was triturated with DIPE. The solid was collected and dried *in vacuo*. Yield: 5 mg of **compound 179** (27 %).

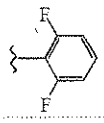
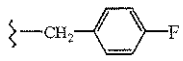
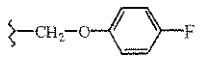
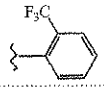
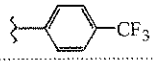
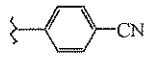
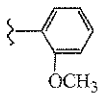
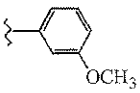
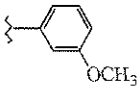
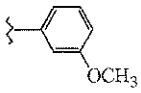
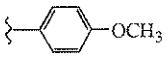
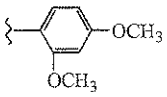
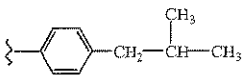
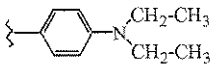
Compounds 1 to 71, 73 to 84, 86 to 91, 94, 98 and 100 to 182 in tables 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 list the compounds that were prepared by analogy to one of the above Examples. In case no salt form is indicated, the compound was obtained as a free base. Compounds 72, 85, 92, 93, 95, 96, 97 and 99 in tables 2, 5 and 6 list the compounds that can be prepared by analogy to one of the above Examples. 'Pr.' refers to the Example number according to which protocol the compound was or can be synthesized. 'Co. No.' means compound number. The Example numbers indicated with an asterisk '*' were described in detail in the Examples section.

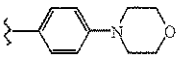
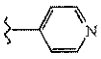
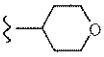
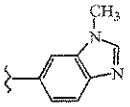
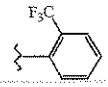
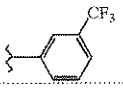
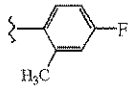
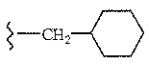
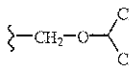
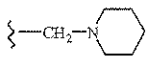
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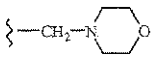
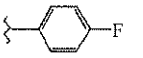
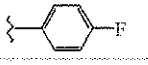
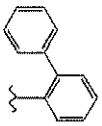
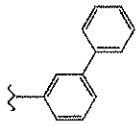
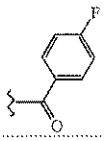
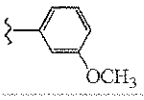
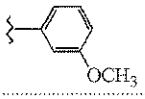
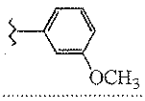
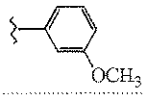
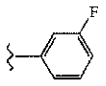
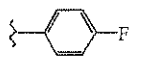
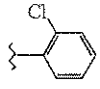
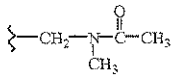


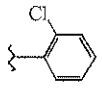
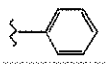
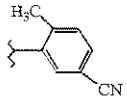
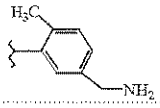
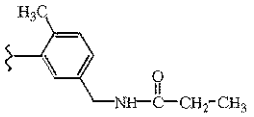
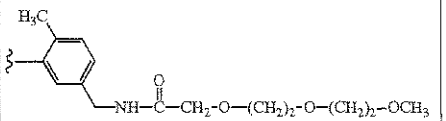
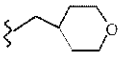
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8	B1.a	H	CH_3	CH_3O	H		
9	B1.a	H	CH_3	CH_3O	$C(CH_3)_3$	H	
10	B1.a	H	CH_3	CH_3O	$(CH_2)_2$-CH_3	CH_2-CH_3	
11	B1.a	H	CH_3	CH_3O	$(CH_2)_3$-CH_3	$(CH_2)_2$-CH_3	
12	B1.a	H	CH_3	CH_3O		H	
5	B4*	H	CH_3	CH_3O		CH_3	
13	B1.a	H	CH_3	CH_3O			

Co. No.	Pr.	R^0	R^1	R^2	R^3	R^4	salt form
14	B1.a	H	CH_3	CH_3O		H	
15	B1.a	H	CH_3	CH_3O		CH_3	
16	B1.a	H	CH_3	CH_3O		H	
17	B1.a	H	CH_3	CH_3O		H	
88	B1.a	H	CH_3	CH_3O		H	
18	B1.a	H	CH_3	CH_3O		CH_3	
19	B1.a	H	CH_3	CH_3O		H	
1	B1.a*	H	CH_3	CH_3O		H	
20	B1.a	CH_3	CH_3	CH_3O		H	
21	B1.a	CH_3	H	CH_3O		H	
22	B1.b	H	CH_3	CH_3O		Br	
2	B1.b*	H	CH_3	CH_3O		Cl	
23	B1.a	H	CH_3	CH_3O		CH_2-CH_3	
24	B2	H	CH_3	CH_3O		$(CH_2)_2$-CH_3	.2HCl
25	B1.a	H	CH_3	CH_3O		H	
26	B1.a	H	CH_3	CH_3O		CH_3	

Co. No.	Pr.	R^0	R^1	R^2	R^3	R^4	salt form
27	B1.a	H	CH_3	CH_3O		CH_3	
3	B2*	H	CH_3	CH_3O		H	.2HCl .$2H_2O$
28	B1.a	H	CH_3	CH_3O		H	
29	B2	H	CH_3	CH_3O		CH_3	.2HCl
30	B1.a	H	CH_3	CH_3O		H	
31	B1.a	H	CH_3	CH_3O		H	
32	B1.a	H	CH_3	CH_3O		H	
33	B1.a	H	CH_3	CH_3O		H	
34	B1.a	H	CH_3	CH_3O		CH_3	
35	B1.a	H	H	CH_3O		CH_3	
36	B1.a	H	CH_3	CH_3O		H	
37	B1.a	H	CH_3	CH_3O		H	
38	B1.a	H	CH_3	CH_3O		CH_3	
39	B1.a	H	CH_3	CH_3O		H	

Co. No.	Pr.	R^0	R^1	R^2	R^3	R^4	salt form
40	B1.a	H	CH_3	CH_3O		H	
41	B1.a	H	CH_3	CH_3O		H	
42	B1.a	H	CH_3	CH_3O		H	
43	B1.a	H	CH_3	CH_3O		H	
4	B3*	H	CH_3	CH_3O		H	
44	B1.a	H	CH_3	CH_3O		H	
47	B1.a	H	CH_3	CH_3O		H	
48	B1.a	H	CH_3	CH_3O		H	
49	B1.a	H	CH_3	CH_3O	H	H	
50	B1.a	H	CH_3	CH_3O	CH_3	H	
69	B1.a	H	CH_3	CH_3O	$(CH_2)_3$-CH_3	H	
51	B2	H	CH_3	CH_3O	$(CH_2)_3$-CH_3	H	.2HCl
52	B1.a	H	CH_3	CH_3O		H	
53	B1.a	H	CH_3	CH_3O		Cl	
54	B1.a	H	CH_3	CH_3O		H	.2HCl
55	B1.a	H	CH_3	CH_3O		H	

Co. No.	Pr.	R^0	R^1	R^2	R^3	R^4	salt form
56	B1.a	H	CH_3	CH_3O		H	
57	B1.c*	H	CH_3	CH_3O		I	
58	B1.d*	H	CH_3	CH_3O		CN	
59	B1.a	H	CH_3	CH_3O	H	$(CH_2)_5$-CH_3	
60	B1.a	H	CH_3	CH_3O	H		
61	B1.a	H	CH_3	CH_3O	H		
62	B1.a	H	CH_3	CH_3O	H		
63	B7*	H	CH_2-CH_3	CH_3O		CH_3	
64	B6	H	CH_3	H		CH_3	
65	B6	CH_3	H	H		CH_3	
66	B6	H	CH_3	F		CH_3	
100	B1-e*	H	CH_3	CH_3O		CH_2-NH-CH=O	
101	B1-f*	H	CH_3	CH_3O		CH_2-OH	
102	B6	H	CH_3	F			

Co. No.	Pr.	R^0	R^1	R^2	R^3	R^4	salt form
103	B6	H	CH_3	F		CH_2-O-CH_3	
104	B6	H	CH_3	F		CH_2-O-CH_3	
105	B6	H	CH_3	CH_3O		H	
106	B6	H	CH_3	CH_3O	C(=O)-O-$C(CH_3)_3$	H	.1.5 HCl
107	B8-a*	H	CH_3	CH_3O		H	
108	B6	H	CH_3	CH_3O	C(=O)-O-$CH(CH_3)_2$	H	
109	B6	H	CH_3	CH_3O	CH_2-CF_3	H	
110	B6	H	CH_3	CH_3O	CHOH-CF_3	H	
111	B8-b*	H	CH_3	CH_3O		H	
112	B6	H	CH_3	F		O-CH_3	
113	B6	H	CH_3	CH_3O	C(=O)-O-CH_2-CH_3	H	
114	B8-c*	H	CH_3	CH_3O		H	.3H_2O .1.7HCl
115	B6	H	CH_3	F		H	.0.25H_2O .1.7HCl
116	B6	H	CH_3	CH_3O		H	
117	B9*	H	CH_3	CH_3O	C(=O)-CH_2-CH_3	H	.H_2O .3HCl

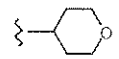
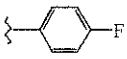
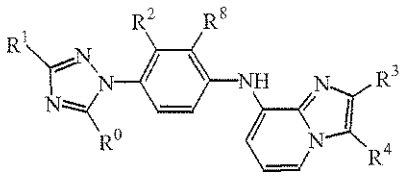
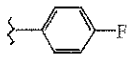
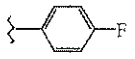
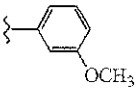
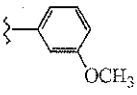
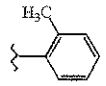
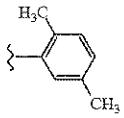
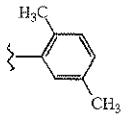
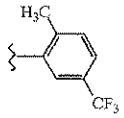
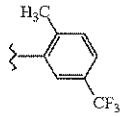
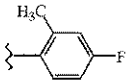
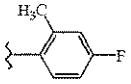
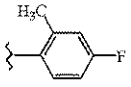
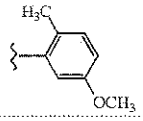
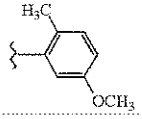
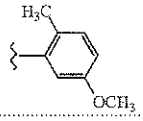
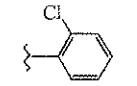
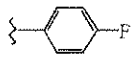
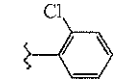
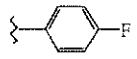
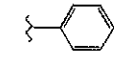
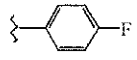
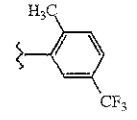
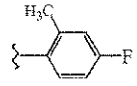
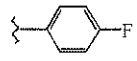
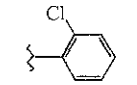
Co. No.	Pr.	R^0	R^1	R^2	R^3	R^4	salt form
118	B6	H	CH_3	F		H	.0.4H_2O .1HCl
119	B6	H	CH_3	F	CH_3	H	
120	B6	H	CH_3	F		H	
121	B6	H	CH_3	CH_3O	$C(OH)(CH_3)_2$	H	
122	B1-e*	H	CH_3	CH_3O		CH_2-NH_2	
123	B6	H	CH_3	CH_3O	$C(=O)$-$N(CH_3)_2$	H	

Table 2



Co. no.	Pr.	R^0	R^1	R^2	R^8	R^3	R^4	salt form
6	B5*	H	CH_3	CH_3O	H		H	
45	B5	CH_3	H	CH_3O	H		H	
7	B6*	H	H	CH_3O	H		CH_3	
67	B6	H	CH_3	CH_3O	H		CH_3	
70	B6	H	CH_3	CH_3O	H		H	

Co. no.	Pr.	R^0	R^1	R^2	R^8	R^3	R^4	salt form
71	B6	H	CH_3	H	H		H	
72	B6	H	CH_3	CH_3O	H		H	
73	B6	H	CH_3	H	H		H	
74	B6	H	CH_3	F	H		H	
75	B6	CH_3	H	H	H		H	
76	B6	H	CH_3	H	H	$(CH_2)_3$-CH_3	H	.2HCl
77	B6	H	CH_3	CH_3O	H	CH_3	H	
78	B6	H	CH_3	H	H	CH_3	H	
79	B6	H	CH_3	H	H	CH_3	CH_3	
80	B6	H	H	CH_3O	H	CH_3	H	
89	B6	H	CH_3	CH_3O	H		H	
90	B6	H	CH_3	H	H		H	
91	B6	H	CH_3	F	H		H	

Co. no.	Pr.	R^6	R^1	R^2	R^8	R^3	R^4	salt form
92	B6	H	CH_3	CH_3O	H		H	
93	B6	H	CH_3	H	H		H	
94	B6	H	CH_3	F	H		H	
124	B6	H	CH_3	CH_3O	H		CH_3	
125	B6	H	CH_3	CH_3O	H		CH_2-O-CH_3	
126	B6	H	CH_3	CH_3O	H		CH_2-N(CH_3)$_2$	
127	B10*	H	CH_3	CH_3O	H		$(CH_2)_2$-O-CH_3	
128	B6	H	CH_3	CH_3O	H		CH_2-N(CH_3)$_2$	
129	B10	H	CH_3	CH_3O	H		$(CH_2)_3$-O-CH_3	.1HCl
130	B6	CH_3	H	F	H		H	
131	B6	CH_3	H	F	H		H	
132	B6	H	CH_3	CH_3O	H		CH_3O	
133	B6	H	CH_3	H	F		CH_3	

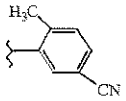
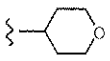
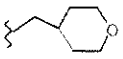
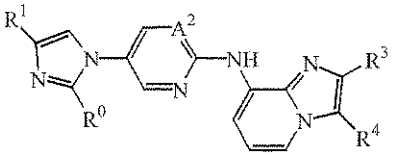
Co. no.	Pr.	R^0	R^1	R^2	R^8	R^3	R^4	salt form
134	B6	H	CH_3	CH_3O	H		H	
135	B6	H	CH_3	CH_3O	H		H	
136	B6	H	CH_3	CH_3O	H		H	.1.5H_2O .1.8HCl
137	B6	H	CH_3	CH_3O	H		H	.2.1H_2O .1.8HCl

