NOVEL SUBSTITUTED TRIAZOLE DERIVATIVES AS GAMMA SECRETASE MODULATORS

Field of the Invention

The present invention is concerned with novel substituted triazole derivatives useful as gamma secretase modulators. The invention further relates to processes for preparing such novel compounds, pharmaceutical compositions comprising said compounds 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). Aß 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 cleavage 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 AD. Therefore, Aß42 is believed by many researchers to be the main culprit of the pathogenesis of AD.

It has now become clear that the γ-secretase activity cannot be ascribed to a single 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 AD.

Various strategies have been proposed for targeting γ-secretase in AD, ranging from targeting the catalytic site directly, developing substrate-specific inhibitors and modulators of γ-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 AD: patents 2000 – 2004. Expert Opin. Ther. Patents 14, 1403-1420).

Indeed, this finding was supported by biochemical studies in which an effect of certain Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on γ-secretase was shown (US

2002/0128319; Eriksen (2003) J. Clin. Invest. 112, 440). Potential limitations for the use of NSAIDs to prevent or treat AD are their inhibition activity of cyclooxygenase (COX) enzymes, which can lead to unwanted side effects, and their low CNS penetration (Peretto et al., 2005, J. Med. Chem. 48, 5705-5720). More recently the NSAID R-flurbiprofen, an enantiomer lacking Cox-inhibitory activity and related gastric toxicity, has failed in large phase III trial since the drug did not improve thinking ability or the ability of patients to carry out daily activities significantly more than those patients on placebo.

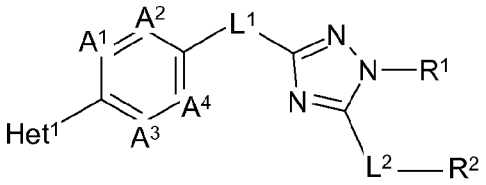
WO-2009/103652 relates to 1H-1,2,4-triazol-3-amine derivatives as modulators for Aβ;
WO-2009/032277 relates to heterocyclic compounds useful as γ secretase modulators;
WO-2009/050227 relates to pyridazine derivatives for inhibiting beta amyloid peptide reduction;
WO-2004/110350 relates to thiazolyl derivatives and their use in modulating Aβ;
WO-2010/010188 relates to [1,2,4]triazolo-[1,5-a]pyridine compounds, useful for the treatment of degenerative joint diseases and inflammatory diseases;
WO-2010/098495 relates to imidazolylpyrazine derivatives as therapeutic agents for AD;
and WO-2010/083141 relates to bicyclic compounds for the reduction of beta-amyloid production.

There is a strong need for novel compounds which modulate γ-secretase activity thereby opening new avenues for the treatment of AD. 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. The compounds of the present invention or part of the compounds of the present invention may have improved metabolic stability properties, improved central brain availability, improved solubilities, or reduced CYP inhibition compared with the compounds disclosed in the prior art. It is accordingly an object of the present invention to provide such novel compounds.

Summary of the invention

It has been found that the compounds of the present invention are useful as γ secretase modulators. The compounds according to the invention and the pharmaceutically acceptable compositions thereof, may be useful in the treatment or prevention of AD.

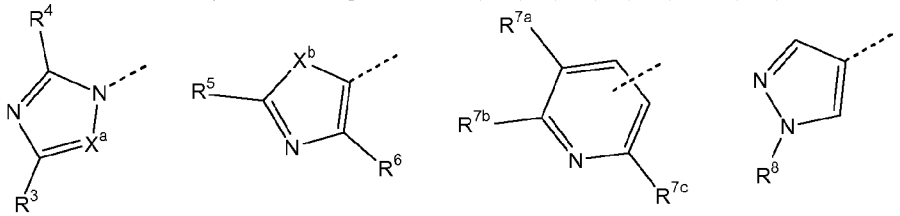
The present invention concerns novel compounds of Formula (I):



(I)

and stereoisomeric forms thereof, wherein

Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3), or (a-4)



(a-1) (a-2) (a-3) (a-4);

R^3 is C_{1-4}alkyl;

R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl optionally substituted with one or more halo substituents;

R^{7a} is hydrogen, halo, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen, halo, cyano, C_{1-4}alkyloxy, cycloC_{3-7}alkyl, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

X^a is CH or N;

X^b is O or S;

A^1 is CR^9 or N; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

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

provided that maximum two of A^1, A^2, A^3 and A^4 are N;

L^1 is O, carbonyl, NR^{10}, NH–(C=O), or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, hexahydro-1H-1,4-diazepin-1-yl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, oxo, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

or a 5- or 6-membered heteroaryl selected from the group consisting of furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl, wherein said 5- or 6-membered heteroaryl may be substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, $NR^{11c}R^{12c}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

each R^{11a}, R^{11b} and R^{11c} independently is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

each R^{12a}, R^{12b} and R^{12c} independently is hydrogen or C_{1-4}alkyl;

each R^{13a}, R^{13b} and R^{13c} independently is hydrogen, or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and cycloC_{3-7}alkyl;

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

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

The present compounds were found to modulate the γ-secretase activity in vitro and in vivo, and therefore may be useful in the treatment or prevention of AD, traumatic brain

injury (TBI), 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 AD and other disorders with Beta-amyloid pathology (e.g. glaucoma).

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

More especially the compounds may be suitable in the treatment or prevention of AD, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome.

The present invention 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 invention may lie in their enhanced CNS-penetration.

The present invention will now be further described. In the following passages, different aspects of the invention 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.

Whenever the term "substituted" is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one or more hydrogens, in particular from 1 to 4 hydrogens, preferably from 1 to 3 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using "substituted" are replaced with a selection from the indicated group, 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.

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

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. 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.

The term "C_{2-6}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 2 to 6. C_{2-6}alkyl groups comprise from 2 to 6 carbon atoms, in particular from 2 to 4 carbon atoms, more in particular from 2 to 3 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_{2-6}alkyl includes all linear, or branched alkyl groups with between 2 and 6 carbon atoms, and thus includes such as for example 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_{1-6}alkyloxy" as a group or part of a group refers to a radical having the Formula OR^b 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 OR^c wherein R^c is C_{1-4}alkyl. Non-limiting examples of suitable

C_{1-4}alkyloxy include methyloxy (also methoxy), ethyloxy (also ethoxy), propyloxy, isopropyloxy, butyloxy, isobutyloxy, *sec*-butyloxy and *tert*-butyloxy.

In the framework of this application, C_{2-6}alkenyl is a straight or branched hydrocarbon radical having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, 1-propen-2-yl, hexenyl and the like.

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 "C_{1-3}alkanediyl" as a group or part of a group defines bivalent straight or branched chained saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as, for example, methylene or methanediyl, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, and the like.

The term "C_{2-6}alkanediyl" as a group or part of a group defines bivalent straight or branched chained saturated hydrocarbon radicals having from 2 to 6 carbon atoms such as, for example, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, pentan-1,5-diyl, hexan-1,6-diyl, 2-methylbutan-1,4-diyl, 3-methylpentan-1,5-diyl and the like.

In a particular embodiment, C_{1-3}alkanediyl and C_{2-6}alkanediyl defines bivalent straight chained saturated hydrocarbon radicals.

The term "C_{2-6}alkenediyl" as a group or part of a group defines bivalent straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, 1,2-ethenediyl, 2-propenediyl, 3-butenediyl, 2-pentenediyl, 3-pentenediyl, 3-methyl-2- butenediyl, and the like.

In a particular embodiment, C_{2-6}alkenediyl defines bivalent straight chain hydrocarbon radicals.

The term "thiophenyl" is equivalent to "thienyl".

When L^1 is defined as for instance as NH-(C=O), this means that the nitrogen is linked to the 6-membered ring structure containing A^1, A^2, A^3 and A^4, and that the carbonyl group is attached to the triazole moiety.

When L^1 is defined as for instance as (C=O)-NH, this means that the carbonyl group is linked to the 6-membered ring structure containing A^1, A^2, A^3 and A^4, and that the nitrogen is attached to the triazole moiety.

When L^2 is defined as for instance as NR^{13b}-C_{1-3}alkanediyl, this means that the nitrogen of NR^{13b} is linked to the triazole moiety, and C_{1-3}alkanediyl is linked to the R^2 group.

When L^2 is defined as for instance as C_{1-3}alkanediyl-NR^{13c}, this means C_{1-3}alkanediyl is linked to the triazole moiety, and that the nitrogen of NR^{13b} is linked to the R^2 group.

The symbol "--" denotes the point of attachment to the remainder of the molecule.

The chemical names of the compounds of the present invention were generated according to the nomenclature rules agreed upon by the Chemical Abstracts Service, using Advanced Chemical Development, Inc., nomenclature software (ACD/Name product version 10.01; Build 15494, 1 Dec 2006).

In case of tautomeric forms, 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 (min) 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.

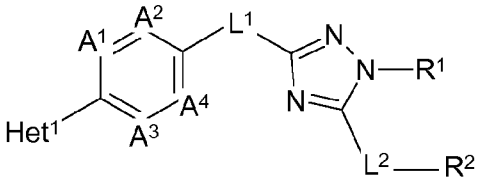
In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. In particular, the radioactive isotope is selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br.

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. For example, "a compound" means 1 compound or more than 1 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.

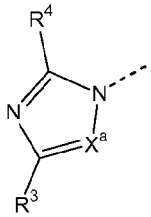
In an embodiment, the present invention concerns novel compounds of Formula (I)



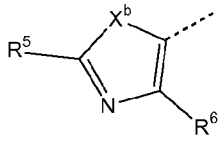
(I)

and stereoisomeric forms thereof, wherein

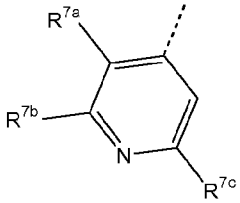
Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3a), or (a-4);



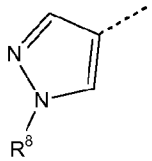
(a-1)



(a-2)



(a-3a)



(a-4);

R^3 is C_{1-4}alkyl;

R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl optionally substituted with one or more halo substituents;

R^{7a} is hydrogen, halo, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen, halo, cyano, C_{1-4}alkyloxy, cycloC_{3-7}alkyl, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

X^a is CH or N;

X^b is O or S;

A^1 is CR^9 or N; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

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

provided that maximum two of A^1, A^2, A^3 and A^4 are N;

L^1 is O, carbonyl, NR^{10}, NH–(C=O), or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, hexahydro-1H-1,4-diazepin-1-yl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, oxo, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents; or a 5- or 6-membered heteroaryl selected from the group consisting of furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl, wherein said 5- or 6-membered heteroaryl may be substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, $NR^{11c}R^{12c}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

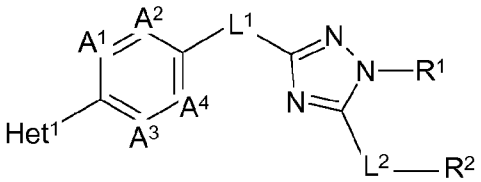
each R^{11a}, R^{11b} and R^{11c} independently is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

each R^{12a}, R^{12b} and R^{12c} independently is hydrogen or C_{1-4}alkyl;

each R^{13a}, R^{13b} and R^{13c} independently is hydrogen, or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and cycloC_{3-7}alkyl;

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

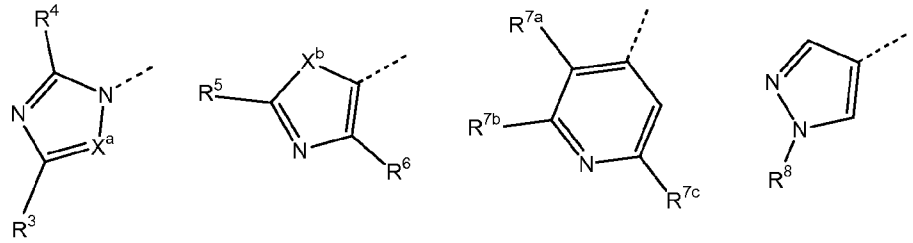
In an embodiment, the present invention concerns novel compounds of Formula (I):



(I)

and stereoisomeric forms thereof, wherein

Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3a), or (a-4)



(a-1) (a-2) (a-3a) (a-4);

R^3 is C_{1-4}alkyl;

R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl optionally substituted with one or more halo substituents;

R^{7a} is hydrogen, halo, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen, halo, cyano, C_{1-4}alkyloxy, cycloC_{3-7}alkyl, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

X^a is CH or N;

X^b is O or S;

A^1 is CR^9 or N; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

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

provided that maximum two of A^1, A^2, A^3 and A^4 are N;

L^1 is O, carbonyl, NR^{10}, NH–(C=O), or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is cycloC_{3-7}alkyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, C_{1-4}alkylcarbonyl, oxo, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents; or a 5- or 6-membered heteroaryl selected from the group consisting of furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl, wherein said 5- or 6-membered heteroaryl may be substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, $NR^{11c}R^{12c}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

each R^{11a}, R^{11b}, and R^{11c} independently is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

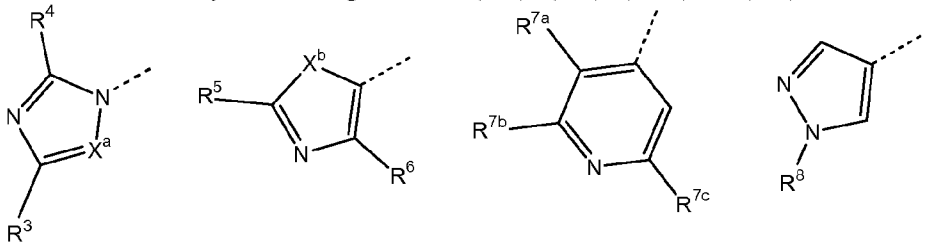
each R^{12a}, R^{12b}, and R^{12c} independently is hydrogen or C_{1-4}alkyl;

each R^{13a}, R^{13b}, and R^{13c} independently is hydrogen, or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and cycloC_{3-7}alkyl;

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

In an embodiment, the present invention concerns novel compounds of Formula (I) and stereoisomeric forms thereof, wherein

Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3a), or (a-4)



(a-1) (a-2) (a-3a) (a-4);

R^3 is C_{1-4}alkyl;

R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl optionally substituted with one ore more halo substituents;

R^{7a} is hydrogen, halo, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen, halo, cyano, C_{1-4}alkyloxy, cycloC_{3-7}alkyl, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

X^a is CH or N;

X^b is O or S;

A^1 is CR^9 or N; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

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

provided that maximum two of A^1, A^2, A^3 and A^4 are N;

L^1 is O, carbonyl, NR^{10}, NH–(C=O), or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is cycloC_{3-7}alkyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; or C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or two geminal hydrogen atoms attached to a carbon atom in said C_{1-3}alkanediyl may optionally be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is tetrahydropyranyl; tetrahydrofuranyl; piperidinyl; morpholinyl; pyrrolidinyl; piperazinyl; cycloC_{3-7}alkyl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, cycloC_{3-7}alkyl, tetrahydrofuranyl, tetrahydropyranyl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, C_{1-4}alkylcarbonyl, oxo, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents; or a 5- or 6-membered heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, oxazolyl, furanyl, thiophenyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridazinyl, and pyrazinyl, wherein said 5- or 6-membered heteroaryl may be substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, $NR^{11c}R^{12c}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

each R^{11a}, R^{11b}, and R^{11c} independently is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

each R^{12a}, R^{12b}, and R^{12c} independently is hydrogen or C_{1-4}alkyl;

each R^{13a}, R^{13b}, and R^{13c} independently is hydrogen, or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and cycloC_{3-7}alkyl;

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

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein one or more of the following restrictions apply:

(i) Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3);

(ii) R^3 is C_{1-4}alkyl;

(iii) R^4, R^5, and R^6 each independently are hydrogen or C_{1-4}alkyl optionally substituted with one or more halo substituents;

(iv) $R^{7a}$is hydrogen, halo, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen, halo, cyano, C_{1-4}alkyloxy, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

(v) R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

(vi) L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; or C_{1-3}alkanediyl optionally substituted with one or more halo substituents; wherein p represents 1 or 2;

(vii) R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 2-oxo-5-(trifluoromethyl)1(2H)-pyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, hexahydro-1H-1,4-diazepin-1-yl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

(viii) each R^{11a}, and R^{11b} independently is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

(ix) each R^{12a}, and R^{12b} independently is hydrogen or C_{1-4}alkyl;

(x) each R^{13a}, R^{13b}, and R^{13c} independently is hydrogen, or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo.

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

Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3);

R^3 is C_{1-4}alkyl; in particular methyl;

R^4 is hydrogen;

R^5 is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

R^6 is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

R^{7a} is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

R^{7b} is hydrogen, C_{1-4}alkyloxy, or C_{1-4}alkyl optionally substituted with one or more halo substituents, in particular hydrogen, methyl, trifluoromethyl or methoxy;

R^{7c} is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

X^a is CH or N;

X^b is O;

A^1 is CR^9; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy; in particular wherein R^9 is hydrogen, fluoro or methoxy;

A^2 is CH or N;

A^3 and A^4 are CH;

L^1 is carbonyl, NR^{10}, NH-(C=O) or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl; in particular wherein R^{10} is hydrogen or methyl;

R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of $NR^{11a}R^{12a}$, 1-pyrrolidinyl, and C_{1-6}alkyloxy;
in particular R^1 is cyclopropyl; 1-propen-3-yl; or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of 1-pyrrolidinyl, $NR^{11a}R^{12a}$, and methoxy;

L^2 represents a direct bond; O; NR^{13a}; or C_{1-3}alkanediyl; in particular L^2 represents a direct bond; O; NR^{13a}; or methylene;

R^2 is pyrrolidinyl; piperidinyl; morpholinyl; piperazinyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-2(1H)-isoquinolinyl; 2-oxo-5-(trifluoromethyl)-1(2*H*)-pyridinyl; or Ar;
wherein pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, and hexahydro-1H-1,4-diazepin-1-yl, may be substituted with one or more substituents each independently selected from the group consisting of cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents; in particular wherein pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and hexahydro-1H-1,4-diazepin-1-yl, may be substituted with one

or more substituents each independently selected from the group consisting of cyclopropyl, acetyl, hydroxyl, fluoro, isopropyloxy, methoxymethyl, tert-butoxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more fluoro substituents;

wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, morpholinyl, C_{1-4}alkyloxy, and C_{1-4}alkyl optionally substituted with one or more halo substituents; in particular each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of chloro, fluoro, morpholinyl, methoxy, methyl and trifluoromethyl;

each R^{11a} is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl; in particular hydrogen, isopropyl, methyl or methylcarbonyl;

each R^{12a} is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

R^{13a} is hydrogen;

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

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

Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3);

R^3 is C_{1-4}alkyl; in particular methyl;

R^4 is hydrogen;

R^5 is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

R^6 is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

R^{7a} is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

R^{7b} is hydrogen, C_{1-4}alkyloxy, or C_{1-4}alkyl optionally substituted with one or more halo substituents, in particular hydrogen, methyl, trifluoromethyl or methoxy;

R^{7c} is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;

X^a is CH or N;

X^b is O;

A^1 is CR^9; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy; in particular wherein R^9 is hydrogen, fluoro or methoxy;

A^2 is CH or N;

A^3 and A^4 are CH;

L^1 is carbonyl, NR^{10}, NH-(C=O) or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl; in particular wherein R^{10} is hydrogen or methyl;

R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of $NR^{11a}R^{12a}$, 1-pyrrolidinyl, and C_{1-6}alkyloxy;
in particular R^1 is cyclopropyl; 1-propen-3-yl; or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of 1-pyrrolidinyl, $NR^{11a}R^{12a}$, and methoxy;

L^2 represents a direct bond; O; NR^{13a}; or C_{1-3}alkanediyl; in particular L^2 represents a direct bond; O; NR^{13a}; or methylene;

R^2 is pyrrolidinyl; piperidinyl; morpholinyl; piperazinyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-2(1H)-isoquinolinyl; 2-oxo-5-(trifluoromethyl)-1(2*H*)-pyridinyl; or Ar;
wherein pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, and hexahydro-1H-1,4-diazepin-1-yl, may be substituted with one or more substituents each independently selected from the group consisting of cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents; in particular wherein pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and hexahydro-1H-1,4-diazepin-1-yl, may be substituted with one or more substituents each independently selected from the group consisting of cyclopropyl, acetyl, hydroxyl, fluoro, isopropyloxy, methoxymethyl, tert-butoxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more fluoro substituents;
wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, morpholinyl, C_{1-4}alkyloxy, and C_{1-4}alkyl optionally substituted with one or more halo substituents; in particular each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of chloro, fluoro, morpholinyl, methoxy, methyl and trifluoromethyl;

each R^{11a} is hydrogen or C_{1-4}alkyl; in particular hydrogen, isopropyl or methyl;
each R^{12a} is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;
R^{13a} is hydrogen;
and the pharmaceutically acceptable addition salts, and the solvates thereof.