Table 3



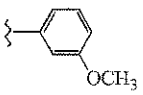
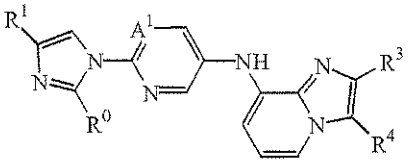
Co. no.	Pr.	R^0	R^1	A^2	R^3	R^4	salt form
68	B6	H	CH_3	CH		CH_3	

Table 4



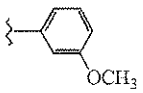
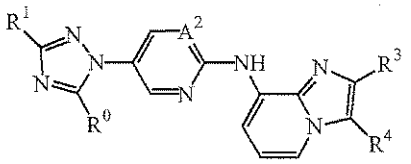
Co. no.	Pr.	R^0	R^1	A^1	R^3	R^4	salt form
46	B6	H	CH_3	N		CH_3	

Table 5



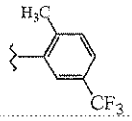
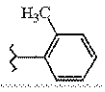
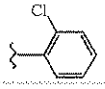
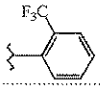
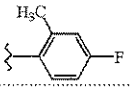
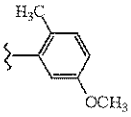
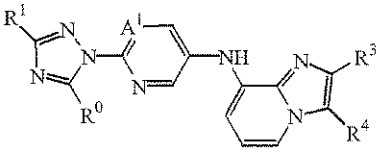
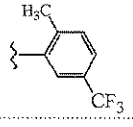
Co. no.	Pr.	R^0	R^1	A^2	R^3	R^4	salt form
81	B6	H	CH_3	CH		H	
82	B6	H	CH_3	CH		H	
83	B6	H	CH_3	CH		CH_3	
95	B6	H	CH_3	CH		CH_3	
96	B6	H	CH_3	CH		H	
97	B6	H	CH_3	CH		H	

Table 6



Co. no.	Pr.	R^0	R^1	A^1	R^3	R^4	salt form
84	B6	H	CH_3	CH		H	

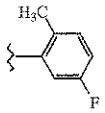
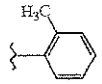
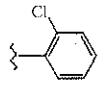
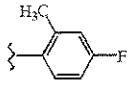
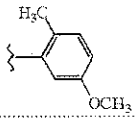
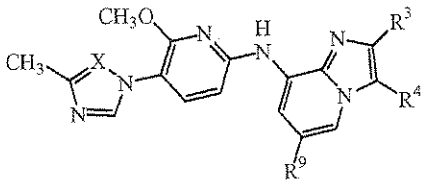
Co. no.	Pr.	R^0	R^1	A^1	R^3	R^4	salt form
85	B6	H	CH_3	CH		H	
86	B6	H	CH_3	CH		H	
87	B6	H	CH_3	CH		CH_3	
98	B6	H	CH_3	CH		H	
99	B6	H	CH_3	CH		H	

Table 7



Co. No.	Pr.	X	R^9	R^3	R^4	salt form
179	B17.b*	CH	H	CH_2-CF_3	H	
182	B17.a*	CH	H		H	
138	B16	CH	H		CH_3	
139	B16	CH	H		CH_3	
140	B16	CH	H		CH_2-O-CH_3	

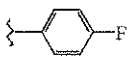
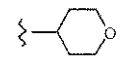
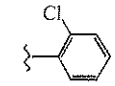
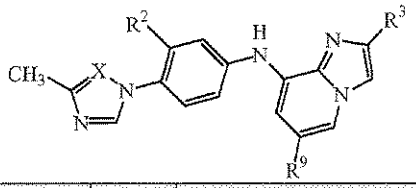
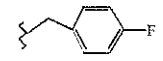
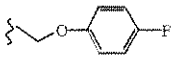
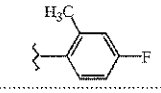
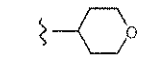
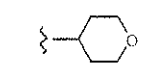
Co. No.	Pr.	X	R^9	R^3	R^4	salt form
141	B16	CH	H		O-CH_3	
142	B16	CH	F	CH_2-$CH(CH_3)_2$	H	
143	B16	CH	H		H	
144	B16	CH	H	CH_3	H	
180	B17	N	H	CH_2-CF_3	H	
145	B16*	N	H		CH_3	

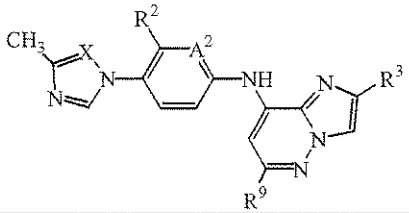
Table 8

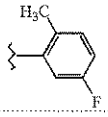
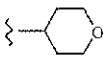
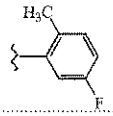
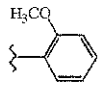
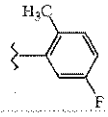
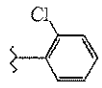


Co. No.	Pr.	X	R^2	R^9	R^3	salt form
146	B6	N	CH_3O	CF_3		
147	B11.c*	N	CH_3O	CF_3		
148	B6	CH	F	F		
149	B6	CH	F	F		.0.9H_2O. 1.8HCl
150	B6	CH	F	Cl		
151	B9	CH	CH_3O	CF_3	$C(OH)(CH_3)_2$	
152	B11.b*	N	CH_3O	CF_3	CH_2-OH	
153	B12.b*	N	CH_3O	CF_3	CH_2-CH_3	

Co. No.	Pr.	X	R^2	R^9	R^3	salt form
154	B12.a*	N	CH_3O	CF_3	$CH=CH_2$	
155	B6	CH	CH_3O	CF_3	$C(=O)\text{-}O\text{-}CH_2CH_3$	.1 HCl
181	B11.a*	N	CH_3O	CF_3	$C(=O)\text{-}O\text{-}CH_2CH_3$	
156	B6	CH	CH_3O	CF_3	COOH	

Table 9



Co. No.	Pr.	X	R^2	A^2	R^9	R^3	salt form
157	B6	CH	CH_3O	CH	Cl		
158	B6	CH	CH_3O	CH	CF_3		
159	B13*	CH	CH_3O	CH	H		
160	B14.c	CH	CH_3O	CH	$CH(CH_3)_2$	CH_3	
161	B14.b	CH	CH_3O	CH		CH_3	
162	B6	N	CH_3O	CH	Cl		
163	B14.c*	CH	CH_3O	N	$CH(CH_3)_2$		
164	B6	CH	CH_3O	CH	CF_3	CH_3	
165	B6	CH	CH_3O	CH	Cl	CH_3	

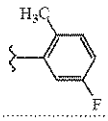
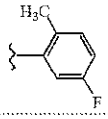
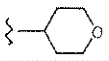
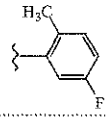
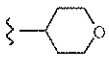
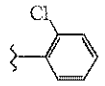
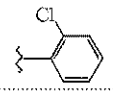
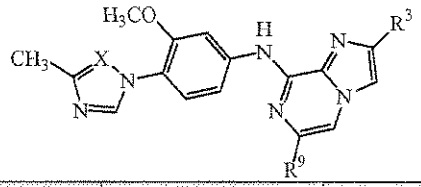
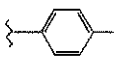
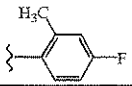
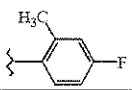
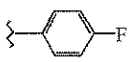
Co. No.	Pr.	X	R^2	A^2	R^9	R^3	salt form
166	B13	CH	F	CH	H		
167	B13	N	CH_3O	CH	H		
168	B6	CH	F	CH	CF_3		
169	B6	CH	F	CH	Cl		
170	B14.c	CH	CH_3O	CH		CH_3	
171	B14.b*	CH	CH_3O	N			
172	B13	CH	CH_3O	CH	H	CH_3	
173	B6	CH	F	CH	CF_3	CH_3	
174	B14.a*	CH	CH_3O	N	Cl		

Table 10



Co. No.	Pr.	X	R^9	R^3	salt form
175	B6	CH	H		
176	B15.b*	N	H		
177	B15.a*	N	Br		

Co. No.	Pr.	X	R^9	R^2	salt form
178	B6	N	H		

Analytical Part

LCMS

General procedure A

The LC measurement was performed using an Acquity UPLC (Waters) system comprising a binary pump, a sample organizer, a column heater (set at 55 °C), a diode-array detector (DAD) and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 100 to 1000 in 0.18 seconds using a dwell time of 0.02 seconds. The capillary needle voltage was 3.5 kV and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

General procedure B

The HPLC measurement was performed using an Agilent 1100 series liquid chromatography system comprising a binary pump with degasser, an autosampler, a column oven, a UV detector and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an electrospray ionization source. The capillary voltage was 3 kV, the quadrupole temperature was maintained at 100 °C and the desolvation temperature was 300 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with an Agilent Chemstation data system.

General procedure C

The HPLC measurement was performed using an Alliance HT 2790 (Waters) system comprising a quaternary pump with degasser, an autosampler, a column oven (set at 40 °C, unless otherwise indicated), a diode-array detector (DAD) and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 100 to 1000 in 1 second using a dwell time of 0.1 second. The capillary needle voltage was 3 kV and the source temperature

was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

General procedure D

The HPLC measurement was performed using a HP 1100 from Agilent Technologies comprising a pump (quaternary or binary) with degasser, an autosampler, a column oven, a diode-array detector (DAD) and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an electrospray ionization source. Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

LCMS Method 1

In addition to general procedure A: Reversed phase UPLC (Ultra Performance Liquid Chromatography) was carried out on a bridged ethylsiloxane/silica hybrid (BEH) C18 column (1.7 µm, 2.1 x 50 mm; Waters Acquity) with a flow rate of 0.8 ml/min. Two mobile phases (25 mM ammoniumacetate (NH_4OAc) in H_2O/CH_3CN 95/5; mobile phase B: CH_3CN) were used to run a gradient condition from 95 % A and 5 % B to 5 % A and 95 % B in 1.3 minutes (min) and hold for 0.3 min. An injection volume of 0.5 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

LCMS Method 2

In addition to general procedure A: Reversed phase (RP) UPLC was carried out on a BEH C18 column (1.7 µm, 2.1 x 50 mm; Waters Acquity) with a flow rate of 0.8 ml/min. 2 Mobile phases (mobile phase A: 0.1 % formic acid in H_2O/MeOH 95/5; mobile phase B: MeOH) were used to run a gradient condition from 95 % A and 5 % B to 5 % A and 95 % B in 1.3 min and hold for 0.2 min. An injection volume of 0.5 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

LCMS Method 3

In addition to general procedure B: RP HPLC was carried out on a YMC-Pack ODS-AQ C18 column (4.6 x 50 mm) with a flow rate of 2.6 ml/min. A gradient run was used from 95 % water and 5 % CH_3CN to 95 % CH_3CN in 4.80 min and was hold for 1.20 min. Mass spectra were acquired by scanning from 100 to 1400. Injection volume was 10 µl. Column temperature was 35 °C.

LCMS Method 4

In addition to general procedure C: Column heater was set at 60 °C. RP HPLC was

carried out on an Xterra MS C18 column (3.5 µm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. 3 Mobile phases (mobile phase A: 95 % 25 mM NH_4OAc + 5 % CH_3CN; mobile phase B: CH_3CN; mobile phase C: MeOH) were employed to run a gradient condition from 100 % A to 50 % B and 50 % C in 6.5 min, to 100 % B in 0.5 min and hold these conditions for 1 min and reequilibrate with 100 % A for 1.5 min. An injection volume of 10 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

LCMS Method 5

In addition to general procedure C: Column heater was set at 45 °C. RP HPLC was carried out on an Atlantis C18 column (3.5 µm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. 2 Mobile phases (mobile phase A: 70 % MeOH + 30 % H_2O; mobile phase B: 0.1 % formic acid in H_2O/MeOH 95/5) were employed to run a gradient condition from 100 % B to 5 % B + 95 % A in 9 min and hold these conditions for 3 min. An injection volume of 10 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

LCMS Method 6

In addition to general procedure C: RP HPLC was carried out on an Xterra MS C18 column (3.5 µm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. 3 Mobile phases (mobile phase A: 95% 25 mM NH_4OAc + 5 % CH_3CN; mobile phase B: CH_3CN; mobile phase C: MeOH) were employed to run a gradient condition from 100 % A to 1 % A, 49 % B and 50 % C in 6.5 min, to 1 % A and 99 % B in 1 min and hold these conditions for 1 min and reequilibrate with 100 % A for 1.5 min. An injection volume of 10 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

LCMS Method 7

In addition to general procedure D: RP HPLC was carried out on an XDB-C18 cartridge (1.8 µm, 2.1 x 30 mm) from Agilent, at 60°C with a flow rate of 1 ml/min, at 60 °C. The gradient conditions used are: 90 % A (0.5 g/l NH_4OAc solution), 5 % B (CH_3CN), 5 % C (MeOH) to 50 % B and 50 % C in 6.5 min, to 100 % B at 7 min and equilibrated to initial conditions at 7.5 min until 9.0 min. Injection volume 2 µl. High-resolution mass spectra (Time of Flight, TOF) were acquired only in positive ionization mode by scanning from 100 to 750 in 0.5 seconds (sec) using a dwell time of 0.1 sec. The capillary needle voltage was 2.5 kV and the cone voltage was 20 V. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

LCMS Method 8

In addition to general procedure A: RP UPLC was carried out on a BEH C18 column (1.7 µm, 2.1 x 50 mm; Waters Acquity) with a flow rate of 0.8 ml/min. 2 Mobile phases (25 mM NH_4OAc in H_2O/CH_3CN 95/5; mobile phase B: CH_3CN) were used to run a gradient condition from 95 % A and 5 % B to 5 % A and 95 % B in 1.3 min and hold for 0.3 min. An injection volume of 0.5 µl was used. Cone voltage was 30 V for positive ionization mode and 30 V for negative ionization mode.

Melting Points

For a number of compounds (indicated with 'DSC'), melting points (m.p.) were determined with a DSC823e (Mettler-Toledo). Melting points were measured with a temperature gradient of 30 °C/minute. Maximum temperature was 400 °C. Values are peak values.

For a number of compounds (indicated with 'M'), melting points were determined in open capillary tubes on a Mettler FP62 apparatus. Melting points were measured with a temperature gradient of 3 or 10 °C/minute. Maximum temperature was 300 °C. The melting point was read from a digital display.

The results of the analytical measurements are shown in table 11.

Table 11: Retention time (R_t) in min., $[M+H]^+$ peak (protonated molecule), LCMS method and m.p. (melting point in °C). (n.d. means not determined; dec. means decomposition)

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
1	1.09	414	1	209.2 DSC
2	6.96	448	6	168.9 DSC
3	1.05	428	1	n.d.
4	1.3	404	3	n.d.
5	5.45	410	5	177.8 DSC
6	1.06	415	1	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
7	1.06	427	1	n.d.
8	4.79	414	7	dec. M
9	1.453	376	3	n.d.
10	1.14	390	1	n.d.
11	5.71	418	5	n.d.
12	1.91	396	3	n.d.
13	2.65	472	3	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
14	2.32	430	3	n.d.
15	1.14	444	1	204.0 DSC
16	2.465	430	3	n.d.
17	2.40	430	3	n.d.
18	5.93	428	5	n.d.
19	2.27	414	3	n.d.
20	6.44	428	5	n.d.
21	1.02	414	1	n.d.
22	1.26	492	1	n.d.
23	1.01	442	2	n.d.
24	1.24	456	1	n.d.
25	2.48	432	3	n.d.
26	6.28	446	5	n.d.
27	0.97	446	2	198.2 DSC
28	2.06	444	3	n.d.
29	1.15	478	1	n.d.
30	2.60	464	3	n.d.
31	6.50	421	5	193.4 DSC
32	1.09	426	1	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
33	2.02	426	3	n.d.
34	1.11	440	1	n.d.
35	1.08	426	1	124.2 DSC
36	1.86	426	3	n.d.
37	6.05	456	4	n.d.
38	1.35	466	1	224.6 DSC
39	1.22	467	1	n.d.
40	1.81	481	3	n.d.
41	1.62	397	3	n.d.
42	1.61	397	3	n.d.
43	1.48	397	3	n.d.
44	1.55	450	3	n.d.
45	1.00	415	1	n.d.
46	1.04	412	1	n.d.
47	2.38	464	3	n.d.
48	2.69	464	3	n.d.
49	1.03	320	3	n.d.
50	1.12	334	3	n.d.
51	1.52	376	3	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
52	2.01	428	3	n.d.
53	3.43	450	3	n.d.
54	1.44	392	3	n.d.
55	1.39	417	3	n.d.
56	1.29	419	3	n.d.
57	7.93	540	5	n.d.
58	7.32	439	5	n.d.
59	1.96	404	3	n.d.
60	2.49	472	3	n.d.
61	2.57	472	3	n.d.
62	2.60	442	3	n.d.
63	1.17	454	1	159.9 DSC
64	0.89	410	2	n.d.
65	0.89	410	2	n.d.
66	1.13	428	1	n.d.
67	1.08	441	1	n.d.
68	1.08	411	1	183.2 DSC
69	1.50	376	3	n.d.
70	7.20	411	5	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
71	7.05	381	5	n.d.
73	9.06	449	5	n.d.
74	9.10	467	5	n.d.
75	8.71	449	5	n.d.
76	1.05	347	1	n.d.
77	0.84	335	1	n.d.
78	0.81	305	1	213.1 DSC
79	0.87	319	1	230.6 DSC
80	0.80	321	1	147.5 DSC
81	1.46	450	2	n.d.
82	1.07	382	1	n.d.
83	1.11	416	1	209.7 DSC
84	9.17	450	5	n.d.
86	1.07	382	1	165.7 DSC
87	1.30	416	2	232.0 DSC
88	2.32	414	3	n.d.
89	6.26	429	4	n.d.
90	1.11	399	1	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
91	7.82	417	5	n.d.
94	1.12	429	1	n.d.
98	7.78	400	5	n.d.
101	0.91	444	2	n.d.
102	5.85	503	6	n.d.
103	1.30	462	2	n.d.
104	1.21	428	2	n.d.
105	1.10	435	8	127.5 DSC
106	n.d.	n.d.	n.d.	203.4 DSC
107	0.80	439	8	n.d.
108	0.96	406	8	235.3 DSC
109	0.97	402	8	n.d.
110	5.38	418	6	n.d.
111	0.97	495	8	n.d.
112	1.16	432	8	163.3 DSC
113	0.89	392	8	203.5 DSC
114	0.98	599	8	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
115	5.72	406	6	n.d.
116	0.97	360	8	n.d.
117	0.88	376	8	n.d.
118	5.60	392	6	n.d.
119	0.87	322	8	n.d.
120	0.58	348	2	n.d.
121	0.80	378	8	180.4 DSC
123	n.d.	n.d.	n.d.	196.2 DSC
124	1.13	445	8	n.d.
125	1.07	459	8	173.0 DSC
126	1.08	488	2	n.d.
127	1.11	473	8	149.5 DSC
128	1.12	454	8	n.d.
129	1.15	487	8	n.d.
130	8.77	467	5	210.0 DSC
131	7.22	417	5	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
132	n.d.	n.d.	n.d.	165.1 DSC
133	1.16	433	8	n.d.
134	0.84	360	2	n.d.
135	3.07	436	3	n.d.
137	0.87	419	8	n.d.
138	1.20	479	8	151.5 DSC
139	1.29	445	8	n.d.
140	1.36	475	2	163.5 DSC
141	1.20	445	8	n.d.
142	1.19	395	8	187.9 DSC
144	0.90	335	8	n.d.
145	6.65	446	6	250.3 DSC
146	3.69	497	3	n.d.
147	3.82	513	3	n.d.
149	0.94	410	8	n.d.
150	1.01	426	8	169.9 DSC

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
151	5.78	446	6	215.7 DSC
152	2.49	419	3	n.d.
153	1.09	417	8	n.d.
154	1.33	415	2	n.d.
155	6.92	460	5	n.d.
156	6.34	432	5	n.d.
157	1.27	464	8	n.d.
158	n.d.	n.d.	n.d.	159.8 DSC
159	1.14	429	8	n.d.
160	1.03	377	8	n.d.
161	1.05	441	8	82.9 DSC
162	1.26	465	8	n.d.
163	1.43	474	8	179.3 DSC
164	1.04	403	8	236.8 DSC
165	0.97	369	8	225.9 DSC
166	1.14	417	8	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
167	1.11	430	8	242.6 DSC
168	1.06	461	8	n.d.
169	1.27	452	8	n.d.
170	0.89	419	8	n.d.
171	1.47	472	8	n.d.
172	0.82	335	8	n.d.
173	1.04	391	8	221.0 DSC
174	1.37	467	8	226.6 DSC

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
175	1.19	415	2	177.7 DSC
176	1.37	430	2	n.d.
177	1.48	509	2	n.d.
178	1.03	416	8	224.1 DSC
179	1.00	403	8	n.d.
180	1.19	404	2	n.d.
182	1.17	437	8	n.d.

For Co. No. 100 the $[M-H]^-$ peak was detected: Rt 6.04; $[M-H]^-$ 469; LCMS Method 5.
For Co. No. 122 the $[M-H]^-$ peak was detected: Rt 5.03; $[M-H]^-$ 441; LCMS Method 5.

NMR

For a number of compounds, ^1H NMR spectra were recorded on a Bruker DPX-360, on a Bruker DPX-400, on a Bruker Avance 500 spectrometer or on a Bruker Avance 600 spectrometer with standard pulse sequences, operating at 360, 400, 500 and 600 MHz respectively, using CHLOROFORM-*d* (deuterated chloroform, $CDCl_3$) or DMSO-d_6 (deuterated DMSO, dimethyl-d6 sulfoxide) as solvents. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal standard.

Compound 1: ^1H NMR (500 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H), 3.85 (s, 3 H), 6.71 (t, *J*=7.1 Hz, 1 H), 6.90 (s, 1 H), 6.93 (d, *J*=7.5 Hz, 1 H), 6.95 (d, *J*=2.3 Hz, 1 H), 7.00 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.15 (t, *J*=8.6 Hz, 2 H), 7.22 (d, *J*=8.4 Hz, 1 H), 7.33 (s, 1 H), 7.65 (d, *J*=1.3 Hz, 1 H), 7.70 (d, *J*=6.6 Hz, 1 H), 7.80 (s, 1 H), 7.94 (dd, *J*=8.5, 5.5 Hz, 2 H).

Compound 2: ^1H NMR (360 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H), 3.81 (s, 3 H), 7.02 (t, *J*=7.2 Hz, 1 H), 7.05 - 7.09 (m, 2 H), 7.15 (d, *J*=7.6 Hz, 1 H), 7.26 (d, *J*=2.2 Hz, 1

H), 7.29 (d, *J*=8.5 Hz, 1 H), 7.39 (t, *J*=8.8 Hz, 2 H), 7.69 (d, *J*=1.3 Hz, 1 H), 7.92 (d, *J*=6.6 Hz, 1 H), 8.18 (dd, *J*=8.7, 5.6 Hz, 2 H), 8.66 (s, 1 H).

Compound 3: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.35 (s, 3 H), 3.83 (s, 3 H), 4.24 (s, 2 H), 7.02 (dd, *J*=8.6, 2.2 Hz, 1 H), 7.17 (d, *J*=2.2 Hz, 1 H), 7.20 (t, *J*=8.8 Hz, 2 H), 7.31 (t, *J*=7.3 Hz, 1 H), 7.50 (dd, *J*=8.4, 5.5 Hz, 2 H), 7.53 (d, *J*=8.6 Hz, 1 H), 7.64 (d, *J*=8.0 Hz, 1 H), 7.67 (s, 1 H), 8.09 (s, 1 H), 8.41 (d, *J*=6.5 Hz, 1 H), 9.32 (d, *J*=1.6 Hz, 1 H), 9.66 (br. s., 1 H), 15.14 (br. s., 1 H).

Compound 5: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H), 2.65 (s, 3 H), 3.80 (s, 3 H), 6.87 (t, *J*=7.1 Hz, 1 H), 7.00 - 7.08 (m, 3 H), 7.23 - 7.28 (m, 2 H), 7.36 (t, *J*=7.3 Hz, 1 H), 7.50 (t, *J*=7.6 Hz, 2 H), 7.67 (d, *J*=1.3 Hz, 1 H), 7.83 - 7.91 (m, 3 H), 8.46 (s, 1 H).

Compound 7: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.65 (s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 6.81 (t, *J*=7.1 Hz, 1 H), 6.93 (ddd, *J*=7.9, 2.7, 1.3 Hz, 1 H), 6.97 (d, *J*=2.3 Hz, 1 H), 6.99 (d, *J*=7.5 Hz, 1 H), 7.08 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.36 (dt, *J*=7.5, 1.4 Hz, 1 H), 7.38 - 7.43 (m, 2 H), 7.50 (s, 1 H), 7.52 (d, *J*=6.7 Hz, 1 H), 7.67 (d, *J*=8.6 Hz, 1 H), 8.08 (s, 1 H), 8.65 (s, 1 H).

Compound 8: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H), 3.85 (s, 3 H), 6.77 (t, *J*=7.2 Hz, 1 H), 6.89 (s, 1 H), 6.94 (d, *J*=2.3 Hz, 1 H), 6.98 (d, *J*=7.2 Hz, 1 H), 6.99 (dd, *J*=8.3, 2.5 Hz, 1 H), 7.20 - 7.26 (m, 3 H), 7.33 (s, 1 H), 7.56 (dd, *J*=8.4, 5.3 Hz, 2 H), 7.59 (s, 1 H), 7.65 (s, 1 H), 7.81 (d, *J*=6.8 Hz, 1 H).

Compound 10: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.01 (t, *J*=7.3 Hz, 3 H), 1.25 (t, *J*=7.5 Hz, 3 H), 1.72 - 1.84 (m, *J*=7.5, 7.5, 7.5, 7.5, 7.5 Hz, 2 H), 2.30 (s, 3 H), 2.69 - 2.76 (m, *J*=8.1, 7.3 Hz, 2 H), 2.90 (q, *J*=7.5 Hz, 2 H), 3.83 (s, 3 H), 6.70 (t, *J*=7.1 Hz, 1 H), 6.88 (s, 1 H), 6.89 - 6.93 (m, 2 H), 6.96 (dd, *J*=8.4, 2.2 Hz, 1 H), 7.19 (d, *J*=8.4 Hz, 1 H), 7.24 (s, 1 H), 7.48 (d, *J*=6.7 Hz, 1 H), 7.64 (s, 1 H).

Compound 11: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.92 (t, *J*=7.4 Hz, 3 H), 0.92 (t, *J*=7.3 Hz, 3 H), 1.30 - 1.42 (m, *J*=7.4, 7.4, 7.4, 7.4, 7.4 Hz, 2 H), 1.52 - 1.63 (m, *J*=7.4, 7.4, 7.4, 7.4, 7.4 Hz, 2 H), 1.63 - 1.72 (m, *J*=7.5, 7.5, 7.5, 7.5 Hz, 2 H), 2.15 (s, 3 H), 2.68 (t, *J*=7.6 Hz, 2 H), 2.86 (t, *J*=7.4 Hz, 2 H), 3.78 (s, 3 H), 6.75 (t, *J*=7.1 Hz, 1 H), 6.95 (d, *J*=7.4 Hz, 1 H), 6.99 - 7.05 (m, 2 H), 7.21 - 7.26 (m, 2 H), 7.66 (s, 1 H), 7.81 (d, *J*=6.7 Hz, 1 H), 8.33 (s, 1 H).

Compound 15: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.14 (s, 3 H), 2.38 (s, 3 H), 3.77 (s, 3 H), 6.90 (t, *J*=7.1 Hz, 1 H), 7.03 - 7.08 (m, 3 H), 7.22 - 7.27 (m, 2 H), 7.41 - 7.50 (m, 2 H), 7.54 - 7.63 (m, 2 H), 7.66 (s, 1 H), 7.86 (d, *J*=6.7 Hz, 1 H), 8.53 (s, 1 H).

Compound 18: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.27 (s, 3 H), 2.46 (d, *J*=2.3 Hz, 3 H), 3.79 (s, 3 H), 6.77 (t, *J*=7.1 Hz, 1 H), 6.85 (s, 1 H), 6.89 (d, *J*=2.3 Hz, 1 H), 6.92 -

6.97 (m, 2 H), 7.13 - 7.20 (m, 2 H), 7.25 (t, *J*=7.1 Hz, 1 H), 7.31 (s, 1 H), 7.32 - 7.39 (m, 1 H), 7.48 (d, *J*=6.7 Hz, 1 H), 7.60 (s, 1 H), 7.69 (td, *J*=7.5, 1.9 Hz, 1 H).

Compound 21: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.11 (s, 3 H), 3.77 (s, 3 H), 6.82 (t, *J*=7.1 Hz, 1 H), 6.86 (d, *J*=1.3 Hz, 1 H), 7.06 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.06 (d, *J*=1.2 Hz, 1 H), 7.08 (s, 1 H), 7.20 (d, *J*=8.4 Hz, 1 H), 7.25 (d, *J*=2.3 Hz, 1 H), 7.30 (t, *J*=8.8 Hz, 2 H), 8.03 - 8.10 (m, 3 H), 8.40 (s, 1 H), 8.52 (s, 1 H).