In an embodiment, the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof wherein
Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3a)

R^3 is C_{1-4}alkyl;

R^4, R^5, and R^6 each independently are hydrogen or C_{1-4}alkyl;

R^{7a} is hydrogen, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen or C_{1-4}alkyl;

X^a is CH or N;

X^b is O;

A^1 is CR^9; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

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

provided that maximum two of A^1, A^2, A^3 and A^4 are N;

L^1 is NR^{10}, carbonyl or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is C_{1-6}alkyl, or C_{2-6}alkyl substituted with one or more NH_2 substituents;

L^2 represents a direct bond; O; NH; or C_{1-3}alkanediyl;

R^2 is pyrrolidinyl; piperidinyl; morpholinyl; 3,4-dihydro-2(1H)-isoquinolinyl; or Ar;

wherein pyrrolidinyl, piperidinyl, morpholinyl, and 3,4-dihydro-2(1H)-isoquinolinyl, may be substituted with one or more substituents each independently selected from the group consisting of Ar and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein one or more of the following restrictions apply:

(a) Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3); in particular Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3a);

(b) R^3 is C_{1-4}alkyl;

(c) R^4, R^5 and R^6 each independently are hydrogen or C_{1-4}alkyl;

(d) R^{7a} is hydrogen or C_{1-4}alkyl;

(e) R^{7b} and R^{7c} each independently are hydrogen, or C_{1-4}alkyl;

(f) X^b is O;

(g) A^1 is CR^9; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

(h) A^2 is CH or N; and A^3 and A^4 are CH;

(i) L^1 is NR^{10}, carbonyl or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

(j) R^1 is C_{1-6}alkyl, or C_{2-6}alkyl substituted with one or more NH_2 substituents;

(k) L^2 represents a direct bond; O; NH; or C_{1-3}alkanediyl;

(l) R^2 is pyrrolidinyl; piperidinyl; morpholinyl; 3,4-dihydro-2(1H)-isoquinolinyl; or Ar;

wherein pyrrolidinyl, piperidinyl, morpholinyl, and 3,4-dihydro-2(1H)-isoquinolinyl, may be substituted with one or more substituents each independently selected from the group consisting of Ar and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, and C_{1-4}alkyl optionally substituted with one or more halo substituents.

Another embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein one or more of the following restrictions apply:

(a) Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3a);

(b) R^3 is methyl;

(c) R^4, R^5 and R^6 each independently are hydrogen or methyl;

(d) R^{7a} is hydrogen or methyl;

(e) R^{7b} and R^{7c} each independently are hydrogen, or methyl;

(f) X^b is O;

(g) A^1 is CR^9; wherein R^9 is hydrogen, fluoro, or methoxy;

(h) A^2 is CH or N; and A^3 and A^4 are CH;

(i) L^1 is NR^{10}, carbonyl or (C=O)-NH; wherein R^{10} is hydrogen or methyl;

(j) R^1 is C_{1-4}alkyl or 2-aminoethyl; in particular R^1 is methyl, ethyl, isopropyl, or 2-aminoethyl;

(k) L^2 represents a direct bond; O; NH; or C_{1-3}alkanediyl;

(l) R^2 is pyrrolidinyl; piperidinyl; morpholinyl; 3,4-dihydro-2(1H)-isoquinolinyl; or Ar;

wherein pyrrolidinyl, piperidinyl, morpholinyl, and 3,4-dihydro-2(1H)-isoquinolinyl, may be substituted with one or more substituents each independently selected from the group consisting of Ar and methyl optionally substituted with one or more fluoro substituents;

wherein each Ar independently is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of chloro, methoxy, and methyl optionally substituted with one or more fluoro substituents.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein one or more of the following restrictions apply:

(i) Het^1 is a heterocycle, having formula (a-1) or (a-3a); in particular (a-1)

(ii) R^3 is C_{1-4}alkyl; in particular methyl;

(iii) R^4 is hydrogen;

(iv) R^{7a} and R^{7b} are hydrogen; R^{7c} is C_{1-4}alkyl; in particular R^{7c} is methyl;

(v) X^a is N;

(vi) A^1 is CR^9 wherein R^9 is C_{1-4}alkyloxy; in particular R^9 is methoxy;

A^2, A^3 and A^4 are CH;

(vii) L^1 is NH;

(viii) R^1 is C_{1-6}alkyl; in particular C_{1-4}alkyl; more in particular isopropyl;

(ix) L^2 represents a direct bond;

(x) R^2 is piperidinyl optionally substituted with one or more C_{1-4}alkyl substituents wherein C_{1-4}alkyl is optionally substituted with one or more halo substituents; in particular R^2 is piperidinyl substituted with one trifluoromethyl moiety; more in particular R^2 is 1-piperidinyl substituted with one trifluoromethyl moiety; even more in particular R^2 is 1-piperidinyl substituted with one trifluoromethyl moiety in the meta position.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 is a heterocycle, having formula (a-1) or (a-3); in particular (a-1) or (a-3a).

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 is a heterocycle, having formula (a-3), in particular (a-3a).

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 is a heterocycle, having formula (a-2) or (a-3); in particular (a-2) or (a-3a).

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 is a heterocycle, having formula (a-1), (a-2) or (a-3).

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other

embodiments, wherein Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3a) or (a-4).

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein Het^1 is a heterocycle, having formula (a-1), (a-2) or (a-3); in particular Het^1 is (a-2) or (a-3).

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein R^9 is hydrogen or C_{1-4}alkyloxy; in particular C_{1-4}alkyloxy.

Another embodiment of the present invention relates to those compounds of formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein at least one of A^1, A^2, A^3 and A^4 is other than CH.

Another embodiment of the present invention relates to those compounds of formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein at least one of A^1, A^2, A^3 and A^4 is N; preferably wherein exactly one of A^1, A^2, A^3 and A^4 is N.

Another embodiment of the present invention relates to those compounds of formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein A^3 and A^4 are CH.

Another embodiment of the present invention relates to those compounds of formula (I) or any subgroup thereof as mentioned in any of the other embodiments, wherein maximum one of A^1, A^2, A^3 and A^4 is N.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein pyrrolidinyl is 1-pyrrolidinyl, piperidinyl is 1-piperidinyl, and morpholinyl is 4-morpholinyl.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subsgroup thereof as mentioned in any of the other embodiments wherein R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L^2 is O or a covalent bond; in particular O.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other

embodiments, wherein L^2 is C_{2-6}alkenediyl; S; $S(=O)_p$; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; or C_{1-3}alkanediyl substituted with one or more halo substituents.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
L^2 is O or a covalent bond, in particular O;
and R^2 is Ar, or piperidinyl substituted with one trifluoromethyl group;
in particular R^2 is Ar, or 1-piperidinyl substituted with one trifluoromethyl group;
more in particular R^2 is Ar.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^2 is not linked with, if applicable, its nitrogen atom or one of its nitrogen atoms to L^2 in case L^2 represents NR^{13a}, S, $S(=O)_p$, O, or C_{1-3}alkanediyl-NR^{13c}; in particular wherein R^2 is not linked with, if applicable, its nitrogen atom or one of its nitrogen atoms to L^2 in case L^2 represents NR^{13a} or C_{1-3}alkanediyl-NR^{13c}.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L^2 does not represent S, $S(=O)_p$, O, NR^{13a} or C_{1-3}alkanediyl-NR^{13c} in case R^2 is linked to L^2 with a nitrogen atom; in particular wherein L^2 does not represent NR^{13a} or C_{1-3}alkanediyl-NR^{13c} in case R^2 is linked to L^2 with a nitrogen atom.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein pyrrolidinyl is 1-pyrrolidinyl, piperidinyl is 1-piperidinyl, morpholinyl is 4-morpholinyl, piperazinyl is 1-piperazinyl.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be

replaced by C_{2-6}alkanediyl; and wherein wherein pyrrolidinyl is 1-pyrrolidinyl, piperidinyl is 1-piperidinyl, morpholinyl is 4-morpholinyl, piperazinyl is 1-piperazinyl.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
L^1 is O, carbonyl, NR^{10}, NH–(C=O), or (C=O)-NH; wherein R^{10} is C_{1-4}alkyl.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^2 is Ar; in particular R^2 is phenyl optionally substituted with one or more substitutents each independently selected from halo or trifluoromethyl; more in particular R^2 is phenyl substituted with one substituent selected from halo or trifluoromethyl; preferably R^2 is phenyl substituted with one chloro atom; most preferably R^2 is phenyl substituted with one chloro atom in a ortho position.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
L^2 is a direct bond or O; in particular a direct bond; and
R^2 is phenyl or piperidinyl, both substituted with one substituent in the ortho or meta position, said substituent being selected from the group consisting of halo and trifluoromethyl;
in particular R^2 is phenyl or piperidinyl, wherein phenyl and piperidinyl are substituted with one trifluoromethyl moiety in the ortho or meta position.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, 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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein R^1 is C_{1-6}alkyl; preferably C_{1-4}alkyl; more preferably isopropyl.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein the following restriction applies: R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl;

tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;
wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, C_{1-4}alkylcarbonyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;
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, $NR^{11b}R^{12b}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein the following restriction applies:
R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; or 1,3-benzodioxolyl;
wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, C_{1-4}alkylcarbonyl, oxo, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents; in particular C_{2-6}alkenyl, C_{1-4}alkylcarbonyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, or C_{1-4}alkyl optionally substituted with one or more halo substituents.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein
R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano,

1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 2-oxo-5-(trifluoromethyl)-1(2*H*)-pyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, hexahydro-1H-1,4-diazepin-1-yl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

or a 5- or 6-membered heteroaryl selected from the group consisting of furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl, wherein said 5- or 6-membered heteroaryl may be substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, $NR^{11c}R^{12c}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein L^2 represents a direct bond.

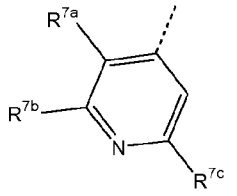
Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein Het^1 is a heterocycle having formula (a-1).

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L^1 is NH.

An embodiment of the present invention relates to those compounds of Formula (I) and stereoisomeric forms thereof, or any subgroup thereof as mentioned in any of the other embodiments, wherein L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; or C_{1-3}alkanediyl optionally substituted with one or more halo substituents; wherein p represents 1 or 2.

Another embodiment of the present invention relates to those compounds of Formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein the structure of the heterocycle (a-3) is restricted to (a-3a)



(a-3a)

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Another embodiment of the present invention relates to those compounds of formula (I) or any subgroup thereof as mentioned in any of the other embodiments wherein the expression "on one or more CH_2 groups" is restricted to "on one or two CH_2 groups".

In an embodiment the compound of Formula (I) is selected from the group comprising:
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-5-(3-phenyl-1-piperidinyl)-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,

5-(3,4-dihydro-2(1H)-isoquinolinyl)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-methyl-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-methyl-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-5-[2-(3-methylphenyl)-4-morpholinyl]-1H-1,2,4-triazol-3-amine,
3-methoxy-4-(4-methyl-1H-imidazol-1-yl)-N-[1-methyl-5-[[3-(trifluoromethyl)phenyl]amino]-1H-1,2,4-triazol-3-yl]-benzamide,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-5-[3-(3-methoxyphenyl)-1-pyrrolidinyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
5-(3,4-dihydro-2(1H)-isoquinolinyl)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
3-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-5-[[3-(trifluoromethyl)phenyl]methyl]-1H-1,2,4-triazole-1-ethanamine,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-methyl-1H-1,2,4-triazol-3-amine,
N^5-(2-chlorophenyl)-N^3-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-methyl-1H-1,2,4-triazole-3,5-diamine,
2-pyridinamine, 6-methoxy-N-[1-(1-methylethyl)-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-yl]-5-(4-methyl-1H-imidazol-1-yl)-
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-methyl-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,
1-methyl-N-[4-(2-methyl-4-pyridinyl)phenyl]-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-(2,6-dimethyl-4-morpholinyl)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
5-[(2R,6S)-2,6-dimethyl-4-morpholinyl]-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine,
[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl][1-methyl-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-yl]-methanone,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .2.2HCl .2.7H_2O,

N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .HCl,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .2.7H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[2-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine .HCl .H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine .HCl .1.5H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-methyl-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .1.6HCl .2H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-methyl-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,
1-methyl-N-[4-(4-pyridinyl)phenyl]-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,
N-[3-fluoro-4-(2-methyl-4-pyridinyl)phenyl]-1-methyl-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-N-[3-fluoro-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-methyl-5-[2-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine,
1-methyl-5-[3-(trifluoromethyl)phenyl]-N-[4-[2-(trifluoromethyl)-4-pyridinyl]phenyl]-1H-1,2,4-triazol-3-amine,
5-(2-chloro-5-methoxyphenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .H_2O,
5-[2-fluoro-5-(trifluoromethyl)phenoxy]-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl,
5-[2-fluoro-5-(trifluoromethyl)phenoxy]-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-methyl-1H-1,2,4-triazol-3-amine,
5-(4-fluoro-2-methylphenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
5-[4-fluoro-2-(trifluoromethyl)phenoxy]-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[4-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .2HCl .2H_2O,

N^3-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-methyl-N^5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazole-3,5-diamine,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[4-(2,2,2-trifluoroethyl)-1-piperazinyl]-1H-1,2,4-triazol-3-amine .1.6HCl .2.1H_2O,
5-(4-fluoro-2-methylphenoxy)-1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .1.8HCl .2.2H_2O,
N-[3-fluoro-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .2.2HCl .2.3H_2O,
5-(2,5-dichlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
4-[3-[[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]amino]-1-(1-methylethyl)-1H-1,2,4-triazol-5-yl]-1-piperazinecarboxylic acid, 1,1-dimethylethyl ester,
5-(3-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
5-(2,4-difluorophenoxy)-1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine .HCl .1.5H_2O,
5-(2-chloro-6-fluorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .H_2O,
5-(2-chloro-5-fluorophenoxy)-1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(3-methoxypropyl)-1H-1,2,4-triazol-3-amine .2HCl,
5-(2-chlorophenoxy)-1-(2-methoxyethyl)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine .2HCl,
5-(2-chloro-6-methylphenoxy)-1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-3-[[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]amino]-1H-1,2,4-triazole-1-ethanamine .2HCl,
1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-5-[2-(trifluoromethyl)-4-morpholinyl]-1H-1,2,4-triazol-3-amine .2HCl .2H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,
1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,

N-[3-fluoro-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-(3-chloro-2-methylphenoxy)-1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-1-(2,2-dimethoxyethyl)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(4-morpholinyl)phenoxy]-1H-1,2,4-triazol-3-amine,
5-(3,3-dimethyl-1-piperidinyl)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .2HCl .2.5H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-(1-piperidinyl)-1H-1,2,4-triazol-3-amine,
5-(2-fluoro-6-methylphenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-5-[3-(1-methylethoxy)-1-piperidinyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
5-[3-(methoxymethyl)-1-piperidinyl]-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .2HCl,
5-[2-fluoro-5-(trifluoromethoxy)phenoxy]-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .1.2HCl 1.3H_2O,
1-[3-[[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]amino]-1-(1-methylethyl)-1H-1,2,4-triazol-5-yl]-5-(trifluoromethyl)-2(1H)-pyridinone,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-(3-propyl-1-piperidinyl)-1H-1,2,4-triazol-3-amine .1.8HCl .2H_2O,
5-(3-cyclopropyl-1-piperidinyl)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .1.5HCl .1.3H_2O,
5-(2-chloro-6-methylphenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .1.5H_2O,
5-(2-chlorophenoxy)-3-[[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]amino]-N-(1-methylethyl)-1H-1,2,4-triazole-1-ethanamine,
5-(2-chloro-6-fluorophenoxy)-1-(1-methylethyl)-N-[4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
5-[hexahydro-4-(2,2,2-trifluoroethyl)-1H-1,4-diazepin-1-yl]-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .2HCl .2.6H_2O,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(2-propenyl)-1H-1,2,4-triazol-3-amine,

5-(2-chlorophenoxy)-1-cyclopropyl-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine .1.4HCl .H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[[3-(trifluoromethyl)cyclohexyl]oxy]-1H-1,2,4-triazol-3-amine .2.4HCl .1.6H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[[3-(trifluoromethyl)cyclohexyl]oxy]-1H-1,2,4-triazol-3-amine .1.7HCl .2.4H_2O,
5-(4-fluoro-2-methylphenoxy)-1-(1-methylethyl)-N-[4-[2-(trifluoromethyl)-4-pyridinyl]phenyl]-1H-1,2,4-triazol-3-amine,
3-cyclopropyl-1-[3-[[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]amino]-1-(1-methylethyl)-1H-1,2,4-triazol-5-yl]-3-piperidinol .HCl .H_2O,
5-(4-fluoro-2-methylphenoxy)-N-[4-(2-methoxy-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
5-(4-fluoro-2-methylphenoxy)-1-(1-methylethyl)-N-[4-(4-pyridinyl)phenyl]-1H-1,2,4-triazol-3-amine,
1-acetylhexahydro-4-[3-[[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]amino]-1-(1-methylethyl)-1H-1,2,4-triazol-5-yl]-1H-1,4-diazepine,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-[2-(1-pyrrolidinyl)ethyl]-1H-1,2,4-triazol-3-amine .2HCl,
5-(2-chlorophenoxy)-3-[[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]amino]-N,N-dimethyl-1H-1,2,4-triazole-1-ethanamine .2HCl,
5-(4-fluoro-2-methylphenoxy)-N-[4-(6-methoxy-3-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
N-[2-[3-[[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]amino]-5-[[3-(trifluoromethyl)phenyl]methyl]-1H-1,2,4-triazol-1-yl]ethyl]-acetamide,
N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-methyl-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine 0.4HCl 1.5H_2O,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperazinyl]-1H-1,2,4-triazol-3-amine 2.3HCl 3.3H_2O,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-5-[4-methyl-3-(trifluoromethyl)-1-piperazinyl]-1H-1,2,4-triazol-3-amine .HCl .H_2O,

5-(3-chloro-2-methylphenoxy)-N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
5-(4-fluoro-2-methylphenoxy)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazole-3-carboxamide,
5-(4-fluorophenyl)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-methyl-1H-1,2,4-triazol-3-amine,
stereoisomeric forms thereof,
and the pharmaceutically acceptable addition salts, the free bases and the solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group comprising:
5-(2-chlorophenoxy)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .2.2HCl .2.7H_2O,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .2.7H_2O,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[2-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine .HCl .H_2O,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine .HCl .1.5H_2O,
stereoisomeric forms thereof,
and the pharmaceutically acceptable addition salts, the free bases and the solvates thereof.

All possible combinations of the above-indicated interesting embodiments are considered to be embraced within the scope of this invention.

Preparation of the compounds

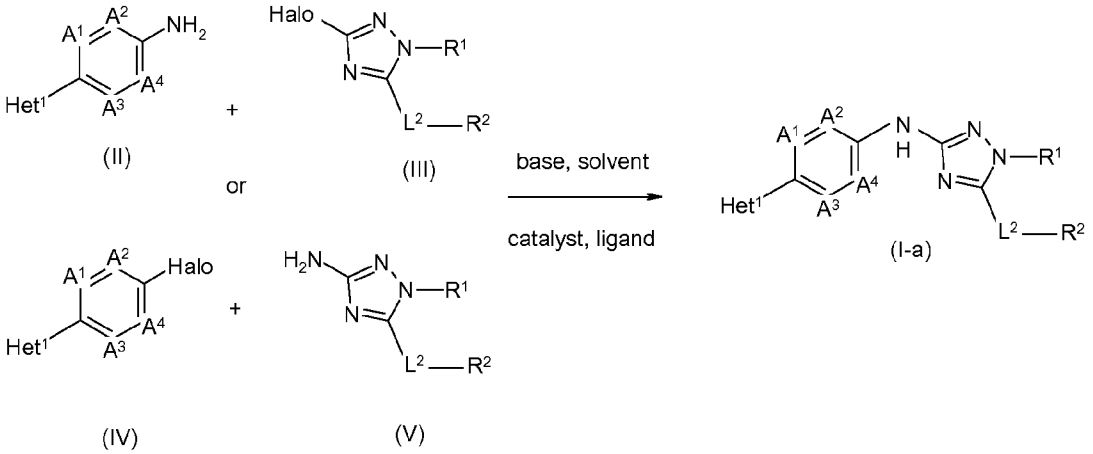
The present invention also encompasses processes for the preparation of compounds of Formula (I) and subgroups thereof. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, or carboxy groups, where these are desired in the final product, to 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. All variables are defined as mentioned hereabove unless otherwise is indicated.

Experimental procedure 1

In general compounds of Formula (I) where L^1 represents NH, hereby named compounds of formula (I-a), can be prepared as set out below in Scheme 1 wherein Halo is defined as Cl, Br or I, and wherein all other variables are defined as mentioned hereabove:



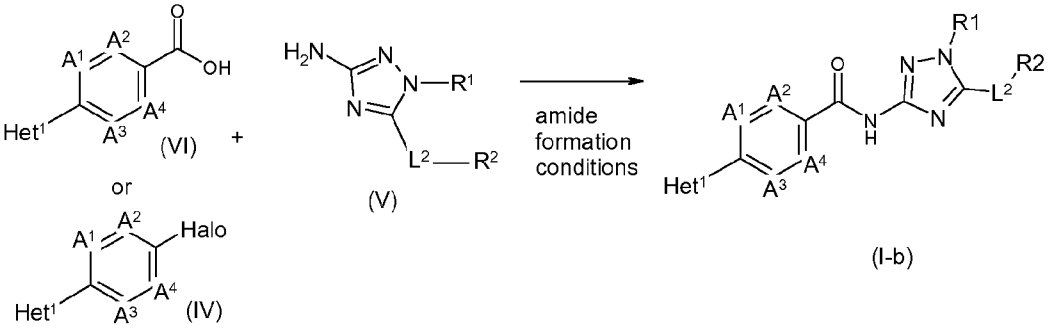
Scheme 1

Compounds of formula (I-a) can be prepared *via* a coupling reaction between an intermediate of formula (II) and an intermediate of formula (III) or alternatively *via* a coupling reaction between an intermediate of formula (IV) and an intermediate of formula (V) (Scheme 1). 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, DMF, *tert*-butanol (*t*-BuOH) or dioxane. The reaction typically is performed in the presence of a catalyst system comprising of 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 nitrogen or argon. Reaction rate and yield may be enhanced by microwave assisted heating.

Experimental procedure 2

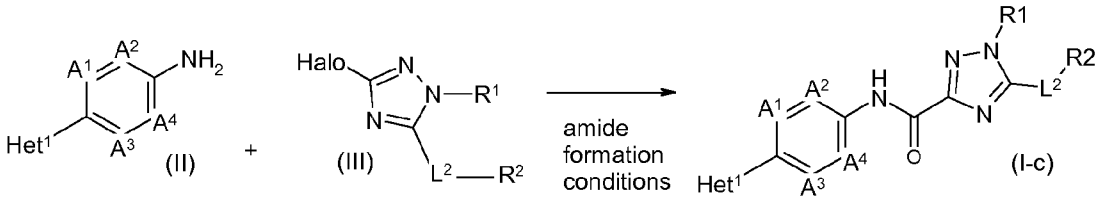
Compounds of Formula (I) wherein L^1 represent (C=O)-NH, hereby named compounds of formula (I-b), can be prepared by standard amide bond formation reaction, using an intermediate of formula (V) as the amine source and an intermediate of formula (VI) as the carboxylic acid source. Alternatively, compounds of formula (I-b) can be prepared by a Pd-catalysed CO-insertion reaction between an intermediate of formula (IV) and an intermediate of formula (V). Both synthesis protocols are illustrated in Scheme 2, wherein Halo is defined as Cl, Br or I, and wherein all other variables are defined as mentioned before. Stirring at elevated temperatures (e.g. 150 °C) and/or pressure may enhance the rate of the reaction. The reaction can be charged with CO gas and may typically be performed in an organic solvent such as THF. The reaction can be catalysed by a Pd source such as, for example, tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$), $Pd(OAc)_2$ or $Pd_2(dba)_3$, in conjunction with an appropriate ligand.



Scheme 2

Experimental procedure 3

Compounds of Formula (I) wherein L^1 represents NH-(C=O), hereby named compounds of formula (I-c), may be prepared by a Pd-catalysed CO-insertion reaction between an intermediate of formula (III) and an intermediate of formula (II), according to Scheme 3, wherein Halo is defined as Cl, Br or I and wherein all other variables are defined as mentioned here above. Stirring at elevated temperatures (for example 150 °C) and/or pressure may enhance the rate of the reaction. The reaction is charged with CO gas and is typically performed in an organic solvent such as, for example, THF. The reaction can be catalysed by a Pd source such as, for example, $Pd(OAc)_2$, $Pd_2(dba)_3$ or $Pd(PPh_3)_4$. An appropriate ligand may be added to the reaction.

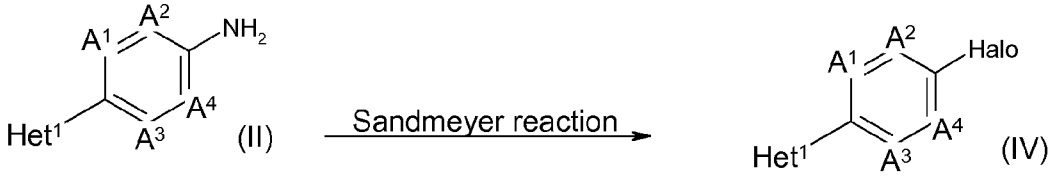


Scheme 3

Alternatively, a compound of formula (I-c) can also be prepared by a standard amide bond formation reaction, using an amine source of formula (II) and the corresponding carboxylic acid derivative of the intermediate of formula (III). This reaction can be performed in typical reaction conditions, similarly to the conditions described in Experimental procedure 2.

Experimental procedure 4

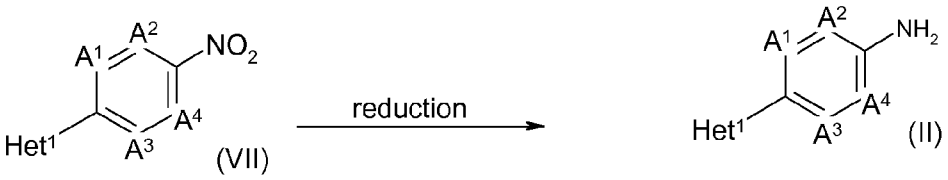
An intermediate of formula (IV), wherein all variables are defined as mentioned before, can be prepared by conversion of the amino-moiety in an intermediate of formula (II) into a halo-group, known as the Sandmeyer reaction (Scheme 4). In Scheme 4, Halo is defined as I, Br or Cl, and all other variables are defined as mentioned hereabove. Intermediate (II) is first converted to the corresponding diazonium salt by treatment with a nitrite source, such as $NaNO_2$ under acidic conditions, then treated with a halide source such as, for example, KI, CuBr or CuCl. Typical reaction conditions known to those skilled in the art can be used.



Scheme 4

Experimental procedure 5

An intermediate of formula (II), wherein all variables are defined as mentioned before, can be prepared by reduction of an intermediate of formula (VII), according to Scheme 5. The reduction of an intermediate of formula (VII) to an intermediate of formula (II) can be conducted by a conventional method such as reductive hydrogenation of reduction with a metal or a metal salt and an acid [for example a metal such as Fe, or a metal salt such as $SnCl_2$ and an acid such as an inorganic acid (HCl, H_2SO_4 or the like) or an organic acid (acetic acid or the like)]. Alternatively, other well-known methods for converting a nitro-group to its corresponding amine may be used.

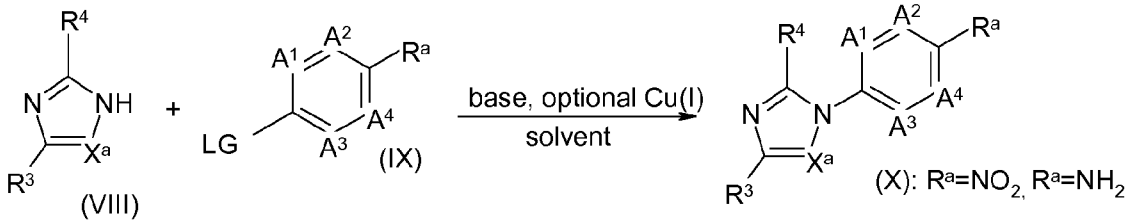


Scheme 5

Experimental procedure 6

Intermediates of formula (VII) or (II), wherein Het^1 is restricted to heterocycles having formula (a-1), wherein R^a is defined as NO_2 or NH_2, and wherein other variables are defined as mentioned before, hereby named an intermediate of formula (X), can be prepared *via* a nucleophilic aromatic substitution of an intermediate of formula (IX) with an intermediate of formula (VIII), according to Scheme 6, wherein LG is defined as a leaving group such as, for example, F, Cl, Br, I, tosylate, mesylate or triflate, in particular F, Cl, Br or I, more in particular Cl, Br or I; and wherein all other variables are defined as mentioned here above. The reaction may be performed under an inert atmosphere such as, for example, N_2. Stirring at elevated temperatures (for example between 70-170 °C) and/or pressure may enhance the rate of the reaction. The reaction typically is performed in an organic solvent such as DMSO, DMF, or NMP (*N*-methylpyrrolidinone) in the presence of a base such as K_2CO_3, Cs_2CO_3, or Et_3N.

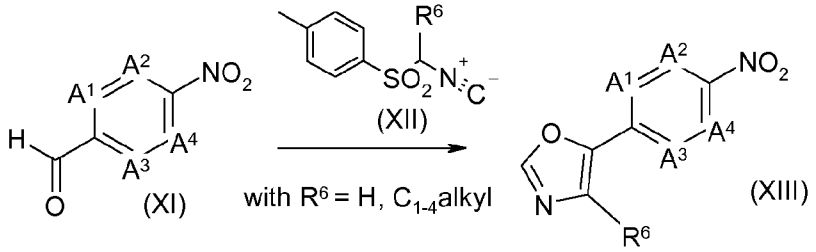
The reaction can be performed in the presence of a copper catalyst. Copper salts such as, for example, Cu_2O, CuI, or CuBr can be used in catalytic or stoichiometric amounts.



Scheme 6

Experimental procedure 7

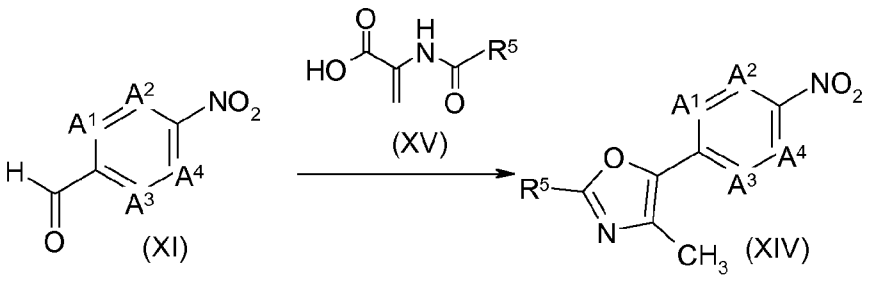
An intermediate of formula (VII) wherein Het^1 is restricted to oxazole substituted with R^6, hereby named intermediate of formula (XIII), can be prepared by a condensation reaction of an intermediate of formula (XI) with an intermediate of formula (XII) as is illustrated in Scheme 7. Intermediate (XI) may be commercially available or may be prepared according to conventional reaction procedures generally know in the art. This condensation reaction is performed in the presence of a suitable base such as, for example, K_2CO_3 or sodium ethoxide (NaOEt). The reaction can be performed in a protic solvent such as, for example, methanol (MeOH) or ethanol (EtOH). Stirring and/or elevated temperatures (for example between 70-110 °C) may enhance the rate of the reaction. In Scheme 7, all variables are defined as mentioned here above.



Scheme 7

Experimental procedure 8

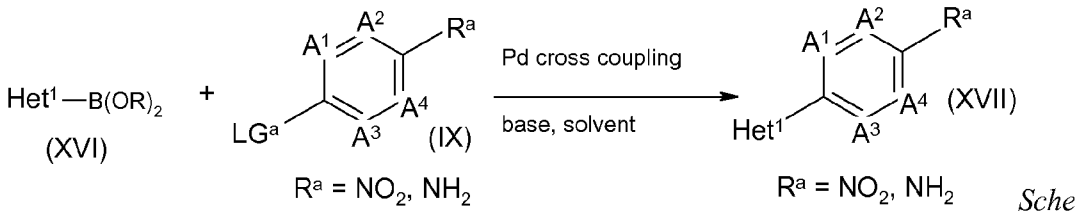
An intermediate of formula (VII) wherein Het^1 is restricted to oxazole substituted with R^5 in the 2-position and CH_3 in the 4-position, hereby named an intermediate of formula (XIV), can be prepared by a condensation reaction of an intermediate of formula (XI) with an intermediate of formula (XV) according to Scheme 8 wherein all variables are defined as hereinbefore. Both intermediates may be commercially available or may be prepared according to conventional reaction procedures generally know in the art. This condensation reaction typically can be performed in a solvent such as pyridine. Stirring and/or elevated temperatures (e.g. between 70-110 °C) may enhance the rate of the reaction.



Scheme 8

Experimental procedure 9

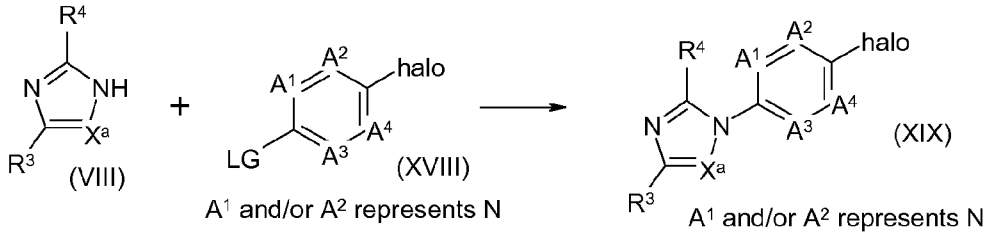
Intermediates of formula (VII) or (II) wherein Het^1 is restricted to heterocycles (a-2), (a-3) or (a-4), hereby named an intermediate of formula (XVII), may be prepared by a Suzuki-Miyaura cross-coupling reaction between an intermediate of formula (XVI), wherein Het^1 is restricted to a heterocycle according to formula (a-2), (a-3) or (a-4), and an intermediate of formula (IX) wherein R^a can be NO_2 or NH_2, according to Scheme 9. In formula (IX), LG^a is defined as a leaving group such as, for example, Cl, Br, I, tosylate, mesylate or triflate, in particular Cl, Br or I; and in formula (XVI) $B(OR)_2$ refers to the boronic acid $B(OH)_2$ or its corresponding boronate ester, such as a pinacol ester. This reaction is catalysed by a Pd catalyst, such as, for example, $Pd(PPh_3)_4$ or [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloropalladium ($PdCl_2$(dppf)). The reaction is performed in the presence of a suitable base, such as, for example K_2CO_3, or K_3PO_4 and in a reaction-inert solvent such as toluene, DMF, MeCN and may also include H_2O. Stirring at elevated temperatures (for example, between 50 -120 °C) and/or pressure may enhance the rate of the reaction, which can be carried out using microwave irradiation, or by conventional heating.



Scheme 9

Experimental procedure 10

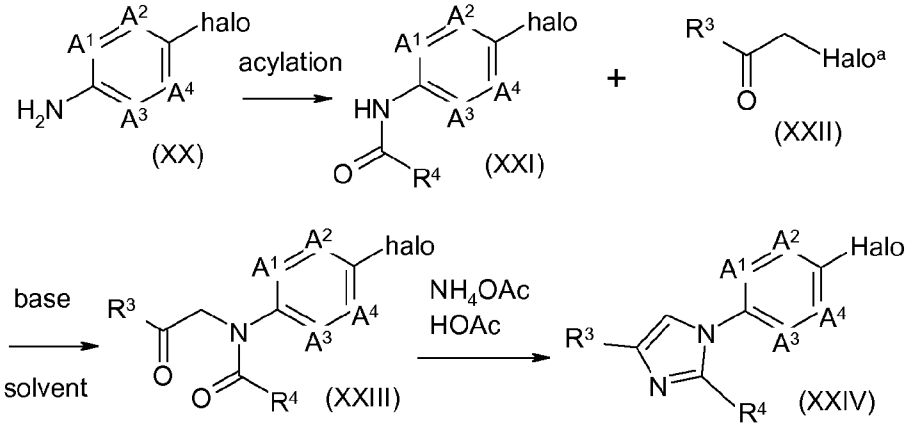
An intermediate of formula (IV) wherein at least one of A^1 or A^3 represents N, and, wherein Het^1 is restricted to formula (a-1), and wherein all other variables are defined as mentioned before, hereby named an intermediate of formula (XIX), can be prepared *via* a nucleophilic aromatic substitution of an intermediate of formula (XVIII), wherein at least one of A^1 or A^3 represents N, with an optionally substituted imidazole or triazole of formula (VIII) according to Scheme 10, wherein LG is as defined as mentioned before, wherein Halo is defined as Br, Cl or I, and wherein all other substituents are defined as mentioned before. The reaction may be performed under similar reaction conditions as described for Experimental procedure 4.



Scheme 10

Experimental procedure 11

An intermediate of formula (IV) wherein Het^1 represents the group of formula (a-1) wherein X^a is restricted to CH, and wherein all other variables are defined as mentioned before, hereby named an intermediate of formula (XXIV), can be prepared *via* acylation of intermediate (XX) to yield intermediate (XXI) in the presence of a reaction inert solvent, such as, for example, THF, and optionally a suitable base, such as Et_3N, according to Scheme 11. An intermediate of formula (XXIII) can subsequently be prepared *via* alkylation of an intermediate of formula (XXI) with an intermediate of formula (XXII), 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, and optionally in the presence of a catalytic amount of a iodide salt such as, for example, KI or NaI. Finally, a condensation reaction of intermediate (XXIII) with an ammonia source such as, for example, ammonium acetate (NH_4OAc) yields a compound of formula (XXIV). In Scheme 11, Halo is defined as Cl, Br, or I, $Halo^a$ is defined as Cl or Br, and all other variables are defined as mentioned hereinbefore.

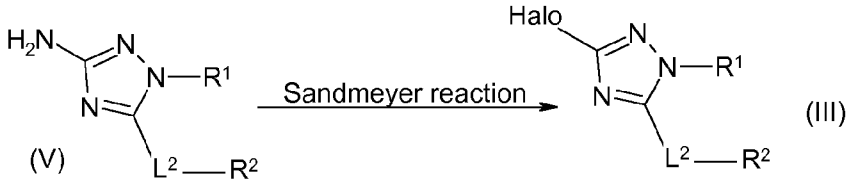


Scheme 11

Experimental procedure 12

An intermediate of formula (III), wherein all variables are defined as mentioned before, can be prepared by conversion of the amino-moiety in intermediate (V) into a halo-group *via* a Sandmeyer reaction (Scheme 12). In Scheme 12, Halo is defined as I, Br or Cl, and all other variables are defined as mentioned here above. Intermediate (V) is first

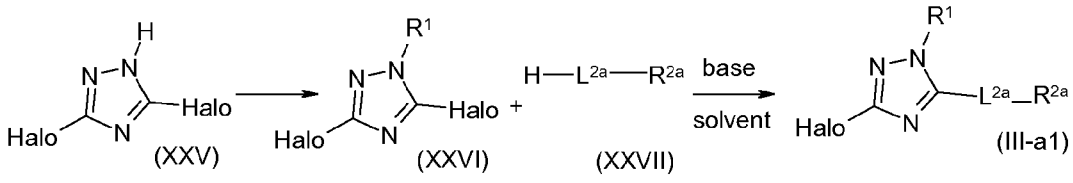
converted to the corresponding diazonium salt by treatment with a nitrite source, such as $NaNO_2$ under acidic conditions or *iso*amyl nitrite or *t*-butyl nitrite in an organic solventy such as CH_3CN, then treated with a halide source such as KI, CuBr or CuCl. Typical reaction conditions known to those skilled in the art can be used.