Compound 22: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H), 3.86 (s, 3 H), 6.88 (t, *J*=7.1 Hz, 1 H), 6.90 (s, 1 H), 6.94 (d, *J*=2.3 Hz, 1 H), 6.98 - 7.03 (m, 2 H), 7.20 (t, *J*=8.7 Hz, 2 H), 7.24 (d, *J*=8.4 Hz, 1 H), 7.29 (s, 1 H), 7.66 (d, *J*=1.3 Hz, 1 H), 7.75 (dd, *J*=6.8, 1.0 Hz, 1 H), 8.12 (dd, *J*=8.8, 5.4 Hz, 2 H).

Compound 23: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.28 (t, *J*=7.4 Hz, 3 H), 2.15 (s, 3 H), 3.10 (q, *J*=7.4 Hz, 2 H), 3.80 (s, 3 H), 6.86 (t, *J*=7.1 Hz, 1 H), 7.02 - 7.07 (m, 3 H), 7.24 - 7.28 (m, 2 H), 7.34 (t, *J*=8.8 Hz, 2 H), 7.67 (d, *J*=1.3 Hz, 1 H), 7.85 (dd, *J*=8.6, 5.6 Hz, 2 H), 7.94 (d, *J*=6.8 Hz, 1 H), 8.47 (s, 1 H).

Compound 24: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.97 (t, *J*=7.3 Hz, 3 H), 1.64 - 1.75 (m, *J*=7.5, 7.5, 7.5, 7.5, 7.5 Hz, 2 H), 2.36 (s, 3 H), 3.11 (t, *J*=7.8 Hz, 2 H), 3.86 (s, 3 H), 7.12 (dd, *J*=8.6, 2.2 Hz, 1 H), 7.24 (t, *J*=6.7 Hz, 1 H), 7.28 (d, *J*=2.2 Hz, 1 H), 7.45 (t, *J*=8.7 Hz, 2 H), 7.49 - 7.57 (m, 1 H), 7.54 (d, *J*=8.6 Hz, 1 H), 7.69 (s, 1 H), 7.91 (dd, *J*=8.6, 5.4 Hz, 2 H), 8.32 (d, *J*=6.7 Hz, 1 H), 9.33 (d, *J*=1.6 Hz, 1 H), 9.64 (br. s., 1 H), 15.12 (br. s., 1 H).

Compound 26: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H), 2.44 (d, *J*=2.1 Hz, 3 H), 3.79 (s, 3 H), 6.90 (t, *J*=7.1 Hz, 1 H), 7.02 - 7.09 (m, 3 H), 7.22 - 7.28 (m, 3 H), 7.41 (td, *J*=10.0, 2.6 Hz, 1 H), 7.67 (s, 1 H), 7.74 (td, *J*=8.6, 6.7 Hz, 1 H), 7.87 (d, *J*=6.8 Hz, 1 H), 8.53 (s, 1 H).

Compound 27: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H), 2.38 (s, 3 H), 3.78 (s, 3 H), 6.91 (t, *J*=7.1 Hz, 1 H), 7.01 - 7.10 (m, 3 H), 7.21 - 7.30 (m, 4 H), 7.57 (tt, *J*=8.4, 6.6 Hz, 1 H), 7.67 (s, 1 H), 7.88 (d, *J*=6.8 Hz, 1 H), 8.52 (s, 1 H).

Compound 29: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H), 2.39 (s, 3 H), 3.84 (s, 3 H), 7.06 (dd, *J*=8.6, 2.2 Hz, 1 H), 7.22 (d, *J*=2.2 Hz, 1 H), 7.44 (t, *J*=7.6 Hz, 1 H), 7.54 (d, *J*=8.6 Hz, 1 H), 7.68 (s, 1 H), 7.69 - 7.75 (m, 2 H), 7.83 - 7.95 (m, 2 H), 8.02 (d, *J*=7.6 Hz, 1 H), 8.35 (d, *J*=6.6 Hz, 1 H), 9.34 (d, *J*=1.6 Hz, 1 H), 9.79 (br. s., 1 H), 15.15 (br. s., 1 H).

Compound 31: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H), 3.81 (s, 3 H), 6.84 (t, *J*=7.1 Hz, 1 H), 7.03 - 7.08 (m, 3 H), 7.22 - 7.28 (m, 2 H), 7.68 (d, *J*=0.5 Hz, 1 H), 7.93 (d, *J*=8.3 Hz, 2 H), 8.08 (d, *J*=6.6 Hz, 1 H), 8.23 (d, *J*=8.3 Hz, 2 H), 8.52 (s, 1 H), 8.60 (s, 1 H).

Compound 32: 1H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H), 3.81 (s, 3 H), 3.99 (s, 3 H), 6.77 (t, *J*=7.1 Hz, 1 H), 7.01 (d, *J*=7.5 Hz, 1 H), 7.04 - 7.11 (m, 3 H), 7.15 (d, *J*=8.3 Hz, 1 H), 7.23 - 7.29 (m, 2 H), 7.29 - 7.36 (m, 1 H), 7.68 (d, *J*=1.3 Hz, 1 H), 8.11 (d, *J*=6.6 Hz, 1 H), 8.39 (s, 1 H), 8.43 (s, 1 H), 8.46 (dd, *J*=7.7, 1.8 Hz, 1 H).

Compound 34: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H), 2.65 (s, 3 H), 3.84 (s, 3 H), 3.90 (s, 3 H), 6.79 (t, *J*=7.1 Hz, 1 H), 6.89 (s, 1 H), 6.91 - 6.97 (m, 3 H), 6.99 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.21 (d, *J*=8.4 Hz, 1 H), 7.35 - 7.42 (m, 4 H), 7.50 (d, *J*=6.7 Hz, 1 H), 7.64 (d, *J*=1.3 Hz, 1 H).

Compound 35: 1H NMR (400 MHz, $CDCl_3$) δ ppm 2.65 (s, 3 H), 3.84 (s, 3 H), 3.90 (s, 3 H), 6.79 (t, *J*=7.1 Hz, 1 H), 6.93 (ddd, *J*=7.8, 2.7, 1.4 Hz, 1 H), 6.97 (d, *J*=7.2 Hz, 1 H), 6.96 (d, *J*=2.1 Hz, 1 H), 7.01 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.16 - 7.18 (m, 2 H), 7.24 (d, *J*=8.4 Hz, 1 H), 7.35 - 7.43 (m, 4 H), 7.51 (d, *J*=6.7 Hz, 1 H), 7.75 (s, 1 H).

Compound 37: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 3.97 (s, 3 H), 6.65 - 6.71 (m, 2 H), 6.75 (t, *J*=7.1 Hz, 1 H), 6.99 (d, *J*=7.5 Hz, 1 H), 7.03 - 7.08 (m, 2 H), 7.22 - 7.28 (m, 2 H), 7.68 (d, *J*=1.3 Hz, 1 H), 8.09 (d, *J*=6.6 Hz, 1 H), 8.26 (s, 1 H), 8.34 (d, *J*=8.2 Hz, 1 H), 8.39 (s, 1 H).

Compound 39: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.12 (t, *J*=7.0 Hz, 6 H), 2.15 (s, 3 H), 3.38 (q, *J*=7.3 Hz, 4 H), 3.80 (s, 3 H), 6.68 - 6.77 (m, 3 H), 6.98 (d, *J*=7.5 Hz, 1 H), 7.01 - 7.06 (m, 2 H), 7.22 - 7.28 (m, 2 H), 7.67 (d, *J*=1.3 Hz, 1 H), 7.80 (d, *J*=8.6 Hz, 2 H), 8.01 (d, *J*=6.6 Hz, 1 H), 8.15 (s, 1 H), 8.38 (s, 1 H).

Compound 45: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 3.78 (s, 3 H) 6.84 (t, *J*=6.86 Hz, 1 H) 7.08 (dd, *J*=8.88, 2.02 Hz, 1 H) 7.11 (d, *J*=7.27 Hz, 1 H) 7.25 (d, *J*=2.02 Hz, 1 H) 7.27 (d, *J*=8.88 Hz, 1 H) 7.29 (t, *J*=8.88 Hz, 2 H) 7.95 (s, 1 H) 8.06 (dd, *J*=8.88, 5.25 Hz, 2 H) 8.10 (dd, *J*=6.46, 0.81 Hz, 1 H) 8.40 (s, 1 H) 8.58 (s, 1 H).

Compound 46: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H) 2.66 (s, 3 H) 3.88 (s, 3 H) 6.75 - 6.84 (m, 2 H) 6.93 (ddd, *J*=7.96, 2.65, 1.10 Hz, 1 H) 7.32 - 7.38 (m, 3 H) 7.40 (t, *J*=7.87 Hz, 1 H) 7.52 - 7.61 (m, 2 H) 8.46 (s, 1 H) 8.68 (s, 2 H).

Compound 57: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H) 3.80 (s, 3 H) 6.99 (t, *J*=7.32 Hz, 1 H) 7.03 - 7.08 (m, 2 H) 7.15 (d, *J*=7.32 Hz, 1 H) 7.25 (d, *J*=2.20 Hz, 1 H) 7.28 (d, *J*=8.42 Hz, 1 H) 7.38 (t, *J*=8.78 Hz, 2 H) 7.68 (s, 1 H) 7.95 (d, *J*=6.95 Hz, 1 H) 8.13 (dd, *J*=8.60, 5.67 Hz, 2 H) 8.62 (s, 1 H).

Compound 58: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H) 3.87 (s, 3 H) 6.91 (s, 1 H) 6.93 - 7.03 (m, 3 H) 7.13 (d, *J*=7.68 Hz, 1 H) 7.21 (t, *J*=8.60 Hz, 2 H) 7.26 (d, *J*=8.42 Hz, 1 H) 7.34 (s, 1 H) 7.67 (d, *J*=0.73 Hz, 1 H) 7.88 (d, *J*=6.59 Hz, 1 H) 8.20 (dd, *J*=8.60, 5.31 Hz, 2 H).

Compound 63: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.50 Hz, 3 H) 2.53 - 2.57 (m, 2 H) 2.65 (s, 3 H) 3.80 (s, 3 H) 3.83 (s, 3 H) 6.87 (t, *J*=7.14 Hz, 1 H) 6.90 -

6.98 (m, 1 H) 7.02 - 7.08 (m, 3 H) 7.25 (d, *J*=2.20 Hz, 1 H) 7.28 (d, *J*=8.42 Hz, 1 H) 7.37 - 7.46 (m, 3 H) 7.69 (s, 1 H) 7.89 (d, *J*=6.59 Hz, 1 H) 8.47 (s, 1 H).

Compound 64: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.32 (s, 3 H) 2.68 (s, 3 H) 3.93 (s, 3 H) 6.87 - 6.96 (m, 1 H) 6.97 - 7.01 (m, 2 H) 7.05 - 7.12 (m, 1 H) 7.35 (d, *J*=8.80 Hz, 2 H) 7.36 - 7.39 (m, 1 H) 7.42 (t, *J*=7.78 Hz, 1 H) 7.45 - 7.49 (m, 3 H) 7.54 (d, *J*=6.75 Hz, 1 H) 7.75 (s, 1 H).

Compound 65: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.19 (s, 3 H) 2.66 (s, 3 H) 3.91 (s, 3 H) 6.80 (t, *J*=7.14 Hz, 1 H) 6.91 (s, 1 H) 6.91 - 6.96 (m, 1 H) 6.99 (d, *J*=7.32 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 7.33 - 7.45 (m, 6 H) 7.52 (d, *J*=6.59 Hz, 1 H) 7.57 (s, 1 H).

Compound 66: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H) 2.66 (s, 3 H) 3.91 (s, 3 H) 6.81 (t, *J*=7.14 Hz, 1 H) 6.91 - 6.96 (m, 2 H) 6.99 (d, *J*=7.32 Hz, 1 H) 7.12 (dd, *J*=8.96, 2.56 Hz, 1 H) 7.28 - 7.46 (m, 6 H) 7.54 (d, *J*=6.59 Hz, 1 H) 7.68 (s, 1 H).

Compound 67: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.65 (s, 3 H) 3.77 - 3.88 (m, 6 H) 6.88 (t, *J*=7.14 Hz, 1 H) 6.93 - 7.00 (m, 1 H) 7.02 - 7.13 (m, 2 H) 7.27 (d, *J*=2.20 Hz, 1 H) 7.39 - 7.43 (m, 3 H) 7.47 (d, *J*=8.78 Hz, 1 H) 7.91 (d, *J*=6.59 Hz, 1 H) 8.55 (s, 1 H) 8.67 (s, 1 H).

Compound 70: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.56 (s, 3 H) 3.84 (s, 3 H) 6.82 (t, *J*=7.14 Hz, 1 H) 7.06 (d, *J*=7.32 Hz, 1 H) 7.10 (dd, *J*=8.78, 2.20 Hz, 1 H) 7.21 - 7.35 (m, 4 H) 7.48 (d, *J*=8.78 Hz, 1 H) 8.02 (d, *J*=7.68 Hz, 1 H) 8.11 (d, *J*=6.59 Hz, 1 H) 8.21 (s, 1 H) 8.54 (s, 1 H) 8.67 (s, 1 H).

Compound 71: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 2.55 (s, 3 H) 6.80 (dd, *J*=7.32, 6.59 Hz, 1 H) 6.95 (dd, *J*=7.68, 0.73 Hz, 1 H) 7.20 - 7.35 (m, 3 H) 7.51 (m, *J*=8.78 Hz, 2 H) 7.73 (m, *J*=9.15 Hz, 2 H) 7.97 - 8.04 (m, 1 H) 8.09 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.19 (s, 1 H) 8.49 (s, 1 H) 9.04 (s, 1 H).

Compound 73: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 2.66 (s, 3 H) 6.83 (dd, *J*=7.32, 6.95 Hz, 1 H) 6.96 (d, *J*=7.68 Hz, 1 H) 7.52 (m, 2 H) 7.56 (d, *J*=8.42 Hz, 1 H) 7.61 (dd, *J*=8.05, 1.83 Hz, 1 H) 7.74 (m, 2 H) 8.10 (dd, *J*=6.59, 1.10 Hz, 1 H) 8.36 (s, 1 H) 8.44 (d, *J*=1.46 Hz, 1 H) 8.59 (s, 1 H) 9.05 (s, 1 H).

Compound 74: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 2.65 (s, 3 H) 6.88 (t, *J*=7.14 Hz, 1 H) 7.11 (d, *J*=7.32 Hz, 1 H) 7.33 (dd, *J*=8.78, 2.20 Hz, 1 H) 7.40 (dd, *J*=13.17, 2.20 Hz, 1 H) 7.51 - 7.67 (m, 3 H) 8.19 (d, *J*=6.59 Hz, 1 H) 8.39 (s, 1 H) 8.42 (s, 1 H) 8.76 (d, *J*=1.83 Hz, 1 H) 8.90 (s, 1 H).

Compound 75: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.47 (s, 3 H) 2.66 (s, 3 H) 6.85 (t, *J*=7.14 Hz, 1 H) 7.05 (d, *J*=7.32 Hz, 1 H) 7.44 - 7.65 (m, 6 H) 8.00 (s, 1 H) 8.14 (d, *J*=6.59 Hz, 1 H) 8.38 (s, 1 H) 8.44 (d, *J*=1.46 Hz, 1 H) 8.70 (s, 1 H).Compound 76: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.94 (t, *J*=7.32 Hz, 3 H) 1.38 (sxt, *J*=7.39 Hz, 2 H) 1.79 (quin, *J*=7.50 Hz, 2 H) 2.39 (s, 3 H) 2.86 (t, *J*=7.50 Hz, 2 H) 7.31 (dd, *J*=8.05,

6.59 Hz, 1 H) 7.47 (m, 2 H) 7.53 (d, *J*=7.68 Hz, 1 H) 7.82 (m, 2 H) 8.15 (s, 1 H) 8.34 (d, *J*=5.85 Hz, 1 H) 9.26 (s, 1 H) 9.66 (s, 1 H) 15.14 (br. s., 1 H).

Compound 77:1H NMR (360 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 2.37 (s, 3 H) 3.82 (s, 3 H) 6.73 (dd, *J*=7.32, 6.95 Hz, 1 H) 6.99 (d, *J*=7.32 Hz, 1 H) 7.04 (dd, *J*=8.78, 2.20 Hz, 1 H) 7.23 (d, *J*=2.56 Hz, 1 H) 7.44 (d, *J*=8.78 Hz, 1 H) 7.68 (d, *J*=0.73 Hz, 1 H) 7.99 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.51 (s, 1 H) 8.65 (s, 1 H).

Compound 78: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 2.36 (d, *J*=0.73 Hz, 3 H) 6.71 (dd, *J*=7.50, 6.77 Hz, 1 H) 6.88 (dd, *J*=7.68, 0.73 Hz, 1 H) 7.46 (m, 2 H) 7.67 (d, *J*=1.10 Hz, 1 H) 7.69 (m, 2 H) 7.97 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.50 (s, 1 H) 9.02 (s, 1 H).

Compound 80: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.37 (s, 3 H) 3.83 (s, 3 H) 6.73 (dd, *J*=7.50, 6.77 Hz, 1 H) 7.01 (dd, *J*=7.68, 0.73 Hz, 1 H) 7.07 (dd, *J*=8.78, 2.20 Hz, 1 H) 7.25 (d, *J*=2.20 Hz, 1 H) 7.46 (d, *J*=8.42 Hz, 1 H) 7.68 (d, *J*=0.73 Hz, 1 H) 8.00 (dd, *J*=6.59, 1.10 Hz, 1 H) 8.15 (s, 1 H) 8.55 (s, 1 H) 8.81 (s, 1 H).

Compound 81: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.51 (s, 3 H) 2.63 (s, 3 H) 6.87 (t, *J*=6.95 Hz, 1 H) 7.10 (d, *J*=8.78 Hz, 1 H) 7.42 (d, *J*=8.05 Hz, 1 H) 7.52 (dd, *J*=7.87, 1.65 Hz, 1 H) 7.75 (s, 1 H) 7.81 (dd, *J*=6.95, 0.73 Hz, 1 H) 7.87 (dd, *J*=8.96, 2.74 Hz, 1 H) 8.22 (s, 1 H) 8.24 (d, *J*=1.10 Hz, 1 H) 8.33 (d, *J*=6.95 Hz, 1 H) 8.37 (s, 1 H) 8.60 (d, *J*=2.56 Hz, 1 H).

Compound 82: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.51 (s, 3 H) 2.57 (s, 3 H) 6.83 (t, *J*=7.14 Hz, 1 H) 7.05 (d, *J*=9.15 Hz, 1 H) 7.28 - 7.36 (m, 3 H) 7.69 (s, 1 H) 7.80 (d, *J*=6.59 Hz, 1 H) 7.84 (dd, *J*=8.78, 2.93 Hz, 1 H) 7.87 - 7.91 (m, 1 H) 8.26 (s, 1 H) 8.29 (d, *J*=7.68 Hz, 1 H) 8.37 (s, 1 H) 8.59 (d, *J*=2.56 Hz, 1 H).

Compound 83: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.44 (s, 3 H) 2.51 (s, 3 H) 6.93 (t, *J*=7.32 Hz, 1 H) 7.01 (dd, *J*=8.78, 0.73 Hz, 1 H) 7.32 - 7.43 (m, 2 H) 7.48 - 7.63 (m, 3 H) 7.82 (dd, *J*=8.78, 2.56 Hz, 1 H) 8.20 (s, 1 H) 8.30 - 8.39 (m, 2 H) 8.58 (d, *J*=2.56 Hz, 1 H).

Compound 84: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.39 (s, 3 H) 2.65 (s, 3 H) 6.85 (t, *J*=6.95 Hz, 1 H) 6.97 (d, *J*=7.32 Hz, 1 H) 7.56 (d, *J*=8.42 Hz, 1 H) 7.60 (dd, *J*=8.05, 1.83 Hz, 1 H) 7.75 (d, *J*=8.78 Hz, 1 H) 7.99 (dd, *J*=8.78, 2.56 Hz, 1 H) 8.15 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.38 (s, 1 H) 8.42 (d, *J*=1.46 Hz, 1 H) 8.54 (d, *J*=2.56 Hz, 1 H) 8.83 (s, 1 H) 9.14 (s, 1 H).

Compound 86: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.39 (s, 3 H) 2.55 (s, 3 H) 6.81 (t, *J*=7.14 Hz, 1 H) 6.95 (d, *J*=6.95 Hz, 1 H) 7.21 - 7.33 (m, 3 H) 7.74 (d, *J*=8.78 Hz, 1 H) 7.91 - 8.02 (m, 2 H) 8.14 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.21 (s, 1 H) 8.53 (d, *J*=2.56 Hz, 1 H) 8.77 (s, 1 H) 9.13 (s, 1 H).

Compound 87: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.44 (s, 3 H) 2.51 (s, 3 H) 6.84 (t, *J*=7.32, 6.59 Hz, 1 H) 6.89 (dd, *J*=7.68, 0.73 Hz, 1 H) 7.32 (s, 1 H) 7.33 - 7.42 (m, 2 H) 7.47 - 7.60 (m, 3 H) 7.81 (d, *J*=1.83 Hz, 2 H) 8.42 (t, *J*=1.83 Hz, 1 H) 8.97 (s, 1 H).

Compound 89: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.56 (s, 3 H) 3.84 (s, 3 H) 6.83 (t, *J*=6.95 Hz, 1 H) 7.04 - 7.21 (m, 4 H) 7.27 (d, *J*=2.20 Hz, 1 H) 7.48 (d, *J*=8.42 Hz, 1 H) 8.03 (dd, *J*=8.42, 6.22 Hz, 1 H) 8.11 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.19 (s, 1 H) 8.54 (s, 1 H) 8.67 (s, 1 H).

Compound 90: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.51 (s, 3 H) 2.55 (s, 3 H) 6.74 (t, *J*=6.95 Hz, 1 H) 6.92 (d, *J*=7.32 Hz, 1 H) 6.95 - 7.05 (m, 2 H) 7.33 (s, 1 H) 7.41 (m, 2 H) 7.62 (m, 2 H) 7.64 (s, 1 H) 7.72 (dd, *J*=6.59, 0.73 Hz, 1 H) 7.83 (dd, *J*=9.15, 6.22 Hz, 1 H) 8.39 (s, 1 H).

Compound 91: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 2.55 (s, 3 H) 6.85 (dd, *J*=6.86 Hz, 1 H) 7.09 (dd, *J*=7.67, 0.81 Hz, 1 H) 7.10 - 7.20 (m, 2 H) 7.31 (dd, *J*=8.88, 2.02 Hz, 1 H) 7.37 (dd, *J*=13.32, 2.42 Hz, 1 H) 7.60 (t, *J*=8.88 Hz, 1 H) 7.99 (dd, *J*=8.68, 6.26 Hz, 1 H) 8.17 (dd, *J*=6.46, 0.81 Hz, 1 H) 8.20 (s, 1 H) 8.74 (d, *J*=2.02 Hz, 1 H) 8.81 (s, 1 H).Compound 94: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.49 (s, 3 H) 2.51 (s, 3 H) 3.87 (s, 3 H) 6.76 (t, *J*=6.95 Hz, 1 H) 6.85 (dd, *J*=8.23, 2.74 Hz, 1 H) 6.98 (d, *J*=7.32 Hz, 1 H) 7.17 - 7.24 (m, 3 H) 7.45 (s, 1 H) 7.49 (d, *J*=2.93 Hz, 1 H) 7.71 (s, 1 H) 7.72 - 7.80 (m, 2 H) 8.46 (d, *J*=2.56 Hz, 1 H).

Compound 98: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.39 (s, 3 H) 2.55 (s, 3 H) 6.83 (t, *J*=6.95 Hz, 1 H) 6.96 (dd, *J*=7.68, 0.73 Hz, 1 H) 7.09 - 7.21 (m, 2 H) 7.74 (d, *J*=8.78 Hz, 1 H) 7.93 - 8.03 (m, 2 H) 8.13 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.20 (s, 1 H) 8.52 (d, *J*=2.56 Hz, 1 H) 8.78 (s, 1 H) 9.13 (s, 1 H).

Compound 107: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H) 2.52 (s, 3 H) 3.76 (s, 2 H) 3.80 (s, 3 H) 6.80 (t, *J*=7.14 Hz, 1 H) 7.02 (d, *J*=7.68 Hz, 1 H) 7.03 - 7.08 (m, 2 H) 7.22 - 7.29 (m, 4 H) 7.68 (d, *J*=1.46 Hz, 1 H) 7.95 (s, 1 H) 8.09 (d, *J*=6.59 Hz, 1 H) 8.18 (s, 1 H) 8.46 (s, 1 H).

Compound 109: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H), 3.65 (q, *J*=10.7 Hz, 2 H), 3.84 (s, 3 H), 6.72 (t, *J*=7.1 Hz, 1 H), 6.89 (s, 1 H), 6.91 - 6.94 (m, 2 H), 6.97 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.16 (s, 1 H), 7.21 (d, *J*=8.4 Hz, 1 H), 7.56 (s, 1 H), 7.65 (d, *J*=1.3 Hz, 1 H), 7.66 (d, *J*=6.6 Hz, 1 H).

Compound 111: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.19 (t, *J*=7.68 Hz, 3 H) 2.26 (q, *J*=7.68 Hz, 2 H) 2.31 (s, 3 H) 2.55 (s, 3 H) 3.86 (s, 3 H) 4.50 (d, *J*=5.49 Hz, 2 H) 5.72 (br. s., 1 H) 6.75 (dd, *J*=7.32, 6.95 Hz, 1 H) 6.90 (t, *J*=1.10 Hz, 1 H) 6.93 - 6.98 (m, 2 H) 7.00 (dd, *J*=8.42, 2.20 Hz, 1 H) 7.19 - 7.24 (m, 2 H) 7.28 (d, *J*=8.05 Hz, 1 H) 7.37 (br. s., 1 H) 7.66 (d, *J*=1.46 Hz, 1 H) 7.70 (s, 1 H) 7.73 (dd, *J*=6.59, 0.73 Hz, 1 H) 7.87 (d, *J*=1.83 Hz, 1 H).

Compound 112: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 3.99 (s, 3 H) 6.87 (t, *J*=7.14 Hz, 1 H) 7.02 (d, *J*=7.68 Hz, 1 H) 7.18 (s, 1 H) 7.26 - 7.42 (m, 4 H) 7.48 (t, *J*=8.78 Hz, 1 H) 7.81 (s, 1 H) 7.88 (d, *J*=6.59 Hz, 1 H) 8.10 (dd, *J*=8.60, 5.67 Hz, 2 H) 8.74 (s, 1 H).

Compound 114: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.50 (s, 3 H) 2.57 (s, 3 H) 3.30 (s, 3 H) 3.44 - 3.51 (m, 2 H) 3.56 - 3.63 (m, 2 H) 3.64 - 3.69 (m, 2 H) 3.69 - 3.75 (m, 2 H) 3.90 (s, 3 H) 4.09 (s, 2 H) 4.55 (d, *J*=6.22 Hz, 2 H) 7.03 (s, 1 H) 7.07 (t, *J*=7.14 Hz, 1 H) 7.13 (dd, *J*=8.60, 2.01 Hz, 1 H) 7.18 (d, *J*=2.20 Hz, 1 H) 7.28 - 7.38 (m, 3 H) 7.63 (t, *J*=5.85 Hz, 1 H) 7.82 (s, 1 H) 7.87 (s, 1 H) 7.92 (d, *J*=6.59 Hz, 1 H) 8.39 (d, *J*=1.10 Hz, 1 H) 9.55 (br. s., 1 H).

Compound 117: 1H NMR (360 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.32 Hz, 3 H) 2.15 (s, 3 H) 3.13 (q, *J*=7.32 Hz, 2 H) 3.80 (s, 3 H) 6.88 (t, *J*=7.14 Hz, 1 H) 7.00 - 7.09 (m, 3 H) 7.20 - 7.32 (m, 2 H) 7.68 (d, *J*=1.10 Hz, 1 H) 8.08 (d, *J*=6.59 Hz, 1 H) 8.51 - 8.62 (m, 2 H).

Compound 124: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.43 (s, 3 H) 2.49 (s, 3 H) 3.88 (s, 3 H) 6.83 (t, *J*=7.14 Hz, 1 H) 6.93 (d, *J*=2.20 Hz, 1 H) 7.00 (d, *J*=7.68 Hz, 1 H) 7.05 (dd, *J*=8.42, 2.20 Hz, 1 H) 7.32 - 7.42 (m, 3 H) 7.48 - 7.54 (m, 2 H) 7.54 - 7.59 (m, 1 H) 7.63 (d, *J*=8.42 Hz, 1 H) 8.50 (s, 1 H).