Scheme 12

Experimental procedure 13

An intermediate of formula (III), wherein L^2 is restricted to L^{2a}, L^{2a} being NR^{13a}, O or a direct bond; wherein R^2 is restricted to R^{2a}, R^{2a} being piperidinyl, morpholinyl or pyrrolidinyl; wherein Halo represents Br, I or Cl; and wherein all other variables are defined as mentioned before, hereby named intermediates of formula (III-a1), may be prepared starting by substitution of an intermediate of formula (XXV) with R^1, for example *via* alkylation with an alkylhalide, followed by a regioselective substitution reaction between the obtained intermediate of formula (XXVI) and an amine or alcohol species (XXVII) according to Scheme 13. In Scheme 13, Halo is defined as I, Br, or Cl and H-L^{2a}-R^{2a} refers to an amine or alcohol derivative. The substitution reaction is performed in the presence of a suitable base, such as, for example K_2CO_3, and in a reaction-inert solvent such as DMF, CH_3CN and may also include H_2O. This reaction is typically performed at room temperature (r.t.), but elevated temperatures (for example 40-160 °C) in microwave and/or under pressure may enhance the rate of the reaction.

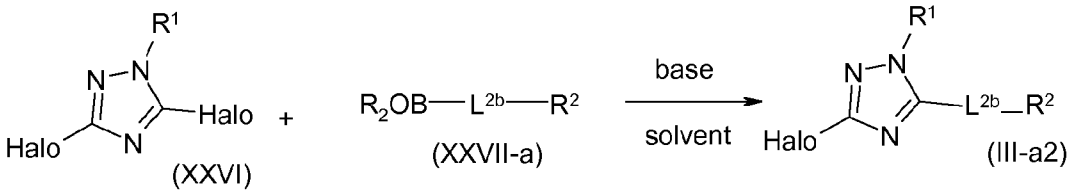


Scheme 13

Experimental procedure 14

An intermediate of formula (III), wherein L^2 is restricted to L^{2b}, L^{2b} representing a direct bond; wherein Halo is defined as I, Br or Cl and wherein all other variables are defined as mentioned before, hereby named intermediates of formula (III-a2), may be prepared by a Suzuki-Miyaura cross-coupling reaction between an intermediate of formula (XXVI) and (XXVII-a) according to Scheme 14. In formula (XXVII), $B(OR)_2$ refers to the boronic acid $B(OH)_2$ or its corresponding boronate ester such as the pinacol ester. This reaction is catalysed by a Pd catalyst such as, for example, $Pd(PPh_3)_4$ or

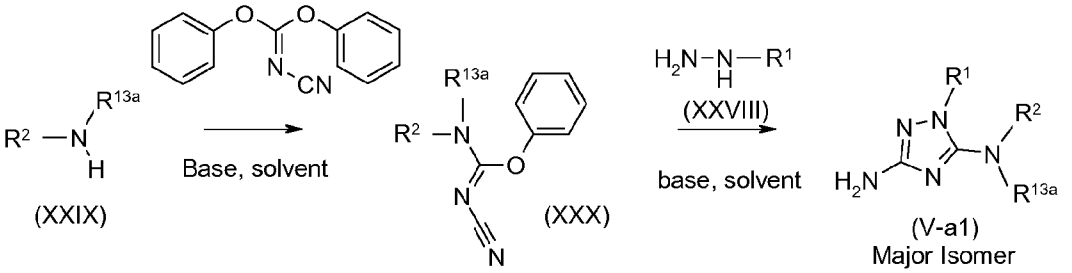
$PdCl_2(dppf)$. The reaction is performed in the presence of a suitable base, such as, for example K_2CO_3, or K_3PO_4 and in a reaction-inert solvent such as toluene, DMF or MeCN and may also include H_2O. Stirring at elevated temperatures (for example, between 50 -120 °C) and/or pressure may enhance the rate of the reaction, which can be carried out using microwave irradiation or by conventional heating.



Scheme 14

Experimental procedure 15

Intermediates of formula (V), wherein L^2 is restricted to L^{2c}, L^{2c} being NR^{13a}, hereby named intermediates of formula (V-a1), may be prepared starting by substitution of a cyanocarbonimidate such as, for example, diphenyl cyanocarbonimidate (shown in scheme 15) by an amine of formula (XXIX) in the presence of an appropriate base such as LiHMDS in a reaction inert solvent such as THF at r.t. Intermediate (XXX) can then be condensed, mostly in a regioselective manner, with the relevant hydrazine R^1-$NHNH_2$ of formula (XXVIII) in an alcoholic solvent such as propan-2-ol. Stirring at elevated temperatures (for example, between 40 -160 °C) and/or pressure may enhance the rate of the reaction, which can be carried out using microwave irradiation or by conventional heating.



Scheme 15

Starting materials in the above described schemes 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), 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 therefore may be useful in the treatment or prevention of AD, TBI, 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 AD.

The compounds according to the present invention and the pharmaceutically acceptable compositions thereof may be useful in the treatment or prevention of a disease or condition selected from the group consisting of AD, TBI, MCI, senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid.

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, without decreasing the

production of smaller, less aggregatable forms of Aβ, i.e. Aβ38 and without concomitant inhibition of Notch processing. 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 use in the modulation of γ-secretase activity.

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 use in the treatment or prevention of diseases or conditions selected from the group consisting of AD, TBI, 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.

In an embodiment, said disease or condition is preferably AD.

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 use in 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 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 assay 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 can be 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.

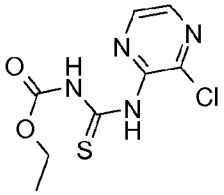
Examples

Hereinafter, the term "THF" means tetrahydrofuran; "DCM" means dichloromethane; "MeOH" means methanol; "EtOH" means ethanol; "HPLC" means high-performance liquid chromatography; "sat." Means saturated; "aq." Means aqueous; "EtOAc" means ethyl acetate; "r.t." means room temperature; "r.m." means reaction mixture; "HOAc" means acetic acid; "Et_3N" means triethylamine; "RP" means reversed phase; "min" means minute(s); "conc." means concentrated; "h" means hour(s); "q.s." means quantum sufficit; "$NaBH(OAc)_3$" means sodium triacetoxyborohydride; "I.D." means internal diameter; "Et_2O" means diethyl ether; "SFC" means Supercritical Fluid Chromatography; "DCE" means 1,2-dichloroethane; "DIPEA" means diisopropylethylamine; "eq." means equivalent; "DIPE" means diisopropyl ether;

"DME" means 1,2-dimethoxyethane; "DMF" means *N,N*-dimethyl formamide; "HBTU" means 1-[bis(dimethylamino)methylene]-1H-benzotriazol-1-ium 3-oxide hexafluorophosphate; "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium; "$Pd(OAc)_2$" means palladium(II) acetate; "$Pd_2(dba)_3$" means tris(dibenzylideneacetone)dipalladium; "X-Phos" means dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]-phosphine; "Dess-Martin periodinane" means 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one; "rac" means racemic mixture; and "iPrOH" means 2-propanol.

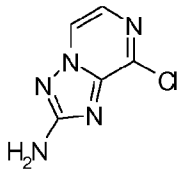
A. Preparation of the intermediates

a) Preparation of intermediate 1



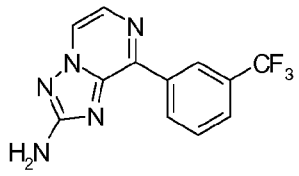
Ethoxycarbonyl isothiocyanate (2.91 g, 22.2 mmol) was added dropwise at r.t. to a mixture of 3-chloro-pyrazin-2-ylamine (2.5 g, 19.3 mmol) in dioxane (80 ml). The r.m. was stirred at r.t. for 24 h. The solvents were then evaporated under reduced pressure. The resulting solid was triturated in DIPE, filtered and dried under vacuum, yielding 2.9 g of **intermediate 1** (58 %).

b) Preparation of intermediate 2



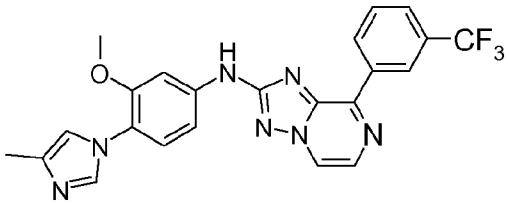
DIPEA (3.57 g, 27.6 mmol) was added dropwise at r.t. to a stirring mixture of hydroxylamine hydrochloride (3.2 g, 46 mmol) in MeOH (100 ml) and EtOH (100ml).Intermediate 1 (2.4 g, 9.2 mmol) was added portionwise and the r.m. was stirred at 70 °C for 4 h. The r.m. was cooled to r.t. and evaporated under reduced pressure. The residue was partitioned between DCM and water. 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 98/2). The product fractions were collected and concentrated *in vacuo*, yielding 1 g of **intermediate 2** (64 %).

c) Preparation of intermediate 3



To a mixture of 3-trifluoromethylphenylboronic acid (1.34 g, 7 mmol), intermediate 2 (0.8 g, 4.7 mmol) and Cs_2CO_3 (4.77 g, 14.6 mmol) in DME (8 ml), and water (4 ml) was added $Pd(PPh_3)_4$ (0.436 g, 0.377 mmol) and the mixture was degassed. The resulting mixture was stirred and heated at 95 °C for 18 h. The r.m. was cooled to r.t. and partitioned between water and 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 silica gel (eluent: DCM/MeOH from 100/0 to 99/1). The product fractions were collected and concentrated *in vacuo*, yielding 1.30 g of **intermediate 3**.

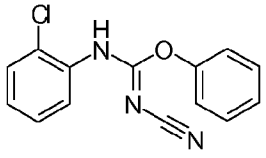
d) Preparation of intermediate 4



Intermediate 42 (1.41 g, 4.66 mmol), $Pd_2(dba)_3$ (426 mg, 0.466 mmol), X-Phos (444 mg, 0.93 mmol) and Cs_2CO_3 (6.07 g, 18.6 mmol) were added to a solution of intermediate 3 (1.3 g, 4.66 mmol) in 2-methyl-2-propanol (50 ml) under a N_2 atmosphere. The r.m. was heated at 100 °C for 20 h. Then, the r.m. was cooled to r.t., water 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 99/1). The product fractions were collected and concentrated *in vacuo*. The residue was triturated in DIPE, yielding 0.95 g of **intermediate 4** (44 %).

Example A2

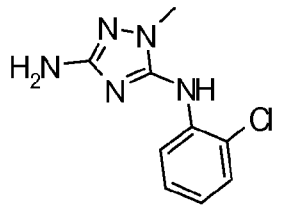
a) Preparation of intermediate 5



A mixture of 2-chloro-aniline (5 g, 39.2 mmol) and diphenyl cyanocarbon-imidate (8.89 g, 37.3 mmol) was heated at reflux in 2-propanol (35 ml) for 20 h. The r.m. was then

concentrated under reduced pressure. The residue was triturated with diethylether and the resulting solid was filtered and dried *in vacuo*, yielding 1.6 g of **intermediate 5** in 93% purity according to LC-MS analysis (Yield 15 %).

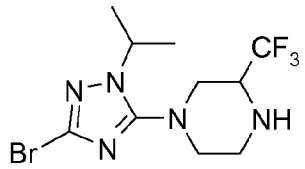
b) Preparation of intermediate 6



Methylhydrazine (0.31 ml, 5.9 mmol) was added to a mixture of intermediate 5 (1.6 g, 5.9 mmol) in 2-propanol. The r.m. was heated at reflux for 2 h. The r.m. was then concentrated under reduced pressure. The resulting solid was triturated with diethylether, filtered and dried under vacuum, yielding 493 mg of **intermediate 6** (37 %).

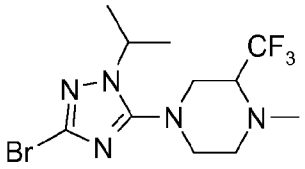
Example A3

a) Preparation of intermediate 7



Intermediate 7 was prepared starting from intermediate 24 and RS-2-(trifluoromethyl)piperazine according to the preparation described in Example A8.c.

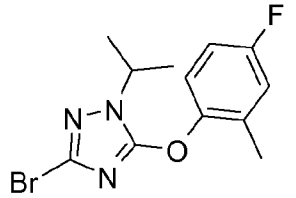
b) Preparation of intermediate 8



To a solution of intermediate 7 (500 mg, 1.46 mmol) in DCM (10 ml) was added an aq. formaldehyde solution (37%, 2.2 ml, 29 mmol) and $NaBH(OAc)_3$ (1.86 g, 8.77 mmol). The r.m. was stirred at r.t. for 30 min. Na_2SO_4 (6.2 g) was added and the r.m. was stirred further at r.t. overnight. The r.m. was partitioned between water and DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give crude **intermediate 8** (570 mg) in 83% purity according to LC-MS analysis (91% yield), which was used as such in the next step.

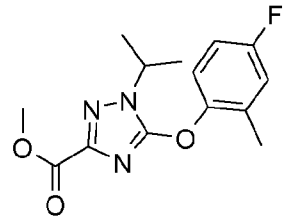
Example A4

a) Preparation of intermediate 9



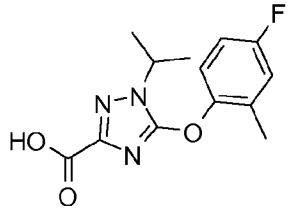
A mixture of 4-fluoro-2-methylphenol (2.35 g, 18.6 mmol), intermediate 24 (5.0 g, 18.6 mmol), and K_2CO_3 (5.14 g, 37.2 mmol) in DMF (20 ml) was heated at 100 °C for 18h. The r.m. was cooled and then poured into H_2O and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (eluent: n-heptane/EtOAc from 100/0 to 70/30). The product fractions were collected and concentrated *in vacuo*, yielding 3.52 g of **intermediate 9** (60 %).

b) Preparation of intermediate 10



A mixture of intermediate 9 (3.52 g, 11.2 mmol), $Pd(OAc)_2$ (51 mg, 0.224 mmol) and 1,3-bis(diphenylphosphino)propane (185 mg, 0.45 mmol) in THF/MeOH (30 ml/10 mL) was prepared in a stainless steel autoclave under an atmosphere of N_2. The vessel was closed and pressurized to 20 bar CO (g) and the ensuing reaction mixture heated at 125 °C for 16 h. The cooled reaction mixture was evaporated under reduced pressure. The residue was suspended in DIPE, and the resulting precipitate was filtered off and dried *in vacuo*, yielding 2.25 g of **intermediate 10** (68%).

c) Preparation of intermediate 11

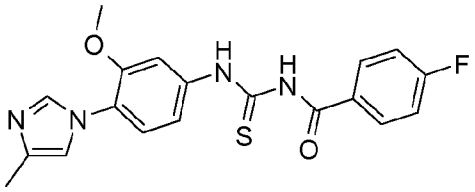


To a solution of intermediate 10 (587 mg, 2.0 mmol) in THF (10 ml) was added an aq. 1N NaOH solution (10 mL, 10 mmol), and the r.m. was stirred at r.t. for 1h. Then an aq. 1N HCl solution was added, and the resulting mixture was extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced

pressure. cooled reaction mixture was evaporated under reduced pressure, yielding 543 mg of **intermediate 11** (97 %).

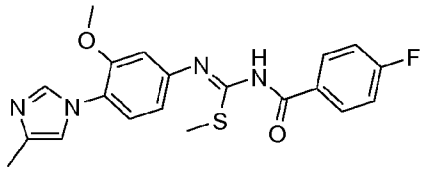
Example A5

a) Preparation of intermediate 12



To a solution of 4-fluorobenzoyl chloride (1.5 g, 9.5 mmol) in acetone (70 ml) was added ammonium thiocyanate (864 mg, 11.4 mmol), and the r.m. was stirred at r.t. for 1.5h. Subsequently, a solution of intermediate 41 (2.12 g, 10.4 mmol) in acetone (20 mL0 was added dropwise, and the resulting r.m. was stirred at r.t. overnight. The mixture was conc. *in vacuo*, and the residue was partitioned between water and DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated with CH_3CN, and the resulting precipitate dried in vacuo, yielding 2.8 g of **intermediate 12** (77 %).

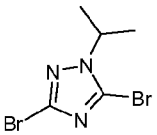
b) Preparation of intermediate 13



To a solution of intermediate 12 (2.88 g, 7.5 mmol) in acetone (200 ml) was added K_2CO_3 (1.04 g, 7.5 mmol), and the r.m. was stirred at r.t. for 30 min. Subsequently, methyliodide (1.06 g, 7.5 mmol) was added, and the resulting r.m. was stirred at r.t. for 30 min. The mixture was poured into ice-water, and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, yielding 2.8 g of crude **intermediate 13** (94 %), which was used as such in the next step.

Example A8

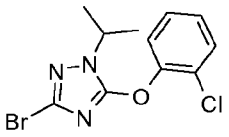
a) Preparation of intermediate 24



NaH (60 % dispersion in mineral oil; 5.29 g, 132 mmol) was added to a stirred solution of 3,5-dibromotriazole (20.0 g, 88.2 mmol) in DMF under an atmosphere of N_2 at r.t..

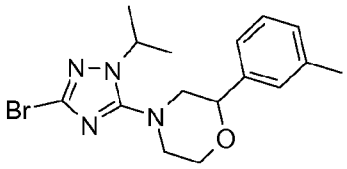
After 30 min, 2-iodopropane (10.6 ml, 106 mmol) was slowly added and the r.m. was heated at 40 °C for 2-3 h. The content was carefully poured onto ice/H_2O (1 l), and the mixture was extracted with DIPE. The combined organic extracts were washed with H_2O (4 x 200 ml), then with brine and dried (Na_2SO_4). Filtration and concentration under reduced pressure yielded a yellow oil. Yield: 16.50 g of **intermediate 24** (70 %).

b) Preparation of intermediate 25



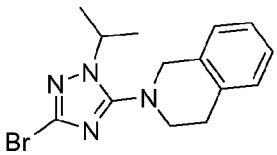
A mixture of 2-chlorophenol (0.72 g, 5.6 mmol), intermediate 24 (1.5 g, 5.6 mmol), and K_2CO_3 (1.54 g, 11 mmol) in DMF (20 ml) was heated at 160 °C for 45 min. using microwave irradiation. The r.m. was cooled and then poured onto H_2O and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated in a solution of DIPE/n-heptane. The resulting solid was filtered and dried *in vacuo* at 50 °C, yielding 1 g of **intermediate 25** (56 %).

c) Preparation of intermediate 26



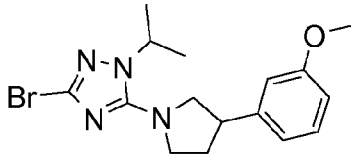
A mixture of intermediate 24 (2.2 g, 7.4 mmol), 2-m-tolyl-morpholine (2.0 g, 7.4 mmol), and K_2CO_3 (4.1 g, 30 mmol) in DMF (20 ml) was heated at 160 °C for 45 min. in a microwave. The r.m. was cooled and then poured onto H_2O and extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (eluent: n-heptane/EtOAc from 100/0 to 50/50). The product fractions were collected and concentrated *in vacuo*, yielding 0.25 g of **intermediate 26** (9 %).

d) Preparation of intermediate 27



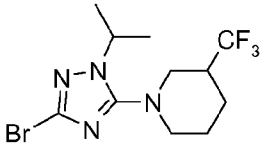
Intermediate 27 was prepared starting from intermediate 24 and 1,2,3,4-tetrahydroisoquinoline according to the preparation described in Example A8.c.

e) Preparation of intermediate 28



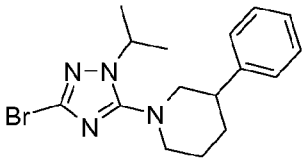
Intermediate 28 was prepared starting from intermediate 24 and 3-(3-methoxyphenyl)pyrrolidine according to the preparation described in Example A8.c.

f) Preparation of intermediate 29



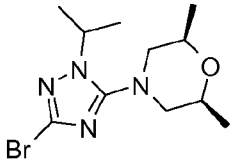
Intermediate 29 was prepared starting from intermediate 24 and DL-3-(trifluoromethyl)piperidine according to the preparation described in Example A8.c.

g) Preparation of intermediate 30



Intermediate 30 was prepared starting from intermediate 24 and 3-phenylpiperidine according to the preparation described in Example A8.c.