Compound 132: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 3.85 (s, 3 H) 4.00 (s, 3 H) 6.87 (t, *J*=7.27 Hz, 1 H) 7.03 (dd, *J*=7.67, 0.81 Hz, 1 H) 7.10 (dd, *J*=8.68, 2.22 Hz, 1 H) 7.28 (d, *J*=2.42 Hz, 1 H) 7.34 (t, *J*=8.88 Hz, 2 H) 7.49 (d, *J*=8.88 Hz, 1 H) 7.84 (dd, *J*=6.86, 0.81 Hz, 1 H) 8.12 (dd, *J*=8.88, 5.65 Hz, 2 H) 8.50 (s, 1 H) 8.67 (s, 1 H).

Compound 136: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.70 - 1.95 (m, *J*=12.30, 12.30, 12.17, 4.21 Hz, 2 H) 2.04 (dd, *J*=12.62, 2.01 Hz, 2 H) 2.34 (s, 3 H) 3.13 - 3.26 (m, *J*=11.62, 11.62, 3.66, 3.48 Hz, 1 H) 3.51 (td, *J*=11.62, 1.65 Hz, 2 H) 3.85 (s, 3 H) 3.98 (dd, *J*=11.71, 2.20 Hz, 2 H) 7.00 (dd, *J*=8.78, 2.20 Hz, 1 H) 7.13 (d, *J*=2.20 Hz, 1 H) 7.32 (t, *J*=7.32 Hz, 1 H) 7.56 (d, *J*=8.42 Hz, 1 H) 7.63 (d, *J*=8.05 Hz, 1 H) 8.18 (s, 1 H) 8.35 (d, *J*=6.59 Hz, 1 H) 8.72 (s, 1 H) 9.56 (br. s., 1 H) 14.97 (br. s., 1 H).

Compound 138: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.31 (s, 3 H) 2.35 (s, 3 H) 4.08 (s, 3 H) 6.56 (d, *J*=8.42 Hz, 1 H) 6.88 (s, 1 H) 6.91 (t, *J*=7.32 Hz, 1 H) 7.43 (d, *J*=8.42 Hz, 1 H) 7.50 (d, *J*=7.32 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 7.61 - 7.69 (m, 2 H) 7.83 (d, *J*=7.68 Hz, 1 H) 8.10 (br. s., 1 H) 8.19 (d, *J*=7.68 Hz, 1 H).

Compound 140: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H) 3.29 (s, 3 H) 4.08 (s, 3 H) 4.70 (s, 2 H) 6.56 (d, *J*=8.42 Hz, 1 H) 6.86 - 6.93 (m, 2 H) 7.38 - 7.42 (m, 2 H) 7.44 (d, *J*=8.05 Hz, 1 H) 7.51 - 7.59 (m, 2 H) 7.65 (s, 1 H) 7.88 (d, *J*=6.59 Hz, 1 H) 8.07 (s, 1 H) 8.23 (d, *J*=7.68 Hz, 1 H).

Compound 141: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H) 4.00 (s, 6 H) 6.95 (t, *J*=7.14 Hz, 1 H) 7.06 - 7.13 (m, 2 H) 7.35 (t, *J*=8.78 Hz, 2 H) 7.70 (d, *J*=8.05 Hz, 1 H) 7.74 (s, 1 H) 7.90 (d, *J*=6.59 Hz, 1 H) 8.10 - 8.22 (m, 3 H) 9.17 (s, 1 H).

Compound 143: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.63 - 1.80 (m, 2 H) 1.98 (dd, *J*=12.99, 2.01 Hz, 2 H) 2.15 (s, 3 H) 2.98 (tt, *J*=11.48, 3.70 Hz, 1 H) 3.48 (td, *J*=11.53, 1.83 Hz, 2 H) 3.91 - 4.00 (m, 5 H) 6.83 (t, *J*=7.32 Hz, 1 H) 7.06 (d, *J*=8.42 Hz, 1 H) 7.09 (s, 1 H) 7.66 (d, *J*=8.42 Hz, 1 H) 7.72 (s, 1 H) 7.73 (d, *J*=1.10 Hz, 1 H) 8.05 (dd, *J*=6.59, 0.73 Hz, 1 H) 8.13 (d, *J*=7.68 Hz, 1 H) 9.10 (s, 1 H).

Compound 144: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H) 2.38 (s, 3 H) 3.97 (s, 3 H) 6.80 (t, *J*=7.14 Hz, 1 H) 7.05 - 7.10 (m, 2 H) 7.65 (d, *J*=8.42 Hz, 1 H) 7.68 (s, 1 H) 7.72 (d, *J*=1.10 Hz, 1 H) 8.03 (d, *J*=6.59 Hz, 1 H) 8.15 (d, *J*=7.68 Hz, 1 H) 9.27 (s, 1 H).

Compound 145: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.38 (s, 3 H) 4.04 (s, 3 H) 7.01 (t, *J*=7.14 Hz, 1 H) 7.09 (d, *J*=8.42 Hz, 1 H) 7.41 - 7.53 (m, 2 H) 7.54 - 7.67 (m, 2 H) 7.82 (d, *J*=8.42 Hz, 1 H) 7.95 (d, *J*=6.22 Hz, 1 H) 8.26 (d, *J*=7.32 Hz, 1 H) 8.71 (s, 1 H) 9.41 (s, 1 H).

Compound 148: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H) 2.54 (s, 3 H) 6.97 (dd, *J*=11.16, 2.01 Hz, 1 H) 7.08 - 7.24 (m, 3 H) 7.39 (dd, *J*=8.60, 2.01 Hz, 1 H) 7.44 - 7.59 (m, 2 H) 7.86 (s, 1 H) 7.97 (dd, *J*=8.42, 6.22 Hz, 1 H) 8.17 (s, 1 H) 8.29 (dd, *J*=4.03, 2.20 Hz, 1 H) 9.06 (s, 1 H).

Compound 157: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.32 (s, 3 H) 2.52 (s, 3 H) 3.88 (s, 3 H) 6.61 (s, 1 H) 6.93 (s, 1 H) 6.95 - 7.01 (m, 2 H) 7.03 (dd, *J*=8.28, 2.22 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 7.33 (d, *J*=8.07 Hz, 1 H) 7.67 (dd, *J*=10.09, 2.83 Hz, 1 H) 7.70 (d, *J*=1.21 Hz, 1 H) 7.90 (br. s., 1 H) 7.99 (s, 1 H).

Compound 158: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.68 - 1.87 (m, 2 H) 1.88 - 2.05 (m, 2 H) 2.16 (s, 3 H) 2.96 - 3.09 (m, 1 H) 3.49 (t, *J*=10.79 Hz, 2 H) 3.81 (s, 3 H) 3.89 - 4.04 (m, 2 H) 6.76 (s, 1 H) 7.08 - 7.15 (m, 2 H) 7.35 (d, *J*=1.83 Hz, 1 H) 7.43 (d, *J*=8.42 Hz, 1 H) 7.77 (s, 1 H) 8.20 (s, 1 H) 10.07 (s, 1 H).

Compound 159: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.56 (s, 3 H) 3.84 (s, 3 H) 6.74 (d, *J*=5.49 Hz, 1 H) 7.08 - 7.15 (m, 2 H) 7.17 (dd, *J*=8.42, 2.20 Hz, 1 H) 7.33 - 7.38 (m, 2 H) 7.40 (d, *J*=8.42 Hz, 1 H) 7.75 (d, *J*=1.10 Hz, 1 H) 7.88 (dd, *J*=10.61, 2.93 Hz, 1 H) 8.17 (d, *J*=5.49 Hz, 1 H) 8.46 (s, 1 H) 9.53 (s, 1 H).

Compound 160: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.24 (d, *J*=6.95 Hz, 6 H) 2.16 (s, 3 H) 2.38 (s, 3 H) 2.96 (sxt, *J*=6.95 Hz, 1 H) 3.81 (s, 3 H) 6.65 (s, 1 H) 7.04 - 7.15 (m, 2 H) 7.32 (d, *J*=2.20 Hz, 1 H) 7.36 (d, *J*=8.42 Hz, 1 H) 7.73 (br. s., 1 H) 7.81 (s, 1 H) 9.41 (s, 1 H).

Compound 161: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H) 2.43 (s, 3 H) 3.81 (s, 6 H) 6.97 (s, 1 H) 7.05 (t, *J*=7.50 Hz, 1 H) 7.09 (s, 1 H) 7.11 - 7.20 (m, 2 H) 7.33 (d, *J*=1.83 Hz, 1 H) 7.38 (d, *J*=8.42 Hz, 1 H) 7.45 (td, *J*=8.42, 1.46 Hz, 1 H) 7.54 (dd, *J*=7.32, 1.46 Hz, 1 H) 7.72 (s, 1 H) 7.93 (s, 1 H) 9.53 (s, 1 H).

Compound 163: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.32 (d, *J*=6.95 Hz, 6 H) 2.16 (s, 3 H) 3.09 (spt, *J*=6.95 Hz, 1 H) 4.09 (s, 3 H) 7.16 (s, 1 H) 7.28 (d, *J*=8.05 Hz, 1 H) 7.41 (td, *J*=7.68, 1.83 Hz, 1 H) 7.50 (td, *J*=7.68, 1.46 Hz, 1 H) 7.58 (dd, *J*=8.05, 1.46 Hz, 1 H) 7.80 (d, *J*=1.46 Hz, 1 H) 7.82 (d, *J*=8.05 Hz, 1 H) 8.17 (s, 1 H) 8.33 (dd, *J*=7.68, 1.83 Hz, 1 H) 8.57 (s, 1 H) 10.05 (s, 1 H).

Compound 170: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.61 - 1.84 (m, 4 H) 2.16 (s, 3 H) 2.38 (s, 3 H) 2.84 - 2.99 (m, 1 H) 3.41 (td, *J*=11.25, 2.74 Hz, 2 H) 3.81 (s, 3 H) 3.88 - 3.99 (m, 2 H) 6.65 (s, 1 H) 7.09 (s, 1 H) 7.12 (dd, *J*=8.42, 2.20 Hz, 1 H) 7.31 (d, *J*=2.20 Hz, 1 H) 7.36 (d, *J*=8.42 Hz, 1 H) 7.73 (d, *J*=1.10 Hz, 1 H) 7.82 (s, 1 H) 9.42 (s, 1 H).

Compound 174: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 4.04 (s, 3 H) 7.16 (s, 1 H) 7.31 (d, *J*=8.42 Hz, 1 H) 7.42 (t, *J*=7.32 Hz, 1 H) 7.51 (t, *J*=7.32 Hz, 1 H) 7.59 (d, *J*=7.68 Hz, 1 H) 7.82 (s, 1 H) 7.85 (d, *J*=8.42 Hz, 1 H) 8.23 - 8.40 (m, 2 H) 8.66 (s, 1 H) 10.47 (s, 1 H).

Compound 175: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 3.84 (s, 3 H) 7.08 (s, 1 H) 7.28 - 7.38 (m, 3 H) 7.47 (d, *J*=4.84 Hz, 1 H) 7.70 (s, 1 H) 7.94 (dd, *J*=8.68, 2.22 Hz, 1 H) 7.99 (d, *J*=2.02 Hz, 1 H) 8.03 (d, *J*=4.44 Hz, 1 H) 8.11 (dd, *J*=8.88, 5.65 Hz, 2 H) 8.45 (s, 1 H) 9.58 (s, 1 H).

Compound 176: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.49 (s, 3 H), 2.54 (s, 3 H), 3.98 (s, 3 H), 6.99 - 7.04 (m, 2 H), 7.40 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.51 (d, *J*=4.6 Hz, 1 H), 7.62 (d, *J*=4.6 Hz, 1 H), 7.64 (s, 1 H), 7.68 (d, *J*=8.6 Hz, 1 H), 7.78 (dd, *J*=8.2, 6.0 Hz, 1 H), 8.02 (d, *J*=2.2 Hz, 1 H), 8.19 (s, 1 H), 8.54 (s, 1 H).

Compound 177: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.50 (s, 3 H), 2.53 (s, 3 H), 4.01 (s, 3 H), 6.99 - 7.04 (m, 2 H), 7.21 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.61 (s, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.75 - 7.78 (m, 1 H), 7.79 (s, 1 H), 8.25 (d, *J*=2.3 Hz, 1 H), 8.31 (br. s., 1 H), 8.59 (s, 1 H).

Compound 171: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.21 (s, 3 H) 4.06 (s, 3 H) 5.51 (s, 1 H) 5.83 (s, 1 H) 7.15 (s, 1 H) 7.29 (d, *J*=8.42 Hz, 1 H) 7.42 (td, *J*=7.68, 1.83 Hz, 1 H) 7.51 (td, *J*=7.59, 1.28 Hz, 1 H) 7.59 (dd, *J*=8.05, 1.10 Hz, 1 H) 7.80 (d, *J*=1.10 Hz, 1 H) 7.83 (d, *J*=8.42 Hz, 1 H) 8.36 (dd, *J*=7.68, 1.83 Hz, 1 H) 8.53 (s, 1 H) 8.63 (s, 1 H) 10.06 (s, 1 H).

Compound 178: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.35 (s, 3 H) 3.89 (s, 3 H) 7.34 (t, *J*=8.78 Hz, 2 H) 7.49 (d, *J*=4.39 Hz, 1 H) 7.53 (d, *J*=8.78 Hz, 1 H) 7.97 - 8.07 (m, 3 H) 8.12 (dd, *J*=8.42, 5.49 Hz, 2 H) 8.47 (s, 1 H) 8.71 (s, 1 H) 9.66 (s, 1 H).
Compound 179: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.33 (s, 3 H) 3.57 - 3.72 (m, 2 H) 4.08 (s, 3 H) 6.60 (d, *J*=8.42 Hz, 1 H) 6.81 (dd, *J*=7.68, 6.95 Hz, 1 H) 6.89 (t, *J*=1.10 Hz, 1 H) 7.47 (d, *J*=8.42 Hz, 1 H) 7.57 (s, 1 H) 7.67 - 7.76 (m, 2 H) 8.00 (s, 1 H) 8.14 (dd, *J*=7.68, 1.10 Hz, 1 H).

Pharmacology

A) Screening of the compounds of the invention for γ-secretase-modulating activity

A1) Method 1

Screening was carried out using SKNBE2 cells carrying the APP 695 – wild type, grown in Dulbecco's Modified Eagle's Medium/Nutrient mixture F-12 (DMEM/NUT-mix F-12) (HAM) provided by Gibco (cat no. 31330-38) containing 5 % Serum/Fe supplemented with 1 % non-essential amino acids. Cells were grown to near confluency.