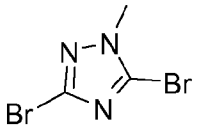
h) Preparation of intermediate 31



Intermediate 31 was prepared starting from intermediate 24 and cis-2,6-dimethylmorpholine according to the preparation described in Example A8.c.

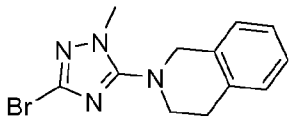
Example A9

a) Preparation of intermediate 32



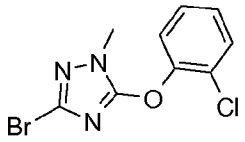
Intermediate 32 was prepared starting from 3,5-dibromotriazole and methyl iodide according to the preparation described in Example A8.a.

b) Preparation of intermediate 33



A mixture of 1,2,3,4-tetrahydroisoquinoline (1.1 g, 8.3 mmol), intermediate 32 (0.2 g, 8.3 mmol), K_2CO_3 (2.3 g, 16.6 mmol) in DMF (20 ml) was heated at 160 °C for 45 min using microwave irradiation. The r.m. was cooled and then poured onto H_2O and extracted with DCM. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. 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*, yielding 900 mg of **intermediate 33** (40 %).

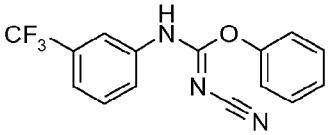
c) Preparation of intermediate 34



Intermediate 34 was prepared starting from intermediate 32 and 2-chlorophenol according to the synthesis protocol described in Example A8b.

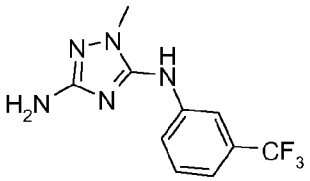
Example A10

a) Preparation of intermediate 35



A mixture of 3-aminobenzotrifluoride (15 g, 93 mmol) and diphenyl cyanocarbonimidate (22.2 g, 93 mmol) was heated at reflux in THF (100 ml) for 20 h. The r.m. was then concentrated under reduced pressure. H_2O was then added and the resulting solid was filtered and dried *in vacuo*, yielding 20.7 g of **intermediate 35** (72 %).

b) Preparation of intermediate 36

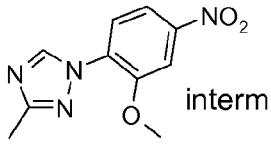


Methylhydrazine (2.1 ml, 39 mmol) was added to a mixture of intermediate 35 (10 g, 33 mmol) in 2-propanol (250 ml). The r.m. was heated at reflux for 20 h. The r.m. was then concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (eluent: DCM/MeOH(NH_3) from 100/0 to 97/3). The

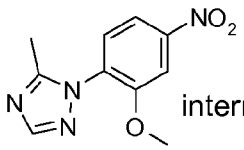
product fractions were collected and concentrated *in vacuo*, yielding 6.70 g of **intermediate 36** (75 %).

Example A11

a) Preparation of intermediate 37 and intermediate 38



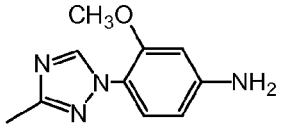
intermediate 37



intermediate 38

A mixture of 1-fluoro-2-methoxy-4-nitrobenzene (821 mg, 4.80 mmol), 5-methyl-1*H*-1,2,4-triazole (800 mg, 9.63 mmol), K_2CO_3 (4.80 mmol) and DMSO (8 ml) was stirred at 120 °C for 1 h. After cooling, the r.m. was poured into ice water. The solid was filtered off, washed with water and dried *in vacuo* at 50 °C. Yield: 0.55 g of **intermediate 37** (49 %). The aq. layer was saturated with NaCl, extracted with DCM and the organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: DCM). The desired fraction was collected and the solvent was evaporated. Yield: 0.15 g of **intermediate 38** (13 %).

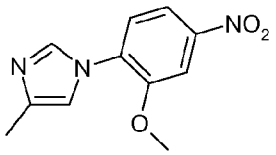
b) Preparation of intermediate 39



MeOH (50 ml) was added to Pd/C 10 % (150 mg) under N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (1 ml) and intermediate 37 (550 mg, 2.35 mmol) were added. The r.m. was stirred at 25°C under 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: 0.35 g of **intermediate 39** (73 %).

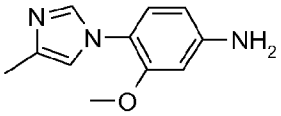
Example A12

a) Preparation of intermediate 40



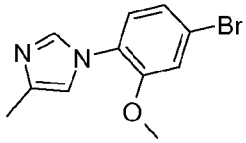
2-Fluoro-5-nitroanisole (50 g, 0.29 mol) was added to a solution of 4-methyl-1*H*-imidazole (36.0 g, 0.44 mol) and K_2CO_3 (40.38 g, 0.29 mol) in DMSO (150 ml) in a stainless steel autoclave under a N_2 atmosphere. The vessel was closed and the r.m. was heated at 125 °C for 16 h. Subsequently, the mixture was cooled and the solvent was evaporated under reduced pressure. H_2O (q.s.) was added to the residue and the precipitated product was collected by filtration. This solid was then triturated with DIPE and collected by filtration to yield a light-brown solid. Yield: 53.8 g of **intermediate 40** (79 %).

b) Preparation of intermediate 41



Intermediate 40 (215 g, 0.92 mol) was added to a stirring mixture of 10 % Pd/C (10 g) in a 4 % thiophene solution in MeOH (700 ml). The r.m. was heated at 50 °C under a H_2 atmosphere. After 3 eq. of H_2 were absorbed, the catalyst was removed by filtration over diatomaceous earth. The filtrate was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: MeOH/DCM 10/90). The product fractions were combined and evaporated to yield a light-brown solid. Yield: 180 g of **intermediate 41** (96 %).

c) Preparation of intermediate 42



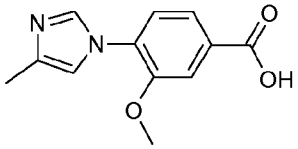
A stirred solution of $NaNO_2$ (7.47 g, 108 mmol) in conc. H_2SO_4 (160 ml) was cooled to 10 °C. A solution of intermediate 41 (20.0 g, 98.4 mmol) in HOAc (200 ml) was added at such a rate that the temperature of the r.m. was maintained below 10 °C. After addition was complete, the mixture was stirred at r.t. for 30 min. This solution was added dropwise, to a stirring solution of CuBr (28.2 g, 197 mmol) in 48 % HBr (200 ml) at r.t. This mixture was stirred for 1 h and was then diluted with ice water (1 l). The resulting white precipitate was collected by filtration and washed with H_2O, yielding a solid (a) and the mother liquor (b).

The solid (a) was suspended in a mixture of DCM and a sat. aq. Na_2CO_3 solution. The resulting slurry was filtered over diatomaceous earth. The organic layer of the filtrate was washed with a diluted NH_4OH solution until the disappearance of blue colour. The organic phase was dried ($MgSO_4$), filtered and evaporated to yield a brown solid.

The mother liquor (b) was basified with solid Na_2CO_3 and was then extracted with DCM. The combined organic extracts were washed with a diluted NH_4OH solution until the disappearance of blue colour. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a brown solid.

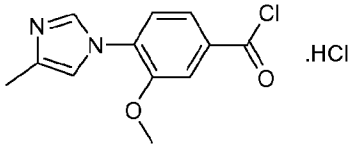
The 2 brown solids were combined, yielding 24.0 g of **intermediate 42** (91 %).

d) Preparation of intermediate 65



To a solution of intermediate 42 (24.0 g, 89.8 mmol), in THF/H_2O (300 ml/3 ml) in a stainless steel autoclave was added $Pd(OAc)_2$ (403 mg, 1.80 mmol) and 1,3-bis(diphenylphosphino)propane (1.48 g, 3.59 mmol) under a N_2 atmosphere. The vessel was closed and pressurized to 20 bar CO (gas), and heated at 150 °C for 24 h. The cooled reaction mixture was evaporated under reduced pressure, and was then acidified with a 30 % aq. HOAc solution. Et_2O was added and the resulting mixture was evaporated until crystallization occurred. The light-brown crystals were collected by filtration. Yield: 18.1 g of **intermediate 65** (87 %).

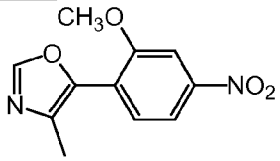
e) Preparation of intermediate 43



A mixture of intermediate 65 (3.24 g, 13.95 mmol), oxalyl chloride (1.68 g, 13 mmol) and DMF (5 ml) in DCM (300 ml) was stirred and heated at reflux for 1 h. The r.m. was then concentrated, and co-evaporated with toluene. The residue was used as such in the next reaction step. Yield: 3.5 g (quantitative) of **intermediate 43**.

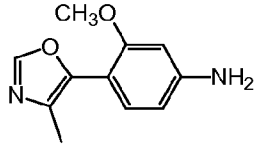
Example A13

a) Preparation of intermediate 44



K_2CO_3 (9.6 g, 69.5 mmol) and 1-methyl-1-tosylmethylisocyanide (8 g, 38.2 mmol) were added to a solution of 2-formyl-5-nitroanisole (6.29 g, 34.7 mmol) in MeOH (150 ml) and the r.m. was refluxed for 4 h. The r.m. was concentrated under reduced pressure, the residue was dissolved in DCM and the organic phase was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel (eluent: n-heptane/EtOAc from 100/0 to 50/50). The product fractions were collected and the solvent was evaporated. Yield: 6.24 g of **intermediate 44** (77 %).

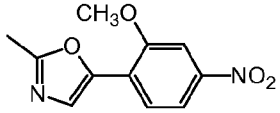
b) Preparation of intermediate 45



MeOH (150 ml) was added to Pd/C 10 % (1 g) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (1 ml) and intermediate 44 (6.24 g, 26.6 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. Yield: 5.4 g of **intermediate 45** (99 %).

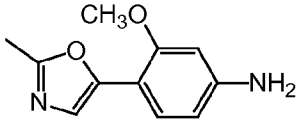
Example A14

a) Preparation of intermediate 46



Iodobenzene diacetate (5.49 g, 18.44 mmoll) and trifluoromethanesulfonic acid (6.08 ml, 69.17 mmol) were stirred in CH_3CN (100 ml) at r.t. for 1 h under N_2. 2'-methoxy-4'-nitro-acetophenone (3.0 g, 15.37 mmol) was added all at once at r.t. to the solution, and the r.m. was then refluxed for 2 h, then cooled to r.t. and carefully added to a stirred saturated aqueous solution of Na_2CO_3 (500 ml). The product was extracted with DCM and the organic phase was dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The resulting dark brown oil was purified by flash column chromatography over silica gel (eluent: DCM/MeOH 95/5). The product fractions were collected and the solvent was evaporated under reduced pressure. Yield: 3.0 g of **intermediate 46** (75 %).

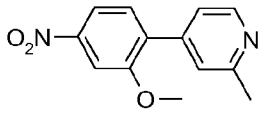
b) Preparation of intermediate 47



MeOH (50 ml) was added to Pd/C 10 % (0.250 g) under a N_2 atmosphere. Subsequently, a 0.4 % thiophene solution in DIPE (2 ml) and intermediate 46 (0.946 g, 4.04 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 product was triturated in DIPE, filtered off and dried under vacuum. Yield: 0.66 g of **intermediate 47** (80 %).

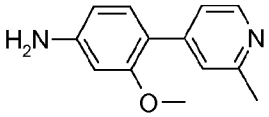
Example A15

a) Preparation of intermediate 48



2-Methylpyridine-4-boronic acid pinacol ester (3.18 g, 14.5 mmol) and $Pd(PPh_3)_4$ (1.22 g, 1.06 mmol) were added to a solution of 2-bromo-5-nitroanisole (3.06 g, 13.2 mmol) and Cs_2CO_3 (1.33 g, 40.9 mmol) in DME (40 ml) and H_2O (16 ml). The r.m. was stirred and heated at reflux for 16 h. The r.m. was cooled to r.t. and partitioned between H_2O and DCM. The organic phase was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. 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 98/2). The product fractions were collected and concentrated *in vacuo*, yielding 2.04 g of **intermediate 48** (63 %).

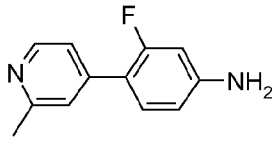
b) Preparation of intermediate 49



Intermediate 48 (2.04g, 9.50 mmol) was added to a stirring mixture of 10 % Pd/C (500 mg) and a 4 % thiophene solution in MeOH (1 ml). The r.m. was heated at 50 °C under a H_2 atmosphere. After 3 eq. of H_2 were absorbed, the catalyst was removed by filtration over diatomaceous earth. The filtrate was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: MeOH/DCM 10/90). The product fractions were combined and evaporated to yield a light-brown solid. Yield: 1.70 g of **intermediate 49** (95 %).

Example A16

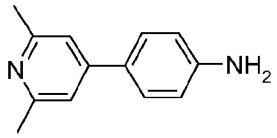
a) Preparation of intermediate 50



2-Methylpyridine-4-boronic acid pinacol ester (5.54 g, 25 mmol) and $Pd(PPh_3)_4$ (1.95 g, 1.68 mmol) were added to a solution of 4-bromo-3-fluoroaniline (4.0 g, 21 mmol) and Cs_2CO_3 (21.3 g, 65.3 mmol) in DME (40 ml) and H_2O (25 ml). The resulting mixture was stirred and heated at 95 °C for 16 hours. The r.m. was cooled to r.t. and partitioned between water and 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 98/2). The product fractions were collected and concentrated *in vacuo*, yielding 4.1 g of **intermediate 50** (96 %).

Example A17

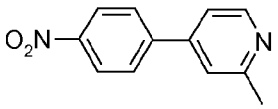
b) Preparation of intermediate 51



2,6-Dimethylpyridine-4-boronic acid pinacol ester (5.96 g, 26 mmol) and $Pd(PPh_3)_4$ (2150 mg, 1.86 mmol) were added to a solution of 4-bromoaniline (4 g, 23 mmol) and Cs_2CO_3 (21.3 g, 65.3 mmol) in DME (40 ml) and H_2O (25 ml). The resulting mixture was stirred and heated at 95 °C for 16 h. The r.m. was cooled to r.t. and partitioned between H_2O and 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 98/2). The product fractions were collected and concentrated *in vacuo*, yielding 2.50 g of **intermediate 51** (54 %).

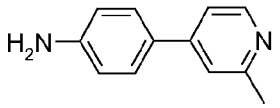
Example A18

a) Preparation of intermediate 52



2-Methylpyridine-4-boronic acid pinacol ester (5 g, 22.8 mmol) and $Pd(PPh_3)_4$ (1.92 g, 1.66 mmol) were added to a solution of 1-iodo-4-nitrobenzene (5.17 g, 20.7 mmol) and Cs_2CO_3 (21 g, 64.3 mmol) in DME (40 ml) and water (25 ml). The resulting mixture was stirred and heated at reflux for 16 h. The r.m. was cooled to r.t. and partitioned between water and DCM. The organic phase was separated, dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. 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 98/2). The product fractions were collected and concentrated *in vacuo*, yielding 3.1 g of **intermediate 52** (70 %).

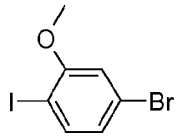
b) Preparation of intermediate 53



Intermediate 52 (2.0 g, 9.34 mmol) was added to a stirred mixture of 10 % Pd/C (1 g) and a 4 % thiophene solution in MeOH (2 ml). The r.m. was heated at 25 °C under a H_2 atmosphere. After 3 eq. of H_2 were absorbed, the catalyst was removed by filtration over diatomaceous earth. The filtrate was evaporated under reduced pressure and the crude product was used as such in the next step. Yield: 1.5 g of **intermediate 53** (87 %).

Example A19

a) Preparation of intermediate 54



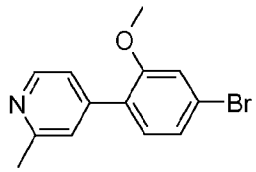
A stirred solution of $NaNO_2$ (5.63 g, 81.7 mmol) in conc. HCl (6.2 ml) was cooled to 10 °C. 4-bromo-2-methoxy-phenylamine (15 g, 74 mmol) in HOAc (100 ml) was added at such a rate that the temperature of the r.m. was maintained below 10 °C. After addition was completed, the mixture was stirred at r.t. for 30 min. This solution was added dropwise, to a stirring solution of KI (37 g, 223 mmol) in 48 % HBr (200 ml) at r.t. This mixture was stirred for 1 h and was then diluted with ice water (1000 ml). The resulting white precipitate was collected by filtration and washed with H_2O, yielding a solid (a) and the mother liquor (b).

The solid (a) was suspended in a mixture of DCM and a sat. aq. Na_2CO_3 solution. The resulting slurry was filtered over diatomaceous earth. The organic layer of the filtrate was washed with a diluted NH_4OH solution until the disappearance of blue colour. The organic phase was dried ($MgSO_4$), filtered and evaporated to yield a brown solid.

The mother liquor (b) was basified by the addition of solid Na_2CO_3 and was then extracted with DCM. The combined organic extracts were washed with a diluted NH_4OH solution until the disappearance of blue colour. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a brown solid.

The 2 brown solids were combined, yielding 24.0 g of **intermediate 54** (91 %).

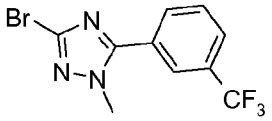
b) Preparation of intermediate 55



2-Methylpyridine-4-boronic acid pinacol ester (5.49 g, 25.1 mmol) and $Pd(PPh_3)_4$ (3.62 g, 3.1 mmol) was added to a solution of intermediate 54 (9.8 g, 31.3 mmol) in dioxane (200 ml), H_2O (50 ml) and K_2CO_3 (13 g, 94 mmol). The resulting mixture was stirred and heated at 100 °C for 18 h. The r.m. was cooled to r.t. and partitioned between H_2O and 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 98/4). The product fractions were collected and concentrated *in vacuo*, yielding 4.5 g of **intermediate 55** (52 %).

Example A22

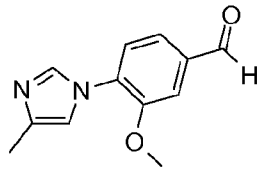
Preparation of intermediate 66



Intermediate 66 was prepared starting from intermediate 32 and 3-(trifluoromethyl)phenylboronic acid according to the synthesis protocol described in Example A1.a.

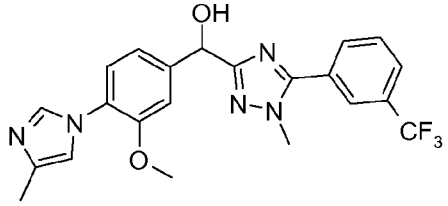
Example A23

a) Preparation of intermediate 67



Intermediate 67 was prepared starting from 4-fluoro-3-methoxybenzaldehyde and 4-methylimidazole according to the synthesis protocol described in Example A12.a.

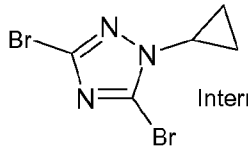
b) Preparation of intermediate 68



To a solution of intermediate 66 (500 mg, 1.63 mmol) in THF (1 ml) at -75 °C was added n-butyl lithium (0.65 ml, 1.63 mmol, 2.5 M in hexanes). The r.m. was stirred for 1 min. at -75 °C after which a solution of intermediate 67 (283 mg, 1.31 mmol) in THF (1 ml) was added. The r.m.was then stirred at -75 °C for 60 min. and quenched by the addition of a sat. aq. solution of NH_4Cl (5 ml). The reaction was allowed to warm to r. t. and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (eluent: DCM/MeOH(NH_3) from 100/0 to 99/1). The product fractions were collected and concentrated *in vacuo*, yielding 150 mg of **intermediate 68** (21 %).

Example A24

Preparation of intermediate 69 and 70



Intermediate 69



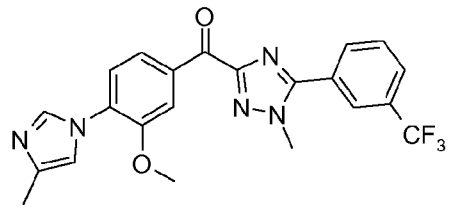
Intermediate 70

2,2'-Bipyridine (3.12, 20 mmol), copper acetate (3.63 g, 20 mmol) and sodium carbonate (4.24 g, 40 mmol) was added to a solution of 3,5-dibromo-1*H*-1,2,4-triazole (4.54 g, 20 mmol) and cyclopropyl boronic acid (3.44 g, 40 mol) in DCE (150 ml). The r.m. was heated at 70 °C for 16 h and was then cooled to r.t. and washed with a sat. aq. solution of ammonium chloride. The combined organic extracts were washed with brine and dried ($MgSO_4$). Filtration and concentration under reduced pressure gave a residue which was purified by flash column chromatography over silica gel (eluent: Heptane/EtOAc from 100/0 to 50/50). The product fractions were collected and concentrated *in vacuo*, yielding 1 g of a 70/30 mixture of **intermediate 69** and **intermediate 70** (21 %) which was used as such in the next reaction step.

B. Preparation of the compounds

Example B1

Preparation of compound 64

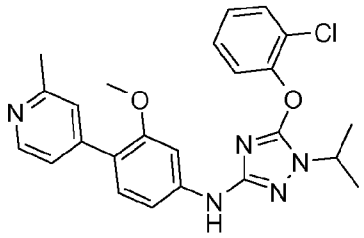


To a solution of intermediate 68 (120 mg, 0.27 mmol) in DCM (5 mL) at r. t. was added Dess-Martin periodinane (172 mg, 0.41 mmol). The r.m. was then stirred for 1 h. The r.m. was then concentrated under reduced pressure. The residue was then purified by flash column chromatography over silica gel (eluent: DCM/MeOH(NH_3) from 100/0 to

99/1). The product fractions were collected and concentrated *in vacuo*, yielding 21 mg of **compound 64** (18 %).

Example B2

Preparation of compound 69

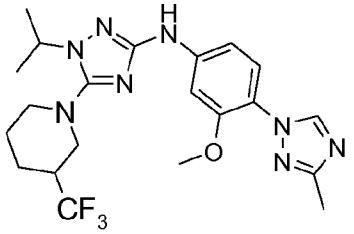


.HCl .2.7 H_2O

Intermediate 49 (237 mg, 1.1 mmol), $Pd_2(dba)_3$ (145 mg, 0.16 mmol), X-Phos (151 mg, 0.32 mmol) and Cs_2CO_3 (1.54 g, 4.7 mmol) were added to a solution of intermediate 25 (500 mg, 1.58 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., water 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 dissolved in DIPE and a 6 N HCl sol. in 2-propanol was added dropwise to the stirring solution.The HCl salt was then collected by filtration and the product was dried *in vacuo* to yield 172 mg of **compound 69** (.HCl .2.7 H_2O; 21 %).

Example B3

Preparation of compound 59, 108, 109



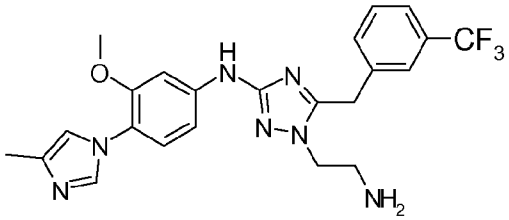
Co. No. 59: rac
Co. No. 108: enantiomer A
Co. No. 109: enantiomer B

Intermediate 39 (2.7 g, 13.2 mmol), $Pd_2(dba)_3$ (1.2 g, 1.3 mmol), X-Phos (1.3 g, 2.6 mmol) and Cs_2CO_3 (12.9 g, 40 mmol) were added to a solution of intermediate 29 (4.5 g, 13.2 mmol) in 2-methyl-2-propanol (100 ml) under a N_2 atmosphere. The r.m. was heated at 110 °C for 20 h. Then, the r.m. was cooled to r.t., water 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), yielding 4.4 g of **compound 59** (72 %; rac). Compound 58 was separated into its enantiomers by

preparative SFC (Chiralpak Diacel OJ 20 x 250 mm; mobile phase (CO_2, MeOH with 0.2% 2-propylamine). Both enantiomers were crystallized from DIPE. The precipitate was filtered off and dried *in vacuo* at 60 °C. Yield: 1.38 g of **Compound 108** (23 %; 1st fraction from the column; enantiomer A) and 1.25 g of **Compound 109** (20 %; 2nd fraction from the column; enantiomer B).

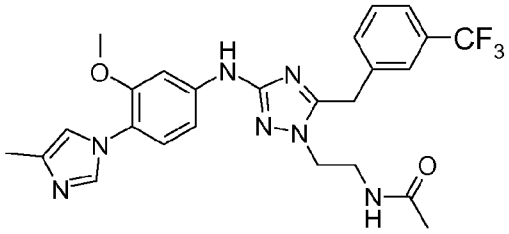
Example B4

a) Preparation of compound 48



MeOH (150 ml) was added to Pd/C 10 % (200 mg) under N_2 atmosphere. A mixture of intermediate 4 (0.9 g, 1.93 mmol) in HCl/iPrOH (6 N; 0.97 ml) was added. The r.m. was stirred at 25 °C under H_2 atmosphere until 2 eq. of H_2 were absorbed. The catalyst was filtered off over diatomaceous earth and the filtrate was evaporated. The residue was partitioned between DCM and water. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was suspended in DIPE, filtered and dried, yielding 0.6 g of **compound 48** (62 %).

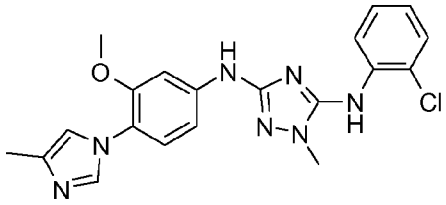
b) Preparation of compound 1



Triethylamine (0.028 ml, 0.2 mmol) was added to a solution of compound 48 (80 mg, 0.17 mmol) in DCM (1 ml). A solution of acetylchloride (0.012 mL, 0.17 mmol) in DCM (1 ml) was added dropwsie ar r.t., and the r.m. was stirred at r.t. for 1 h. Subsequently, water (1 ml) was added, and the mixture was filtered over an isolute HM-N filter (diatomaceous earth) and the filtrate was concentrated. The residue was suspended in DIPE and CH_3CN, filtered and dried, yielding 0.037 g of **compound 1** (42 %).

Example B5

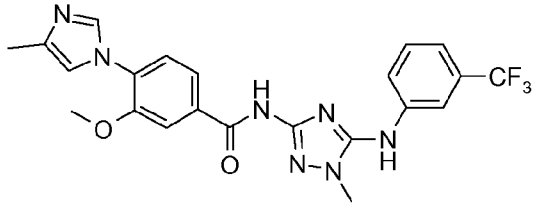
Preparation of compound 49



Intermediate 42 (594 mg, 2.22 mmol), $Pd_2(dba)_3$ (203 mg, 0.222 mmol), X-Phos (233 mg, 0.489 mmol) and Cs_2CO_3 (2.17 g, 6.67 mmol) were added to a solution of intermediate 6 (700 mg, 2.22 mmol) in 2-methyl-2-propanol (20 ml) under a N_2 atmosphere. The r.m. was heated at 110 °C over weekend. Then, the r.m. was cooled to r.t., water and DCM were added and the mixture was was filtered over diatomaceous earth. The layers were separated and the aq. layer 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(NH_3) from 100/0 to 98/2). The product fractions were collected and concentrated *in vacuo* to give 15 mg of pure **compound 49** and impure fractions which were purified further via 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)/MeOH]. The product fractions were collected and worked up. Yield: 111 mg of **compound 49** (combined yield 14 %).

Example B6

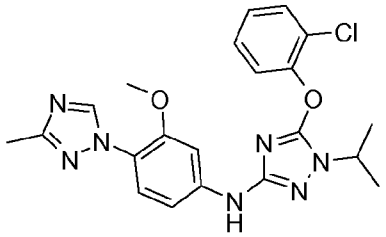
Preparation of compound 50



To a mixture of intermediate 65 (75 mg, 0.32 mmol) and DIPEA (64 mg, 0.48 mmol) in DMF (2 ml) was added HBTU (160 mg, 0.42 mmol). The r.m. was stirred at r.t. for 10 min. Then, intermediate 36 (100 mg, 0.39 mmol) was added and the r.m. was stirred at r.t. overnight. The r.m. was concentrated *in vacuo*, and the residue was purified by flash column chromatography over silica gel (eluent: DCM/MeOH(NH_3) from 100/0 to 95/5). The product containing fractions were collected and concentrated *in vacuo*. The residue was purified further via 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)/MeOH]. The product fractions were collected and worked up. Yield: 11 mg of **compound 50** (combined yield 7 %).

Example B7

Preparation of compound 3

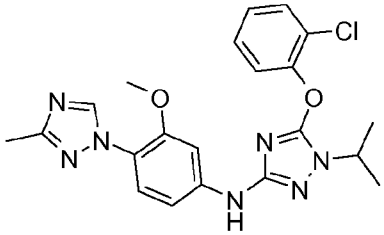


0.4.HCl, 1.5 H_2O

Intermediate 39 (260 mg, 1.27 mmol), $Pd_2(dba)_3$ (166 mg, 0.18 mmol), X-Phos (173 mg, 0.36 mmol) and Cs_2CO_3 (1.78 g, 5.5 mmol) were added to a solution of intermediate 25 (576 mg, 1.82 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., water 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 dissolved in CH_3CN and a 6 N HCl sol. in 2-propanol was added dropwise to the stirring solution.The precipitate was then collected by filtration and the product was dried *in vacuo* to yield 225 mg of **compound 3** (0.4.HCl .1.5 H_2O; 26 %).

Example B8

Preparation of compound 4

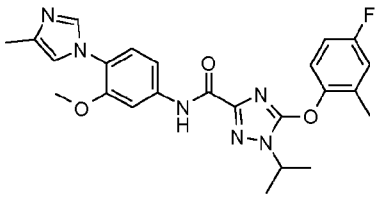


Intermediate 39 (1.8 g, 8.81 mmol), $Pd_2(dba)_3$ (1.15 g, 1.26 mmol), X-Phos (1.2 g, 2.52 mmol) and Cs_2CO_3 (12.3 g, 37.8 mmol) were added to a solution of intermediate 25 (3.99 g, 12.6 mmol) in 2-methyl-2-propanol (200 ml) under a N_2 atmosphere. The r.m. was heated at 80 °C for 16 h. Then, the r.m. was cooled to r.t., water 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 containing fractions were collected and concentrated *in vacuo*. The residue was purified further by flash column chromatography over silica gel (eluent: n-heptane/EtOAc from 100/0 to 50/50). The product containing fractions were collected and concentrated *in*

vacuo. The residue was purified further via 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)/MeOH]. The product fractions were collected and worked up. The residue was crystallized form DIPE. Yield: 1.31 g of **compound 4** (yield 24 %).

Example B9

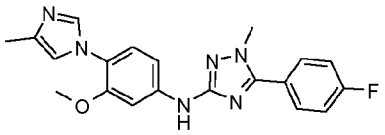
Preparation of compound 9



To a mixture of intermediate 11 (540 mg, 1.93 mmol), intermediate 41 (327 mg, 1.61 mmol) and DIPEA (1.39 ml, 8.06 mmol) in DMF (25 ml) was added HBTU (921 mg, 2.42 mmol). The r.m. was stirred at r.t. for 30 min. The mixture was partitioned between water and 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 containing fractions were collected and concentrated *in vacuo*. The residue was purified further via 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 residue was crystallized from DIPE. Yield: 229 mg of **compound 9** (yield 31 %).

Example B10

Preparation of compound 10



A mixture of intermediate 13 (1.75 mg, 4.39 mmol) and methylhydrazine (826 mg, 17.6 mmol) in n-butanol (q.s.) was heated at reflux for 16 h. The r.m. was conc. *in vacuo*, and the residue was partitioned between water and DCM. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was triturated with CH_3CN and the precipitate dried *in vacuo*. Yield: 740 mg of **compound 10** (yield 45 %).

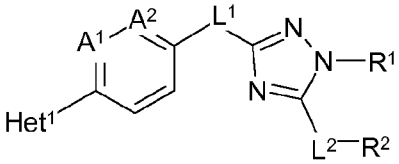
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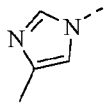
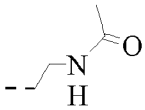
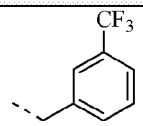
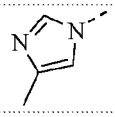
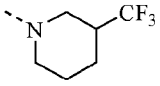
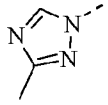
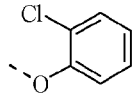
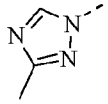
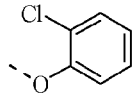
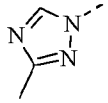
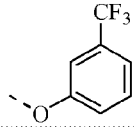
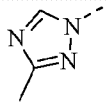
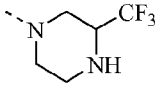
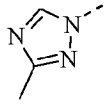
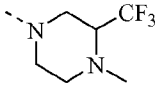
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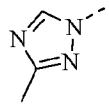
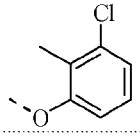
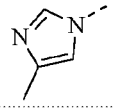
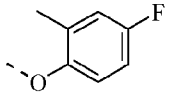
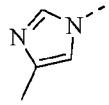
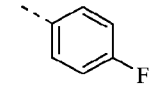
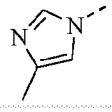
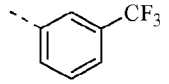
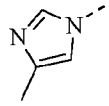
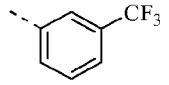
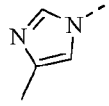
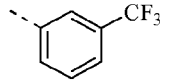
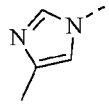
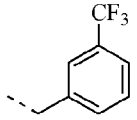
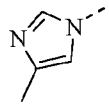
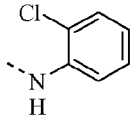
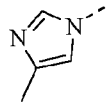
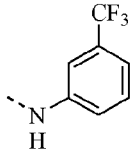
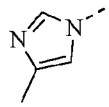
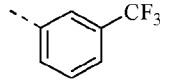
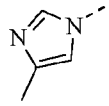
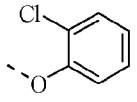
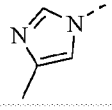
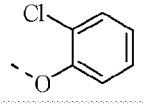
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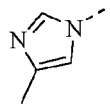
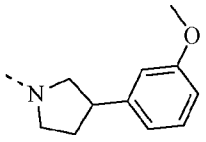
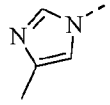
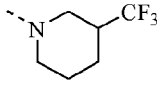
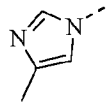
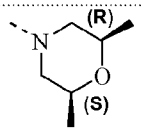
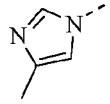
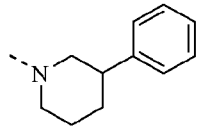
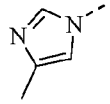
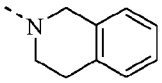
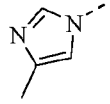
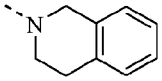
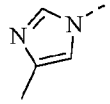
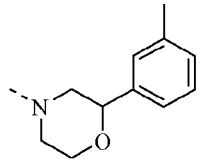
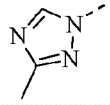
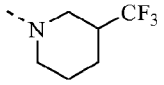
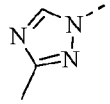
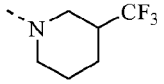
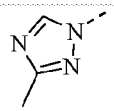
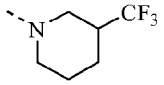
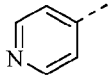
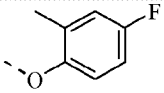
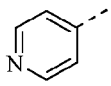
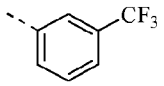
In case no salt form is indicated, the compound was obtained as a free base. Salt forms of the free bases such as, for example, HCl salt forms, can easily be obtained by using typical procedures known to those skilled in the art. In a typical procedure for the conversion to a HCl salt form, for example, the free base was dissolved in a solvent such as, for example, DIPE or Et_2O, and subsequently a HCl solution in a solvent such as 2-propanol or Et_2O was added dropwise. Stirring for a certain period of time, typically about 10 min, could enhance the rate of the reactions.

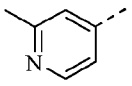
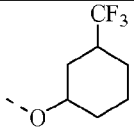
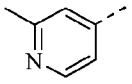
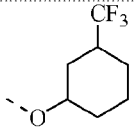
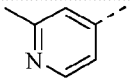
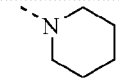
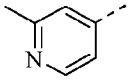
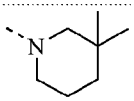
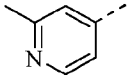
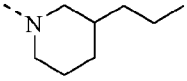
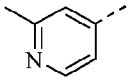
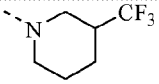
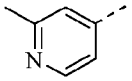
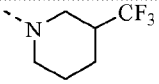
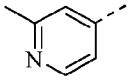
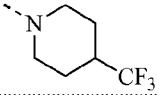
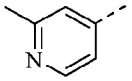
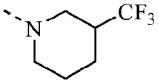
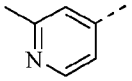
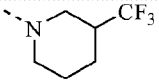
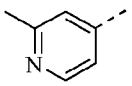
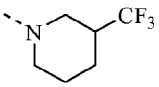
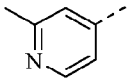
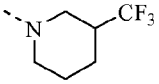
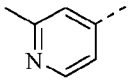
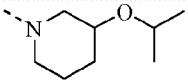
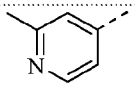
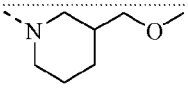
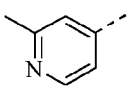
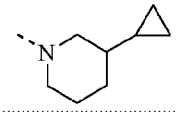
Table 1

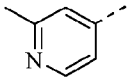
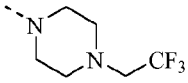
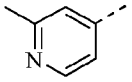
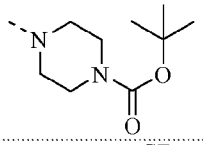
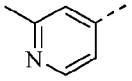
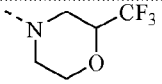
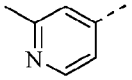
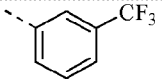
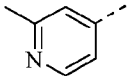
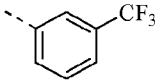
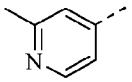
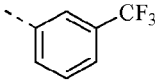
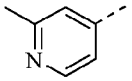
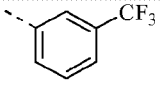
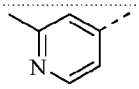
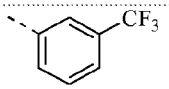
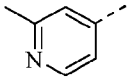
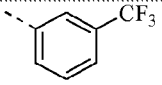
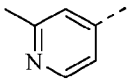
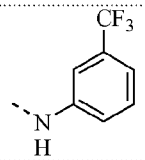
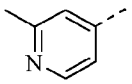
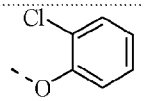
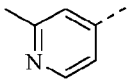
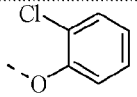
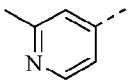
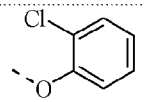
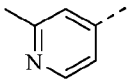
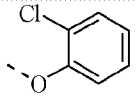
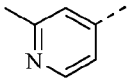
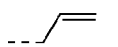
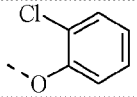