The screening was performed using the assay as described in Citron et al (1997) Nature Medicine 3: 67. Briefly, cells were plated in a 96-well plate at about 10^5 cells/ml one day prior to addition of compounds. Compounds were added to the cells in Ultraculture (Lonza, BE12-725F) supplemented with 1 % glutamine (Invitrogen, 25030-024) for 18 hours. The media were assayed by two sandwich ELISAs, for Aß42 and Aßtotal. Toxicity of the compounds was assayed by WST-1 cell proliferation reagent (Roche, 1 644 807) according to the manufacturer's protocol.

To quantify the amount of Aβ42 in the cell supernatant, commercially available Enzyme-Linked-Immunosorbent-Assay (ELISA) kits were used (Innotest® β-Amyloid$_{(1-42)}$, Innogenetics N.V., Ghent, Belgium). The Aβ42 ELISA was performed essentially according to the manufacturer's protocol. Briefly, the standards (dilutions of synthetic Aβ1-42) were prepared in polypropylene Eppendorf with final concentrations of 8000 down to 3.9 pg/ml (1/2 dilution step). Samples, standards and blanks (100 µl) were added to the anti-Aβ42-coated plate supplied with the kit (the capture antibody selectively recognizes the C-terminal end of the antigen). The plate was allowed to incubate 3 h at 25 °C in order to allow formation of the antibody-amyloid complex. Following this incubation and subsequent wash steps a selective anti-Aβ-antibody conjugate (biotinylated 3D6) was added and incubated for a minimum of 1 hour in order to allow formation of the antibody-Amyloid-antibody-complex. After incubation

and appropriate wash steps, a Streptavidine-Peroxidase-Conjugate was added, followed 30 minutes later by an addition of 3,3',5,5'-tetramethylbenzidine (TMB)/peroxide mixture, resulting in the conversion of the substrate into a coloured product. This reaction was stopped by the addition of sulfuric acid (0.9 N) and the colour intensity was measured by means of photometry with an ELISA-reader with a 450 nm filter.

To quantify the amount of Aßtotal in the cell supernatant, samples and standards were added to a 6E10-coated plate. The plate was allowed to incubate overnight at 4 °C in order to allow formation of the antibody-amyloid complex. Following this incubation and subsequent wash steps a selective anti-Aß-antibody conjugate (biotinylated 4G8) was added and incubated for a minimum of 1 hour in order to allow formation of the antibody-Amyloid-antibody-complex. After incubation and appropriate wash steps, a Streptavidine-Peroxidase-Conjugate was added, followed 30 minutes later by an addition of Quanta Blu fluorogenic peroxidase substrate according to the manufacturer's instructions (Pierce Corp., Rockford, Il).

To obtain the values reported in Table 12a, the sigmoidal dose response curves were analysed by computerised curve-fitting, with percent of inhibition plotted against compound concentration. A 4-parameter equation (model 205) in XL*fit* was used to determine the IC_{50}. The top and the bottom of the curve were fixed to 100 and 0, respectively, and the hill slope was fixed to 1. The IC_{50} represents the concentration of a compound that is required for inhibiting a biological effect by 50 % (Here, it is the concentration where Aß peptide level is reduced by 50 %).

The IC_{50} values are shown in Table 12a:

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
1	0.101	>5
2	0.065	>3
3	0.030	>1
4	0.053	>3
5	0.014	>1

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
6	0.239	>10
7	0.037	>1
8	0.541	>20
9	0.384	>10
10	0.054	>3

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
11	0.039	>3
12	0.064	>3
13	0.089	>3
14	0.057	>3
15	0.012	>3

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
16	0.058	>3
17	0.080	>3
18	0.025	>10
19	0.059	>3
21	0.263	>5
22	0.113	>3
23	0.025	>3
24	0.024	>1
25	0.251	>10
26	0.011	>3
27	0.025	>3
28	0.020	>1
29	0.010	>1
30	0.057	>3
31	0.595	>5
32	0.114	>5
33	0.031	>3

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
34	0.009	>3
35	0.019	>1
36	0.064	>3
37	0.190	>10
38	0.054	>3
39	0.075	>3
40	0.062	>3
41	0.344	8.54
42	0.430	>10
45	0.232	>5
46	0.052	>3
47	0.031	>3
48	0.060	>3
49	0.305	10
50	0.253	>3
51	0.039	>3
52	0.010	>3

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
54	0.070	>3
56	0.601	>10
57	0.058	>1
59	0.123	>3
61	0.423	>10
62	0.477	>10
63	0.029	>3
64	0.013	>3
65	0.782	27.2
67	0.051	>3
68	0.018	>1
71	0.288	>3
77	2.691	>10
78	6.442	>10
88	0.184	>3

To obtain the values reported in Table 12b, the data are calculated as percentage of the maximum amount of amyloid Beta 42 measured in the absence of the test compound.

The sigmoidal dose response curves were analyzed using non–linear regression analysis with percentage of the control plotted against the log concentration of the compound. A 4-parameter equation was used to determine the IC_{50}. The values reported in Table 12b are averaged IC_{50} values.

The IC_{50} values are shown in Table 12b:

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
1	0.098	>5.012
2	0.055	>3.020
3	0.148	12.589
4	0.085	>3.020
5	0.012	>3.020
6	0.263	>10
7	0.036	>3.020
8	0.562	>19.953
9	0.282	>10
10	0.051	>3.020
11	0.035	>3.020
12	0.055	>3.020
13	0.087	>3.020
14	0.041	>3.020
15	0.011	>3.020
16	0.049	>3.020
17	0.071	>3.020
18	0.025	>10
19	0.056	>3.020
20	0.871	5.754
21	0.204	>5.012
22	0.112	>3.020
23	0.022	>3.020
24	0.020	>10
25	0.240	>10
26	0.011	>3.020
27	0.025	>3.020
28	0.018	>3.020
29	0.008	>10
30	0.045	>3.020
31	0.589	>30.200
32	0.105	>5.012
33	0.027	>3.020
34	0.009	>3.020
35	0.019	>3.020
36	0.060	>3.020
37	0.174	>10
38	0.051	>3.020
39	0.068	>3.020
40	0.056	>3.020
41	0.363	7.413
42	0.427	>10
43	>3.02	>3.020
44	0.617	>3.020
45	0.200	>5.012
46	0.050	>3.020
47	0.031	>3.020
48	0.052	>3.020

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
49	0.407	>10
50	0.251	>5.012
51	0.038	>3.020
52	0.010	>3.020
53	0.027	>3.020
54	0.068	>3.020
55	1.288	>3.020
56	0.204	>10
57	0.051	>3.020
58	<0.11	>3.020
59	0.145	>3.020
60	<0.11	>3.020
61	0.437	>10
62	0.417	>3.020
63	0.029	>3.020
64	0.017	>3.020
65	0.661	17.783
66	0.076	n.d.
67	0.040	>3.020

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
68	0.018	>3.020
74	0.123	>3.020
75	0.126	>3.020
76	1.950	>10
77	4.365	>10
78	9.550	>10
79	7.413	>10
80	3.802	>10
81	0.380	>10
82	0.562	>3.020
83	0.355	>10
84	0.115	>3.020
86	0.117	>10
87	0.025	>10
88	0.174	>10
89	0.085	>3.020
90	0.398	>3.020
91	0.072	18.621
94	0.115	>3.020

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
98	0.032	>3.020
100	0.011	>3.020
101	0.013	>1
102	0.010	>3.020
103	0.013	>3.020
105	0.089	>3.020
109	0.015	>3.020
113	0.038	>3.020
116	0.295	>3.020
118	0.331	>3.020
119	1.660	>3.020
120	0.589	>30.200
124	0.011	>3.020
125	0.030	>3.020
127	0.089	>10
129	0.046	>10
130	0.178	>3.020
131	0.245	>10
133	0.468	>3.020

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
134	0.575	>3.020
135	0.631	>10
136	0.676	>30.200
137	1.380	>3.020
138	0.009	>3.020
144	0.100	>3.020
146	0.032	>3.020
147	0.042	>3.020
149	0.389	>10

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
151	0.513	>3.020
152	1.778	>3.020
153	1.905	>3.020
154	>3.02	>3.020
155	0.024	>3.020
156	>3.02	>3.020
157	0.102	>3.020
164	0.178	>10
168	3.020	>3.020

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
173	>3.02	>3.020
175	0.041	>3.020
176	0.324	>10
177	0.234	>3.020

A2) Method 2

Screening was carried out using SKNBE2 cells carrying the APP 695 – wild type, grown in Dulbecco's Modified Eagle's Medium/Nutrient mixture F-12 (DMEM/NUT-mix F-12) (HAM) provided by Invitrogen (cat no. 10371-029) containing 5 % Serum/Fe supplemented with 1 % non-essential amino acids, l-glutamine 2 mM, Hepes 15 mM, penicillin 50 U/ml (units/ml) en streptomycin 50 μg/ml. Cells were grown to near confluency.

The screening was performed using a modification of the assay as described in Citron et al (1997) Nature Medicine 3: 67. Briefly, cells were plated in a 384-well plate at 10^4 cells/well in Ultraculture (Lonza, BE12-725F) supplemented with 1 % glutamine (Invitrogen, 25030-024), 1 % non-essential amino acid (NEAA), penicillin 50 U/ml en streptomycin 50 μg/ml in the presence of test compound at different test concentrations. The cell/compound mixture was incubated overnight at 37 °C, 5 % CO_2. The next day the media were assayed by two sandwich immuno-assays, for Aß42 and Aßtotal.

Aßtotal and Aß42 concentrations were quantified in the cell supernatant using the Aphalisa technology (Perkin Elmer). Alphalisa is a sandwich assay using biotinylated antibody attached to streptavidin coated donorbeads and antibody conjugated to acceptor beads. In the presence of antigen, the beads come into close proximity. The excitation of the donor beads provokes the release of singlet oxygen molecules that trigger a cascade of energy transfer in the acceptor beads, resulting in light emission. To quantify the amount of Aβ42 in the cell supernatant, monoclonal antibody specific to the C-terminus of Aß42 (JRF/cAß42/26) was coupled to the receptor beads and biotinylated antibody specific to the *N*-terminus of Aß (JRF/AßN/25) was used to react with the donor beads. To quantify the amount of Aβtotal in the cell supernatant, monoclonal antibody specifc to the *N*-terminus of Aß (JRF/AßN/25) was coupled to the receptor beads and biotinylated antibody specific to the mid region of Aß (biotinylated 4G8) was used to react with the donor beads.

To obtain the values reported in Table 12c, the data are calculated as percentage of the maximum amount of amyloid Beta 42 measured in the absence of the test compound. The sigmoidal dose response curves were analyzed using non–linear regression analysis with percentage of the control plotted against the log concentration of the compound. A 4-parameter equation was used to determine the IC_{50}.

The IC_{50} values are shown in Table 12c:

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
1	0.155	7.413
4	0.166	>10
15	0.038	5.495
29	0.013	7.079
33	0.071	5.754
50	0.309	>10
69	0.046	>10

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
70	0.068	>3.020
71	0.407	>3.020
73	0.166	>3.020
102	0.014	>10
103	0.019	>10
104	0.029	7.244
105	0.032	6.607

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
106	0.034	4.571
107	0.048	2.042
108	0.054	>10
109	0.060	>10
110	0.129	>10
111	0.065	5.495
112	0.107	>10

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
113	0.145	>10
114	0.151	3.631
115	0.257	8.318
117	0.331	>10
118	0.372	>10
119	0.603	6.166
120	0.363	>10
121	1.318	>10
123	5.370	>10
124	0.018	9.120
125	0.051	7.943
126	0.052	>10
127	0.056	>10
128	0.062	>10
129	0.074	>10
132	0.251	6.918
134	0.437	1.738
135	0.102	>10

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
136	0.813	>10
137	0.871	>10
138	0.005	5.888
139	0.005	4.266
140	0.006	4.074
141	0.013	>10
142	0.031	6.607
143	0.060	3.388
144	0.120	>10
145	0.007	>10
148	0.043	>10
149	0.174	>10
150	0.200	>10
151	0.219	>10
155	0.028	>10
157	0.050	7.413
158	0.071	8.913
159	0.055	4.786

Co. No.	IC_{50} Aβ42 (μM)	IC_{50} Aβtotal (μM)
160	0.087	>10
161	0.132	>10
162	0.138	>10
163	0.166	8.318
165	0.178	>10
166	0.251	>10
167	0.288	>10
168	0.380	10
169	0.417	7.943
170	0.447	>10
171	0.537	8.318
172	0.646	>10
173	>10	>10
175	0.072	5.248
176	0.107	8.318
178	0.380	>10
179	0.078	>10
180	0.562	6.25

B) Demonstration of in vivo efficacy

Aβ42 lowering agents of the invention can be used to treat AD in mammals such as humans or alternatively demonstrating efficacy in animal models such as, but not limited to, the mouse, rat, or guinea pig. The mammal may not be diagnosed with AD, or may not have a genetic predisposition for AD, but may be transgenic such that it overproduces and eventually deposits Aβ in a manner similar to that seen in humans afflicted with AD.

Aβ42 lowering agents can be administered in any standard form using any standard method. For example, but not limited to, Aβ42 lowering agents can be in the form of liquid, tablets or capsules that are taken orally or by injection. Aβ42 lowering agents can be administered at any dose that is sufficient to significantly reduce levels of Aβ42 in the blood, blood plasma, serum, cerebrospinal fluid (CSF), or brain.

To determine whether acute administration of an Aβ42 lowering agent would reduce Aβ42 levels in vivo, non-transgenic rodents, e.g. mice or rats were used. Alternatively, two to three month old Tg2576 mice expressing APP695 containing the "Swedish" variant can be used or a transgenic mouse model developed by Dr. Fred Van Leuven (K.U.Leuven, Belgium) and co-workers, with neuron-specific expression of a clinical mutant of the human amyloid precursor protein [V717I] (Moechars et al., 1999 J. Biol. Chem. 274, 6483). Young transgenic mice have high levels of Aβ in the brain but no detectable Aβ deposition. At approximately 6-8 months of age, the transgenic mice start to display spontaneous, progressive accumulation of β-amyloid (Aβ) in the brain, eventually resulting in amyloid plaques within the subiculum, hippocampus and cortex. Animals treated with the Aβ42 lowering agent were examined and compared to those untreated or treated with vehicle and brain levels of soluble Aβ42 and total Aβ would be quantitated by standard techniques, for example, using ELISA. Treatment periods varied from hours to days and were adjusted based on the results of the Aβ42 lowering once a time course of onset of effect could be established.