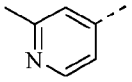
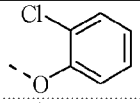
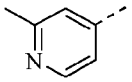
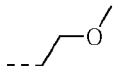
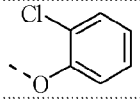
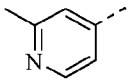
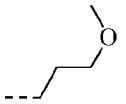
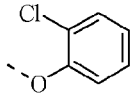
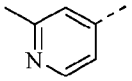
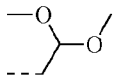
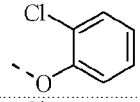
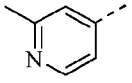
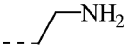
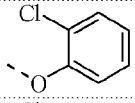
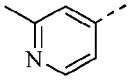
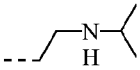
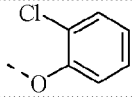
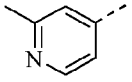
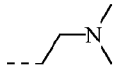
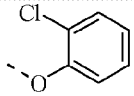
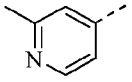
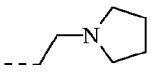
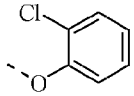
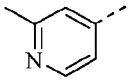
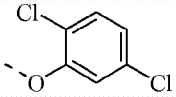
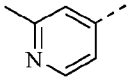
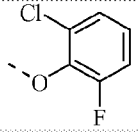
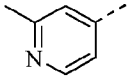
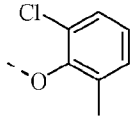
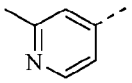
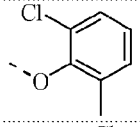
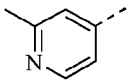
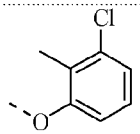
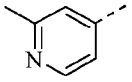
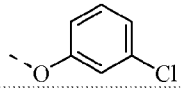
Co. No.	Pr.	Het[1]	A^1	A^2	L^1	R^1	L^2R^2	Salt Forms/ Stereo-chemistry
1	B4b		$COCH_3$	CH	NH			
2	B8		$COCH_3$	CH	NH	CH_3		
3	B7		$COCH_3$	CH	NH	$CH(CH_3)_2$		0.4 HCl 1.5 H_2O
4	B8		$COCH_3$	CH	NH	$CH(CH_3)_2$		
5	B8		$COCH_3$	CH	NH	$CH(CH_3)_2$		
6	B7		$COCH_3$	CH	NH	$CH(CH_3)_2$		2.3 HCl 3.3 H_2O
7	B7		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .H_2O

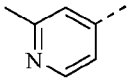
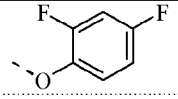
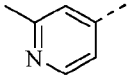
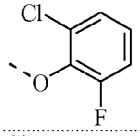
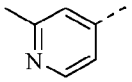
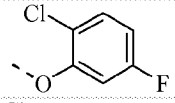
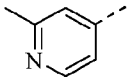
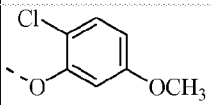
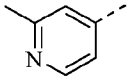
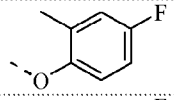
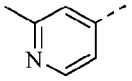
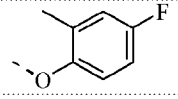
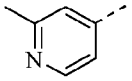
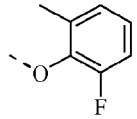
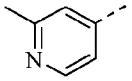
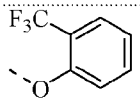
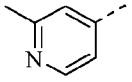
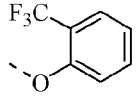
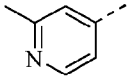
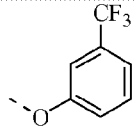
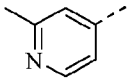
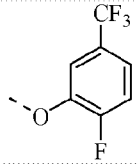
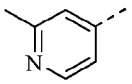
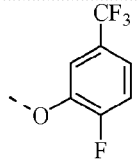
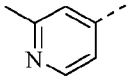
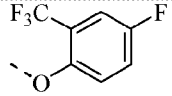
Co. No.	Pr.	Het[1]	A[1]	A[2]	L[1]	R[1]	L[2]R[2]	Salt Forms/ Stereo-chemistry
8	B8		$COCH_3$	CH	NH	$CH(CH_3)_2$		
9	B9		$COCH_3$	CH	NH(C=O)	$CH(CH_3)_2$		
10	B10		$COCH_3$	CH	NH	CH_3		
17	B2		$COCH_3$	N	NH	$CH(CH_3)_2$		
46	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
47	B2		$COCH_3$	CH	NH	CH_3		
48	B4.a		$COCH_3$	CH	NH	$CH_2CH_2NH_2$		
49	B5		$COCH_3$	CH	NH	CH_3		
50	B6		$COCH_3$	CH	(C=O)NH	CH_3		
64	B1		$COCH_3$	CH	(C=O)	CH_3		
51	B2		$COCH_3$	CH	NH	CH_3		
52	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		

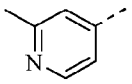
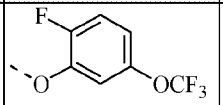
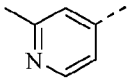
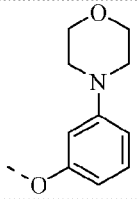
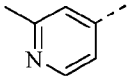
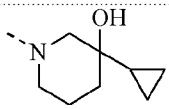
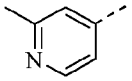
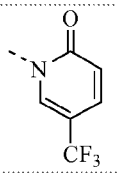
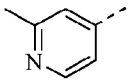
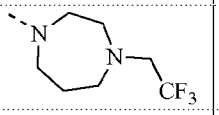
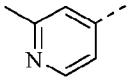
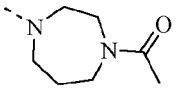
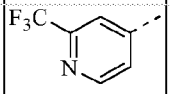
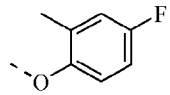
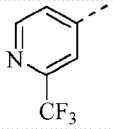
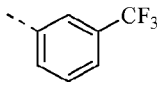
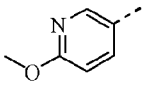
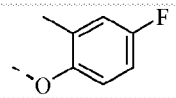
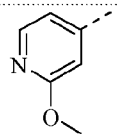
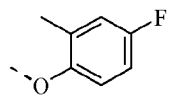
Co. No.	Pr.	Het[1]	A^1	A^2	L^1	R^1	L^2R^2	Salt Forms/ Stereo-chemistry
53	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
54	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
55	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
18	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
56	B2		$COCH_3$	CH	NH	CH_3		
57	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
58	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
59	B3		$COCH_3$	CH	NH	$CH(CH_3)_2$		
108	B3		$COCH_3$	CH	NH	$CH(CH_3)_2$		Enantio-mer A
109	B3		$COCH_3$	CH	NH	$CH(CH_3)_2$		Enantio-mer B
112	B2		CH	CH	NH	$CH(CH_3)_2$		
113	B2		CH	CH	NH	CH_3		

Co. No.	Pr.	Het[1]	A^1	A^2	L^1	R^1	L^2R^2	Salt Forms/ Stereo-chemistry
117	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$	 CIS (rac)	.1.7 HCl .2.4 H_2O
118	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$	 TRANS (rac)	.2.4 HCl .1.6 H_2O
119	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
120	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.2 HCl .2.5 H_2O
121	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.1.8 HCl .2 H_2O
122	B2		CH	CH	NH	$CH(CH_3)_2$		.1.8 HCl .2.2 H_2O
123	B2		CF	CH	NH	$CH(CH_3)_2$		.2.2 HCl .2.3 H_2O
124	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.2 HCl .2 H_2O
125	B2		$COCH_3$	CH	NH	CH_3		.1.6 HCl .2 H_2O
67	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.2.2 HCl .2.7 H_2O
126	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl Enantio-mer A
127	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl Enantio-mer B
128	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
129	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.2 HCl
130	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.1.5 HCl .1.3 H_2O

Co. No.	Pr.	Het[1]	A^1	A^2	L^1	R^1	L^2R^2	Salt Forms/ Stereo-chemistry
131	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.1.6 HCl .2.1 H_2O
132	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
133	B2		CH	CH	NH	$CH(CH_3)_2$		.2 HCl .2 H_2O
60	B2		CH	CH	NH	CH_3		
134	B2		CF	CH	NH	CH_3		
135	B2		$COCH_3$	CH	NH	CH_3		
136	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
137	B2		CH	CH	NH	$CH(CH_3)_2$		
138	B2		CF	CH	NH	$CH(CH_3)_2$		
139	B2		$COCH_3$	CH	NH	CH_3		
61	B2		$COCH_3$	CH	NH	CH_3		
69	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .2.7 H_2O
140	B2		CH	CH	NH	$CH(CH_3)_2$		
141	B2		CF	CH	NH	$CH(CH_3)_2$		.HCl .H_2O
142	B2		$COCH_3$	CH	NH			

Co. No.	Pr.	Het[1]	A^1	A^2	L^1	R^1	L^2R^2	Salt Forms/ Stereo-chemistry
143	B2		$COCH_3$	CH	NH			.1.4 HCl .H_2O
145	B2		$COCH_3$	CH	NH			.2 HCl
146	B2		$COCH_3$	CH	NH			.2 HCl
147	B2		$COCH_3$	CH	NH			
148	B2		$COCH_3$	CH	NH			.2 HCl
149	B2		$COCH_3$	CH	NH			
150	B2		$COCH_3$	CH	NH			.2 HCl
152	B2		$COCH_3$	CH	NH			.2 HCl
153	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
154	B2		CH	CH	NH	$CH(CH_3)_2$		
155	B2		CH	CH	NH	$CH(CH_3)_2$		
156	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .1.5 H_2O
157	B2		CH	CH	NH	$CH(CH_3)_2$		
158	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		

Co. No.	Pr.	Het[1]	A^1	A^2	L^1	R^1	L^2R^2	Salt Forms/ Stereo-chemistry
159	B2		CH	CH	NH	$CH(CH_3)_2$		.HCl .1.5 H_2O
160	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .H_2O
161	B2		CH	CH	NH	$CH(CH_3)_2$		
162	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .H_2O
163	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
164	B2		CH	CH	NH	$CH(CH_3)_2$		
165	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .H_2O
166	B2		$COCH_3$	CH	NH	CH_3		
70	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .H_2O
71	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .1.5H_2O
167	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl
168	B2		$COCH_3$	CH	NH	CH_3		
169	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		

Co. No.	Pr.	Het[1]	A^1	A^2	L^1	R^1	L^2R^2	Salt Forms/ Stereo-chemistry
170	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.1.2 HCl .1.3 H_2O
171	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
173	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.HCl .H_2O
174	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
175	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		.2 HCl .2.6 H_2O
176	B2		$COCH_3$	CH	NH	$CH(CH_3)_2$		
177	B2		CH	CH	NH	$CH(CH_3)_2$		
178	B2		CH	CH	NH	CH_3		
179	B2		CH	CH	NH	$CH(CH_3)_2$		
180	B2		CH	CH	NH	$CH(CH_3)_2$		

Analytical Part

LCMS (Liquid Chromatography/Mass spectrometry)

General procedure A

The LC measurement was performed using an Acquity UPLC (Ultra Performance Liquid Chromatography) (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 (sec) using a dwell time of 0.02 sec. The capillary needle voltage was 3.5 kV and the source temperature was maintained at 140 °C. N_2 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 Alliance HT 2790 (Waters) system comprising a quaternary pump with degasser, an autosampler, a column oven (set at 45 °C, unless otherwise indicated), a 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 sec using a dwell time of 0.1 sec. The capillary needle voltage was 3 kV and the source temperature was maintained at 140 °C. N_2 was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

General procedure C

The HPLC measurement was performed using an Agilent 1100 module comprising a pump, a DAD (wavelength 220 nm), a column heater and a column as specified in the respective methods below. Flow from the column was split to a Agilent MSD Series G1946C and G1956A. MS detector was configured with API-ES (atmospheric pressure electrospray ionization). Mass spectra were acquired by scanning from 100 to 1000. The capillary needle voltage was 2500 V for positive ionization mode and 3000 V for negative ionization mode. Fragmentation voltage was 50 V. Drying gas temperature was maintained at 350 °C at a flow of 10 l/min.

LCMS Method 1

In addition to general procedure A: Reversed phase UPLC 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/minute (min). 2 Mobile phases (25 mM ammonium acetate (NH_4OAc)/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.

LCMS Method 2

In addition to general procedure B: Column heater was set at 40 °C. Reversed phase 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 3

In addition to general procedure C: Reversed phase HPLC was carried out on a YMC-Pack ODS-AQ, 50x2.0 mm 5µm column with a flow rate of 0.8 ml/min. 2 Mobile phases (mobile phase A: water with 0.1 % trifluoroacetic acid (TFA); mobile phase B: CH_3CN with 0.05 % TFA) were used. First, 90 % A and 10 % B was hold for 0.8 min. Then a gradient was applied to 20 % A and 80 % B in 3.7 min and hold for 3 min. Typical injection volumes of 2 µl were used. Oven temperature was 50 °C. (MS polarity: positive)

LCMS Method 4

In addition to general procedure B: Column heater was set at 45 °C. Reversed phase 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 5

In addition to general procedure A: Reversed phase 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 and 20 V for negative ionization mode.

Melting Points

Unless otherwise mentioned, melting points (m.p.) were determined with a DSC823e (Mettler-Toledo). Melting points were measured with a temperature gradient of 30 °C/min. Maximum temperature was 400 °C. Values are peak values.

For Co. No. 112, 177, 179 and 180, melting points (m.p.) were determined with a WRS-2A m.p. apparatus that was purchased from Shanghai Precision and Scientific Instrument Co. Ltd. M.p. were measured with a linear heating up rate of 0.2-5.0 °C/min. The reported values are melt ranges. The maximum temperature was 300 °C.

The results of the analytical measurements are shown in table 2a.

Table 2a: 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)

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
1	0.89	514	1	179.0
2	6.52	436	4	199.9
3	n.d.	n.d.	-	n.d.
4	1.30	440	5	202.7
5	1.19	474	1	166.6
6	0.89	466	1	n.d.
7	1.00	480	1	n.d.
8	6.40	454	2	157.2
9	6.83	465	4	158.4
10	0.92	379	1	247.1
17	6.40	458	2	185.1
18	1.25	472	1	164.2
46	1.15	457	1	186.8
47	0.95	429	5	n.d.
48	0.83	472	1	n.d.
49	0.97	410	1	n.d.
50	0.91	472	1	n.d.
51	1.01	411	1	210.1
52	1.17	439	1	167.1
53	1.15	488	1	169.9
54	1.15	464	1	173.0
55	5.86	426	2	189.4
56	1.01	416	1	170.1
57	6.44	444	2	214.5
58	1.18	488	1	n.d.
59	1.12	465	1	134.0
60	0.95	410	5	184.2
61	1.10	422	1	175.0
64	5.77	442	2	n.d.

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
67	7.54	475	4	n.d.
69	1.12	450	5	n.d.
70	1.29	484	1	n.d.
71	1.31	484	1	n.d.
108	1.12	465	1	141.6
109	1.12	465	1	140.1
112	3.96	404	3	204.1-205.4
113	1.08	396	1	220.7
117	1.34	490	1	131.5
118	1.31	490	1	n.d.
119	1.19	407	1	n.d.
120	1.16	435	5	n.d.
121	1.40	449	1	n.d.
122	1.24	445	1	n.d.
123	1.28	463	1	n.d.
124	1.22	475	1	n.d.
125	1.10	447	1	n.d.
126	1.24	475	1	n.d.
127	1.24	475	1	n.d.
128	1.21	465	1	n.d.
129	1.16	451	1	n.d.
130	1.23	447	5	n.d.
131	6.32	490	2	n.d.
132	1.19	508	1	177.1
133	0.97	447	5	n.d.
134	1.15	428	1	n.d.
135	1.12	440	1	n.d.
136	1.23	468	1	221.9
137	1.22	438	1	210.3

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
138	1.26	456	1	199.6
139	0.99	455	5	n.d.
140	1.07	420	5	142.5
141	8.16	438	4	n.d.
142	1.19	448	1	n.d.
143	1.18	448	1	n.d.
145	1.12	466	1	n.d.
146	1.16	480	1	n.d.
147	1.04	496	5	90.1
148	0.83	451	1	n.d.
149	5.70	493	2	138.6
150	1.07	479	1	n.d.
152	1.10	505	1	n.d.
153	1.35	484	1	n.d.
154	1.26	438	1	n.d.
155	1.32	434	1	222.6
156	1.31	464	1	n.d.
157	1.34	434	1	159.6
158	1.09	450	5	125.4
159	1.06	422	5	n.d.
160	1.27	468	1	n.d.
161	1.09	438	5	132.7

Co. No.	R_t	$[M+H]^+$	LCMS Method	m.p. (°C)
162	1.28	480	1	n.d.
163	1.25	448	1	172.7
164	1.26	418	1	138.9
165	1.09	448	5	n.d.
166	1.15	456	1	159.6
167	7.85	502	4	n.d.
168	1.16	474	1	145.1
169	1.30	502	1	134.8
170	1.17	518	5	n.d.
171	1.17	501	1	169.3
173	1.03	463	5	n.d.
174	1.06	485	1	n.d.
175	6.40	504	2	n.d.
176	0.87	464	1	158.4
177	5.30	472	3	165.9-166.9
178	1.26	464	1	179.2
179	4.82	434	3	142.7-144.7
180	4.63	434	3	132.8-143.6

SFC-MS

For SFC-MS, an analytical SFC system from Berger Instruments (Newark, DE, USA) was used comprising a dual pump control module (FCM-1200) for delivery of CO_2 and modifier, a thermal control module for column heating (TCM2100) with temperature control in the range 1-150 °C and column selection valves (Valco, VICI, Houston, TX, USA) for 6 different columns. The photodiode array detector (Agilent 1100, Waldbronn, Germany) is equipped with a high-pressure flow cell (up to 400 bar) and configured with a CTC LC Mini PAL auto sampler (Leap Technologies, Carrboro, NC , USA). A ZQ mass spectrometer (Waters, Milford, MA, USA) with an orthogonal Z-electrospray interface is coupled with the SFC-system. Instrument control, data collection and processing were performed with an integrated platform consisting of the SFC ProNTo software and Masslynx software.

Co. No. 108-109: SFC-MS was carried out on a OJ-H column (500 x 4.6 mm) (Daicel Chemical Industries Ltd) with a flow rate of 3 ml/min. Two mobile phases (mobile phase A: CO_2; mobile phase B: iPrOH containing 0.2 % $iPrNH_2$) were employed. First 25 % B was hold for 17 min. Then a gradient was applied from 25 % B to 50 % B in 2.5 min and hold for 4.1 min. Column temperature was set at 50°C. Under these conditions, Co. No. 108 ('enantiomer A') had a shorter R_t on the column than Co. No. 109 ('enantiomer B') . The measurement was compared against the racemic mixture.

Co. No. 126-127: SFC-MS was carried out on a AD-H column (500 x 4.6 mm) (Daicel Chemical Industries Ltd) with a flow rate of 3 ml/min. Two mobile phases (mobile phase A: CO_2; mobile phase B: iPrOH containing 0.2 % $iPrNH_2$) were employed. 25 % B was hold for 15 min. Column temperature was set at 50°C. Under these conditions, Co. No. 126 ('enantiomer A') had a shorter R_t on the column than Co. No. 127 ('enantiomer B'). The measurement was compared against the racemic mixture.

NMR

For a number of compounds, ^1H NMR spectra were recorded on a Bruker DPX-360 or on a Bruker DPX-400 spectrometer with standard pulse sequences, operating at 360 MHz and 400 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.