A typical protocol for measuring Aβ42 lowering in vivo is shown but it is only one of many variations that could be used to optimize the levels of detectable Aβ. For example, Aβ42 lowering compounds were formulated in 20 % of Captisol® (a sulfobutyl ether of β-cyclodextrin) in water or 20 % hydroxypropyl β cyclodextrin. The Aβ42 lowering agents were administered as a single oral dose or by any acceptable route of administration to overnight fasted animals. After four hours, the animals were sacrificed and Aβ42 levels were analysed.

Blood was collected by decapitation and exsanguinations in EDTA-treated collection tubes. Blood was centrifuged at 1900 g for 10 minutes at 4 °C and the plasma recovered and flash frozen for later analysis. The brain was removed from the cranium and hindbrain. The cerebellum was removed and the left and right hemisphere were separated. The left hemisphere was stored at -18 °C for quantitative analysis of test compound levels. The right hemisphere was rinsed with phosphate-buffered saline (PBS) buffer and immediately frozen on dry ice and stored at -80 °C until homogenization for biochemical assays.

Mouse brains were resuspended in 10 volumes of 0.4 % DEA (diethylamine) /50 mM NaCl pH 10 (for non-transgenic animals) or 0.1 % 3-[(3-cholamidopropyl)-dimethyl-ammonio]-1-propanesulfonate (CHAPS) in tris buffered saline (TBS) (for transgenic animals) containing protease inhibitors (Roche-11873580001 or 04693159001) per gram of tissue, e.g. for 0.158 g brain, add 1.58 ml of 0.4 % DEA. All samples were sonicated for 30 seconds on ice at 20 % power output (pulse mode). Homogenates were centrifuged at 221.300 x g for 50 min. The resulting high speed supernatants were then transferred to fresh tubes and were optionally further purified before the next step. A portion of the supernatant was neutralized with 10 % 0.5 M Tris-HCl and this was used to quantify Aßtotal.

The obtained supernatants were purified with Water Oasis HLB reverse phase columns (Waters Corp., Milford, MA) to remove non-specific immunoreactive material from the brain lysates prior subsequent Aβ detection. Using a vacuum manifold, all solutions were passed through the columns at a rate of approximately 1 ml per minute, so the vacuum pressure was adjusted accordingly throughout the procedure. Columns were preconditioned with 1 ml of 100 % MeOH, before equilibration with 1 ml of H_2O. Non-neutralized brain lysates were loaded onto the columns. The loaded samples were then washed twice with the first wash performed with 1 ml of 5 % MeOH, and the second wash with 1 ml of 30 % MeOH. Finally, the Aβ was eluted from the columns and into 100 x 30 mm glass tubes, with a solution of 90 % MeOH with 2 % NH_4OH. The eluate was then transferred into 1.5 ml tubes and concentrated in a speed-vac concentrator on high heat for about 1.5-2 hours at 70°C. The concentrated Aβ was then resuspended in UltraCULTURE General Purpose Serum-Free Medium (Cambrex Corp., Walkersville, MD) plus Protease Inhibitors added according to the manufacturers recommendation.

To quantify the amount of Aβ42 in the soluble fraction of the brain homogenates, commercially available Enzyme-Linked-Immunosorbent-Assay (ELISA) kits were used (e.g. Innotest® β-Amyloid$_{(1-42)}$, Innogenetics N.V., Ghent, Belgium).

The Aβ42 ELISA was performed using the plate provided with the kit only. Briefly, the standards (a dilution of synthetic Aβ1-42) were prepared in 1.5 ml Eppendorf tube in Ultraculture, with final concentrations ranging from 25000 to 1.5 pg/ml. Samples, standards and blanks (60 µl) were added to the anti-Aβ42-coated plate (the capture antibody selectively recognizes the C-terminal end of the antigen). The plate was allowed to incubate overnight at 4 °C in order to allow formation of the antibody-amyloid complex. Following this incubation and subsequent wash steps a selective anti-Aβ-antibody conjugate (biotinylated detection antibody, e.g., biotinylated 4G8 (Covance Research Products, Dedham, MA) was added and incubated for a minimum of 1 hour in order to allow formation of the antibody-Amyloid-antibody-complex. After incubation and appropriate wash steps, a Streptavidine-Peroxidase-Conjugate was added, followed 50 minutes later by an addition of Quanta Blu fluorogenic peroxidase substrate according to the manufacturer's instructions (Pierce Corp., Rockford, Il). A kinetic reading was performed every 5 minutes for 30 minutes (excitation 320 / emission 420). To quantify the amount of Aßtotal in the soluble fraction of the brain homogenates, samples and standards were added to JRF/rAß/2-coated plate. The plate was allowed to incubate overnight at 4 °C in order to allow formation of the antibody-amyloid complex. The ELISA was then performed as for Aß42 detection.

In this model at least 20 % Aß42 lowering compared to untreated animals would be advantageous.

The results are shown in table 13:

Co. No.	Aβ42 (%Ctrl) _Mean	Aβtotal (%Ctrl) _Mean	Co. No.	Aβ42 (%Ctrl) _Mean	Aβtotal (%Ctrl) _Mean	Co. No.	Aβ42 (%Ctrl) _Mean	Aβtotal (%Ctrl) _Mean
1	65	103	8	88	96	29	56	86
2	100	106	10	67	104	32	81	113
3	56	95	15	62	94	33	80	98
4	93	111	18	73	101	34	63	100
5	66	96	26	75	94	39	82	108
7	68	105	27	59	94	40	80	99

Co. No.	Aβ42 (%Ctrl) _Mean	Aβtotal (%Ctrl) _Mean
50	67	96
52	66	91
70	84	99
71	91	103

Co. No.	Aβ42 (%Ctrl) _Mean	Aβtotal (%Ctrl) _Mean
74	95	102
83	89	104
86	86	96
87	86	101

Co. No.	Aβ42 (%Ctrl) _Mean	Aβtotal (%Ctrl) _Mean
94	96	101
98	84	97
138	65	102

C. Composition examples

"Active ingredient" (a.i.) as used throughout these examples relates to a compound of formula (I), including any stereochemically isomeric form thereof, a pharmaceutically acceptable salt thereof or a solvate thereof; in particular to any one of the exemplified compounds.

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

2. Suspension

An aqueous suspension is prepared for oral administration so that each milliliter contains 1 to 5 mg of active ingredient , 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3. Injectable

A parenteral composition is prepared by stirring 1.5 % (weight/volume) of active ingredient in 0.9 % NaCl solution or in 10 % by volume propylene glycol in water.

4. Ointment

Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g

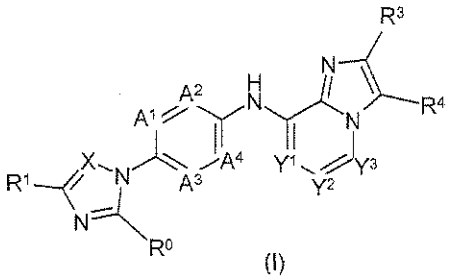
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

Claims

1. A compound of formula (I)



(I)

or a stereoisomeric form thereof, wherein

R^0 is hydrogen, halo or C_{1-4}alkyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

X is CR^7 or N; wherein R^7 is hydrogen or halo;

A^1 is CR^2 or N;

A^2 is CR^8 or N;

A^3 and A^4 each independently are CH or N;

provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^8 is hydrogen or halo;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, morpholinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, Ar, C_{1-6}alkyloxy, cycloC_{3-7}alkyloxy, and cycloC_{3-7}alkyl; carboxyl; C_{2-4}alkenyl; NR^5R^6-carbonyl; cycloC_{3-7}alkyl; Ar; tetrahydropyranyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; or Ar-O-CH_2-;

wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, and NR^5R^6; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

each R^5 independently is hydrogen, C_{1-4}alkyl, C_{1-6}alkylcarbonyl, or C_{1-4}alkyloxy$(CH_2CH_2O)_n$-CH_2-carbonyl;

n is an integer selected from 1, 2, 3, 4, 5 or 6.

each R^6 independently is hydrogen or C_{1-4}alkyl;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-4}alkyloxy; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, NR^5R^6, C_{1-4}alkyloxy, hydroxyl, and formylamino;

Y^1 is CH or N;

Y^2 is CR^9 or N;

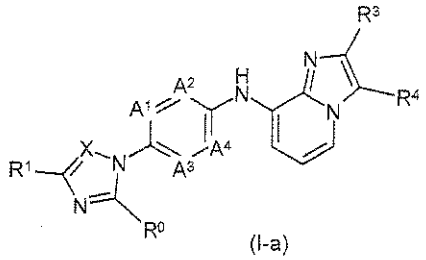
Y^3 is CH or N;

provided that only one of Y^1, Y^2 and Y^3 may represent N;

R^9 is hydrogen; halo; C_{1-4}alkyloxy; cyano; cycloC_{3-7}alkyl; tetrahydropyranyl; C_{2-4}alkenyl; phenyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and C_{1-4}alkyloxy;

or a pharmaceutically acceptable addition salt or a solvate thereof.

2. The compound according to claim 1 wherein the compound is a compound of formula (I-a)



(I-a)

or a stereoisomeric form thereof, wherein

R^0 is hydrogen or C_{1-4}alkyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

X is CR^7 or N; wherein R^7 is hydrogen or halo;

A^1 is CR^2 or N;

A^2, A^3 and A^4 each independently are CH or N;

provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, morpholinyl, piperidinyl, pyrrolidinyl, Ar, C_{1-6}alkyloxy, cycloC_{3-7}alkyloxy, and

cycloC_{3-7}alkyl; cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-; wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo; wherein each R^5 independently is hydrogen or C_{1-4}alkyl; wherein each R^6 independently is hydrogen or C_{1-4}alkyl;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

or a pharmaceutically acceptable addition salt or a solvate thereof.

3. The compound according to claim 1, or a stereoisomeric form thereof, wherein

R^0 is hydrogen or C_{1-4}alkyl;

R^1 is hydrogen or C_{1-4}alkyl;

X is CH or N;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of hydroxyl, halo, morpholinyl, piperidinyl, tetrahydropyranyl, Ar, C_{1-6}alkyloxy, and cycloC_{3-7}alkyl; carboxyl; C_{2-4}alkenyl; NR^5R^6-carbonyl; cycloC_{3-7}alkyl; Ar; tetrahydropyranyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; or Ar-O-CH_2-; wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from the group consisting of halo and NR^5R^6; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl;

n is 2;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-4}alkyloxy; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of NR^5R^6, C_{1-4}alkyloxy, hydroxyl, and formylamino;

Y^1 is CH or N;

Y^2 is CR^9;

Y^3 is CH or N;

provided that only one of Y^1 and Y^3 may represent N;

R^9 is hydrogen; halo; tetrahydropyranyl; C_{2-4}alkenyl; phenyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or

C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from halo;

or a pharmaceutically acceptable addition salt or a solvate thereof.

4. The compound according to claim 1, or a stereoisomeric form thereof, wherein

R^0 is hydrogen or C_{1-4}alkyl;

R^1 is hydrogen, C_{1-4}alkyl or halo;

X is CR^7 or N; wherein R^7 is hydrogen or halo;

A^1 is CR^2 or N;

A^2, A^3 and A^4 each independently are CH or N;

provided that no more than two of A^1, A^2, A^3 and A^4 are N;

R^2 is hydrogen, halo or C_{1-4}alkyloxy;

R^3 is hydrogen; C_{1-6}alkyl optionally substituted with one substituent selected from the group consisting of morpholinyl, piperidinyl, Ar, C_{1-6}alkyloxy and cycloC_{3-7}alkyl; tetrahydropyranyl; Ar; or Ar-O-CH_2-;

wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo; benzimidazolyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyl; or pyridinyl;

wherein each R^5 independently is C_{1-4}alkyl;

wherein each R^6 independently is C_{1-4}alkyl;

R^4 is hydrogen; cyano; halo; phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and phenyl; phenylcarbonyl optionally substituted with one or more substituents each independently selected from halo; C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from C_{1-4}alkyloxy; or C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

or a pharmaceutically acceptable addition salt or a solvate thereof.

5. The compound according to claim 1, or a stereoisomeric form thereof, wherein

R^3 is phenyl;

R^4 is methyl;

or

R^3 is phenyl substituted in a meta position and optionally further substituted in other positions;

R^4 is hydrogen or methyl;

or

R^3 is phenyl substituted in an ortho position and optionally further substituted in other positions;

R^4 is hydrogen or methyl;

or a pharmaceutically acceptable addition salt or a solvate thereof.

6. The compound according to claim 1, or a stereoisomeric form thereof, wherein

R^3 is methyl substituted with one or more phenyl groups, wherein phenyl is optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, NR^5R^6, morpholinyl, C_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo;

R^4 is hydrogen;

or a pharmaceutically acceptable addition salt or a solvate thereof.

7. The compound according to claim 1, or a stereoisomeric form thereof, wherein

X is N;

or a pharmaceutically acceptable addition salt or a solvate thereof.

8. The compound according to claim 1, or a stereoisomeric form thereof, wherein

R^0 is hydrogen;
R^1 is C_{1-4}alkyl;
X is CH or N;
A^1 is CR^2;
A^2 is N;
A^3 and A^4 are CH;
R^2 is C_{1-4}alkyloxy;
R^3 is Ar; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from halo;
wherein Ar is phenyl optionally substituted with one or more substituents each independently selected from halo;
R^4 is hydrogen or C_{1-6}alkyl;
or a pharmaceutically acceptable addition salt or a solvate thereof.

9. The compound according to any one of claims 1 and 3 to 8, wherein
Y^1 is CH;
Y^2 is CH;
Y^3 is CH.

10. The compound according to claim 1, wherein the compound is
2-(2-chlorophenyl)-*N*-[6-methoxy-5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-3-methyl-imidazo[1,2-a]pyridin-8-amine, or
N-[6-methoxy-5-(4-methyl-1H-imidazol-1-yl)-2-pyridinyl]-2-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridin-8-amine, or
N-[6-methoxy-5-(3-methyl-1H-1,2,4-triazol-1-yl)-2-pyridinyl]-2-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridin-8-amine,
any stereochemically isomeric form thereof or a pharmaceutically acceptable addition salt or a solvate thereof.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined in any one of claims 1 to 10.

12. A compound as defined in any one of claims 1 to 10 for use as a medicament.

13. A compound as defined in any one of claims 1 to 10 for the treatment or prevention of a disease or condition selected from Alzheimer's disease, traumatic brain injury,

mild cognitive impairment, senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid.

14. The compound according to claim 13 wherein the disease is Alzheimer's disease.

15. Use of a compound as defined in any of claims 1 to 10 for the manufacture of a medicament for the modulation of gamma-secretase activity.