Co. No.	NMR result
3	(400 MHz, DMSO-d_6) δ ppm 1.49 (d, *J*=6.5 Hz, 6 H) 2.31 (s, 3 H) 3.76 (s, 3 H) 4.62 (spt, *J*=6.6 Hz, 1 H) 6.93 (dd, *J*=8.7, 2.2 Hz, 1 H) 7.30 - 7.39 (m, 2 H) 7.46 (td, *J*=7.9, 1.6 Hz, 1 H) 7.56 - 7.68 (m, 3 H) 8.58 (s, 1 H) 9.52 (s, 1 H)
17	(360 MHz, DMSO-d_6) δ ppm 1.47 (d, *J*=6.6 Hz, 6 H) 2.14 (s, 3 H) 3.90 (s, 3 H) 4.61 (spt, *J*=6.5 Hz, 1 H) 7.07 (s, 1 H) 7.48 (d, *J*=8.4 Hz, 1 H) 7.64 - 7.75 (m, 2 H) 7.79 - 7.89 (m, 1 H) 7.93 - 8.03 (m, 3 H) 9.91 (s, 1 H)
46	(360 MHz, DMSO-d_6) δ ppm 1.48 (d, *J*=6.6 Hz, 6 H) 2.14 (s, 3 H) 3.80 (s, 3 H) 4.62 (spt, *J*=6.4 Hz, 1 H) 7.00 (s, 1 H) 7.12 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.20 (d, *J*=8.4 Hz, 1 H) 7.62 (s, 1 H) 7.67 (d, *J*=1.8 Hz, 1 H) 7.78-7.89 (m, 1 H) 7.90 - 8.07 (m, 3 H) 9.61 (s, 1 H)
47	(360 MHz, DMSO-d_6) δ ppm 2.14 (s, 3 H) 3.79 (s, 3 H) 3.95 (s, 3 H) 7.00 (s, 1 H) 7.13-7.28 (m, 2 H) 7.50 (d, *J*=1.8 Hz, 1 H) 7.62 (d, *J*=1.5 Hz, 1 H) 7.83 (t, *J*=8.1 Hz, 1 H) 7.94 (d, *J*=7.7 Hz, 1 H) 8.08 - 8.19 (m, 2 H) 9.56 (s, 1 H)
48	(400 MHz, DMSO-d_6) δ ppm 2.13 (s, 3 H) 2.96 (t, *J*=6.1 Hz, 2 H) 3.71 (s, 3 H) 4.10 (t, *J*=6.1 Hz, 2 H) 4.27 (s, 2 H) 6.97 (s, 1 H) 7.08 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.14 (d, *J*=8.5 Hz, 1 H) 7.49 (d, *J*=2.0 Hz, 1 H) 7.55-7.68 (m, 4 H) 7.74 (s, 1 H) 9.35 (s, 1 H)

Co. No.	NMR result
49	(360 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H) 3.73 (s, 3 H) 3.85 (s, 3 H) 6.60 (s, 1 H) 6.74 (s, 1 H) 6.85 (s, 1 H) 6.90 (dd, *J*=8.6, 2.4 Hz, 1 H) 6.93 - 7.02 (m, 1 H) 7.12 (d, *J*=8.4 Hz, 1 H) 7.21 - 7.30 (m, 1 H) 7.39 (dd, *J*=8.1, 1.1 Hz, 1 H) 7.43 (d, *J*=2.2 Hz, 1 H) 7.60 (s, 1 H) 8.03 (dd, *J*=8.1, 1.1 Hz, 1 H)
50	(360 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H) 3.74 (s, 3 H) 3.94 (s, 3 H) 6.98 (s, 1 H) 7.02 (s, 1 H) 7.23 - 7.26 (m, 1 H) 7.34 (d, *J*=8.4 Hz, 1 H) 7.41 (t, *J*=7.9 Hz, 1 H) 7.49 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.53 (dd, *J*=8.4, 1.5 Hz, 1 H) 7.62 (s, 1 H) 7.65 (d, *J*=1.5 Hz, 1 H) 7.79 (d, *J*=1.5 Hz, 1 H) 8.65 (s, 1 H)
51	(360 MHz, DMSO-d_6) δ ppm 2.12 (s, 3 H) 3.69 (s, 3 H) 3.72 (s, 3 H) 6.97 (s, 1 H) 7.04 (dd, *J*=8.4, 2.2 Hz, 1 H) 7.15 (d, *J*=8.4 Hz, 1 H) 7.30 - 7.39 (m, 2 H) 7.46 (td, *J*=7.9, 1.5 Hz, 1 H) 7.55 - 7.68 (m, 3 H) 9.43 (s, 1 H)
52	(360 MHz, DMSO-d_6) δ ppm 1.48 (d, *J*=7.0 Hz, 6 H) 2.12 (s, 3 H) 3.71 (s, 3 H) 4.61 (spt, *J*=6.6 Hz, 1 H) 6.92 (dd, *J*=8.8, 2.2 Hz, 1 H) 6.97 (s, 1 H) 7.14 (d, *J*=8.4 Hz, 1 H) 7.35 (td, *J*=7.7, 1.5 Hz, 1 H) 7.46 (td, *J*=7.8, 1.6 Hz, 1 H) 7.55 (d, *J*=2.2 Hz, 1 H) 7.57 - 7.68 (m, 3 H) 9.46 (s, 1 H)
59	(360 MHz, DMSO-d_6) δ ppm 1.38 (d, *J*=6.6 Hz, 6 H) 1.49 (qd, *J*=11.9, 4.2 Hz, 1 H) 1.62 - 1.84 (m, 2 H) 1.90 - 2.06 (m, 1 H) 2.31 (s, 3 H) 2.76 - 2.99 (m, 3 H) 3.25 - 3.32 (m, 1 H) 3.41 - 3.51 (m, 1 H) 3.81 (s, 3 H) 4.39 (spt, *J*=6.5 Hz, 1 H) 6.99 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.34 (d, *J*=8.8 Hz, 1 H) 7.74 (d, *J*=1.8 Hz, 1 H) 8.58 (s, 1 H) 9.44 (s, 1 H)
64	(400 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H) 3.95 (s, 3 H) 4.15 (s, 3 H) 7.29 (s, 1 H) 7.63 (d, *J*=8.1 Hz, 1 H) 7.88 (t, *J*=8.0 Hz, 1 H) 7.96 (d, *J*=1.2 Hz, 1 H) 8.00 (d, *J*=8.5 Hz, 1 H) 8.03 - 8.08 (m, 2 H) 8.18 - 8.24 (m, 2 H)
67	(360 MHz, DMSO-d_6) δ ppm 1.38 (d, *J*=6.6 Hz, 6 H) 1.43 - 1.58 (m, 1 H) 1.60 - 1.85 (m, 2 H) 1.92 - 2.07 (m, 1 H) 2.72 (s, 3 H) 2.75 - 2.99 (m, 3 H) 3.25 - 3.37 (m, 1 H) 3.42 - 3.53 (m, 1 H) 3.88 (s, 3 H) 4.40 (spt, *J*=6.5 Hz, 1 H) 7.12 (d, *J*=8.1 Hz, 1 H) 7.59 (d, *J*=8.8 Hz, 1 H) 7.74 (s, 1 H) 8.05 (d, *J*=6.2 Hz, 1 H) 8.09 (s, 1 H) 8.60 (d, *J*=6.2 Hz, 1 H) 9.78 (s, 1 H)
69	(360 MHz, DMSO-d_6) δ ppm 1.50 (d, *J*=6.6 Hz, 6 H) 2.70 (s, 3 H) 3.81 (s, 3 H) 4.64 (spt, *J*=6.5 Hz, 1 H) 7.02 (dd, *J*=8.8, 1.8 Hz, 1 H) 7.37 (td, *J*=7.9, 1.5 Hz, 1 H) 7.48 (td, *J*=7.9, 1.5 Hz, 1 H) 7.55 (d, *J*=8.4 Hz, 1 H) 7.59 - 7.68 (m, 3 H) 7.99 (d, *J*=6.2 Hz, 1 H) 8.03 (s, 1 H) 8.60 (d, *J*=6.2 Hz, 1 H) 9.85 (s, 1 H)
70	(360 MHz, DMSO-d_6) δ ppm 1.48 (d, *J*=6.6 Hz, 6 H) 2.71 (s, 3 H) 3.83 (s, 3 H) 4.59 (spt, *J*=6.6 Hz, 1 H) 7.05 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.49 - 7.56 (m, 1 H) 7.58 (d, *J*=8.4 Hz, 1 H) 7.63 (d, *J*=1.8 Hz, 1 H) 7.74 - 7.85 (m, 2 H) 7.87 (d, *J*=7.7 Hz, 1 H) 8.04 (dd, *J*=6.2, 1.8 Hz, 1 H) 8.08 (d, *J*=1.5 Hz, 1 H) 8.63 (d, *J*=6.6 Hz, 1 H) 9.88 (s, 1 H)
71	(360 MHz, DMSO-d_6) δ ppm 1.48 (d, *J*=6.6 Hz, 6 H) 2.70 (s, 3 H) 3.82 (s, 3 H) 4.62 (spt, *J*=6.5 Hz, 1 H) 7.07 (dd, *J*=8.6, 1.6 Hz, 1 H) 7.56 (d, *J*=8.8 Hz, 1 H) 7.64 (d, *J*=1.8 Hz, 1 H) 7.66 - 7.80 (m, 3 H) 7.90 (s, 1 H) 7.99 (dd, *J*=6.4, 1.6 Hz, 1 H) 8.03 (d, *J*=1.5 Hz, 1 H) 8.59 (d, *J*=6.2 Hz, 1 H) 9.85 (s, 1 H)
108	(360 MHz, DMSO-d_6) δ ppm 1.38 (d, *J*=6.6 Hz, 6 H) 1.42 - 1.56 (m, 1 H) 1.60 - 1.83 (m, 2 H) 1.93 - 2.03 (m, 1 H) 2.31 (s, 3 H) 2.76 - 2.97 (m, 3 H) 3.25 - 3.32 (m, 1 H) 3.43 - 3.51 (m, 1 H) 3.80 (s, 3 H) 4.39 (spt, *J*=6.8 Hz, 1 H) 6.99 (dd, *J*=8.8, 2.2 Hz, 1 H) 7.34 (d, *J*=8.4 Hz, 1 H) 7.74 (d, *J*=2.2 Hz, 1 H) 8.58 (s, 1 H) 9.44 (s, 1 H)

Co. No.	NMR result
109	(360 MHz, DMSO-d_6) δ ppm 1.37 (d, *J*=6.2 Hz, 6 H) 1.49 (qd, *J*=12.0, 4.2 Hz, 1 H) 1.61 - 1.73 (m, 1 H) 1.73 - 1.83 (m, 1 H) 1.93 - 2.03 (m, 1 H) 2.31 (s, 3 H) 2.76 - 2.97 (m, 3 H) 3.24 - 3.32 (m, 1 H) 3.42 - 3.50 (m, 1 H) 3.80 (s, 3 H) 4.39 (spt, *J*=6.4 Hz, 1 H) 6.99 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.34 (d, *J*=8.8 Hz, 1 H) 7.74 (d, *J*=1.8 Hz, 1 H) 8.58 (s, 1 H) 9.44 (s, 1 H)

Pharmacology

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

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. T 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 3, 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}.

Table 3:

Co. No.	IC50 Aβ42 (μM)	IC50 Aβtotal (μM)
1	0.089	>10
2	0.040	>10
3	0.079	9.55
4	0.068	>10
5	0.046	>15
6	0.380	>10
7	0.209	>10
8	0.035	>10
9	0.200	7.59
10	0.407	>10
17	0.240	8.13
18	0.010	6.76
46	0.021	5.37
47	0.132	>10
48	0.042	3.89
49	0.030	>10
50	0.257	>10
51	0.039	8.91
52	0.008	7.08
53	0.013	8.511
54	0.011	5.888
55	0.132	>10
56	0.020	10
57	0.018	10
58	0.013	3.55
59	0.036	9.55
60	0.389	>10
61	0.098	>10
64	3.802	>10
67	0.028	8.32
69	0.042	5.37
70	0.089	4.17
71	0.04	8.13

Co. No.	IC50 Aβ42 (μM)	IC50 Aβtotal (μM)
108	0.038	>10
109	0.081	8.13
112	0.245	>10
113	1.905	>10
117	0.026	7.41
118	0.089	8.71
119	0.059	7.24
120	0.063	7.94
121	0.058	>10
122	0.029	>10
123	0.025	>10
124	0.071	8.51
125	0.055	>10
126	0.047	>10
127	0.037	8.913
128	0.120	>10
129	0.071	>10
130	0.056	>10
131	0.100	7.94
132	0.069	7.244
133	0.071	>10
134	0.347	>10
135	0.200	>10
136	0.056	>10
137	0.078	>10
138	0.126	>10
139	0.028	8.511
140	0.052	8.71
141	0.060	8.71
142	0.044	6.457
143	0.038	3.09
145	0.037	>10
146	0.032	8.71

Co. No.	IC50 Aβ42 (μM)	IC50 Aβtotal (μM)
147	0.028	6.61
148	0.692	>10
149	0.107	6.46
150	0.102	8.71
152	0.126	8.13
153	0.047	6.918
154	0.091	7.586
155	0.037	9.33
156	0.048	>10
157	0.017	>10
158	0.032	6.607
159	0.037	10.72
160	0.148	6.761
161	0.043	9.12
162	0.023	7.24
163	0.040	7.59
164	0.028	8.91
165	0.078	7.76
166	0.282	>10
167	0.045	6.457
168	0.093	>10
169	0.091	9.33
170	0.066	>10
171	0.068	7.08
173	0.052	6.607
174	0.759	>10
175	0.068	9.12
176	0.603	>10
177	0.363	>10
178	5.012	>10
179	>10	>10
180	0.282	>10

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. 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 were quantitated by standard techniques, for example, using ELISA. Treatment periods varied from hours (h) 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 4 h, 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 (min) 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 from non-transgenic animals were resuspended in 8 volumes of 0.4 % DEA (diethylamine) /50 mM NaCl containing protease inhibitors (Roche-11873580001 or 04693159001) per gram of tissue, e.g. for 0.158 g brain, add 1.264 ml of 0.4 % DEA. All samples were homogenized in the FastPrep-24 system (MP Biomedicals) using lysing matrix D (MPBio #6913-100) at 6m/s for 20 seconds. Homogenates were centrifuged at 221.300 x g for 50 min. The resulting high speed supernatants were then transferred to fresh eppendorf tubes. Nine parts of supernatant were neutralized with 1 part 0.5 M Tris-HCl pH 6.8 and used to quantify Aßtotal and Aß42.

To quantify the amount of Aßtotal and Aß42 in the soluble fraction of the brain homogenates, Enzyme-Linked-Immunosorbent-Assays were used . Briefly, the standards (a dilution of synthetic Aβ1-40 and Aβ1-42, Bachem) were prepared in 1.5 ml Eppendorf tube in Ultraculture, with final concentrations ranging from 10000 to 0.3 pg/ml. The samples and standards were co-incubated with HRPO-labelled N-terminal antibody for Aß42 detection and with the biotinylated mid-domain antibody 4G8 for Aßtotal detection. 50 µl of conjugate/sample or conjugate/standards mixtures were then added to the antibody-coated plate (the capture antibodies selectively recognize the C-terminal end of Aß42, antibody JRF/cAß42/26, for Aß42 detection and the N-terminus of Aß, antibody JRF/rAß/2, for Aßtotal detection). 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 the ELISA for Aß42 quantification was finished by addition of Quanta Blu fluorogenic peroxidase substrate according to the manufacturer's instructions (Pierce Corp., Rockford, Il). A reading was performed after 10 to 15 min (excitation 320 nm /emission 420 nm).

For Aßtotal detection, a Streptavidine-Peroxidase-Conjugate was added, followed 60 min later by an addional wash step and addition of Quanta Blu fluorogenic peroxidase substrate according to the manufacturer's instructions (Pierce Corp., Rockford, Il). A reading was performed after 10 to 15 min (excitation 320 nm /emission 420 nm).

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

The results are shown in **Table 4** (dose 30 mg/kg oral dosing) (value for untreated animals as control (Ctrl) was set at 100):

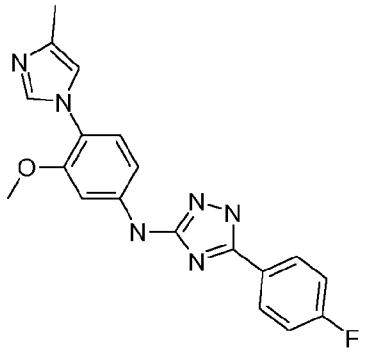
Co. No.	Aβ42 (% vs Ctrl) _Mean	Aβtotal (% vs Ctrl)_Mean
10	68	110
A	101	106
52	45	112

Co. No.	Aβ42 (% vs Ctrl) _Mean	Aβtotal (% vs Ctrl)_Mean
46	61	98
58	88	89
54	46	88

Co. No.	Aβ42 (% vs Ctrl) _Mean	Aβtotal (% vs Ctrl)_Mean
59	69	94
67	60	89
69	63	97
140	83	86
141	78	98
160	77	83

Co. No.	Aβ42 (% vs Ctrl) _Mean	Aβtotal (% vs Ctrl)_Mean
133	67	94
108	70	94
109	85	117

The Compound A referred to in Table 4, is the derivative of present compound 10 wherein R^1 is hydrogen instead of methyl, and was disclosed in WO2009/103652:



Structure of Compound A (WO2009/103652)

Also the central brain availability of Compounds 3, 5, 10 and A were measured:
The results are shown in **Table 5** (dose 30 mg/kg oral dosing; 4 hours):

Co. No.	Plasma (ng/ml)	Brain (ng/g)
3	7740	8510
5	1632	1630
10	2695	4645
A	0	0

C) Liver metabolic stability assay

Each compound was spiked into a suspension of liver microsomes prepared from the species under investigation, at a final substrate concentration of 1 μM, and a protein concentration of 1 mg/ml, and pre-incubated at 37 °C for 11 minutes. The incubation also contains a NADPH (β-nicotinamide adenine dinucleotide phosphate, reduced) regenerating system. After this preincubation period, NADP (β-nicotinamide adenine dinucleotide phosphate) was added to the active incubations, and the incubations maintained at 37 °C for 15 minutes, during which period metabolism can take place. After 15 minutes, 2 volumes of DMSO (dimethylsulfoxide) were added to each active

incubation to inactivate and precipitate proteins. Control incubations were not preincubated at 37 °C, but instead were quenched by the addition of DMSO prior to the addition of NADP. Following centrifugation, the supernatant from each incubation was transferred to a separate analysis plate, and analysed for the concentration of the parent compound by LC/MS/MS using a compound-specific LC/MS/MS method and a generic HPLC gradient. The turnover of the parent compound is expressed as the % reduction in concentration in the analyte samples compared to that in the control incubations. Each incubation is performed in triplicate.

The results for compound 10 (present invention) and compound A (WO2009/103652) are shown in **Table 6**:

Co. No.	**human liver microsomes**	**mouse liver microsomes**
10	14 %	10 %
A	64 %	22 %

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

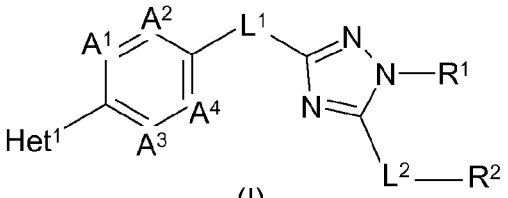
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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

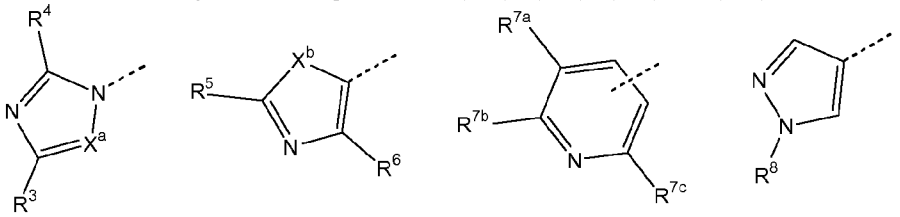
1. A compound of Formula (I)



(I)

or a stereoisomeric form thereof, wherein

Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3), or (a-4)



(a-1) (a-2) (a-3) (a-4);

R^3 is C_{1-4}alkyl;

R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl optionally substituted with one or more halo substituents;

R^{7a} is hydrogen, halo, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen, halo, cyano, C_{1-4}alkyloxy, cycloC_{3-7}alkyl, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

X^a is CH or N;

X^b is O or S;

A^1 is CR^9 or N; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

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

provided that maximum two of A^1, A^2, A^3 and A^4 are N;

L^1 is O, carbonyl, NR^{10}, NH–(C=O), or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, hexahydro-1H-1,4-diazepin-1-yl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, oxo, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

or a 5- or 6-membered heteroaryl selected from the group consisting of furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl, wherein said 5- or 6-membered heteroaryl may be substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, $NR^{11c}R^{12c}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

each R^{11a}, R^{11b} and R^{11c} independently is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

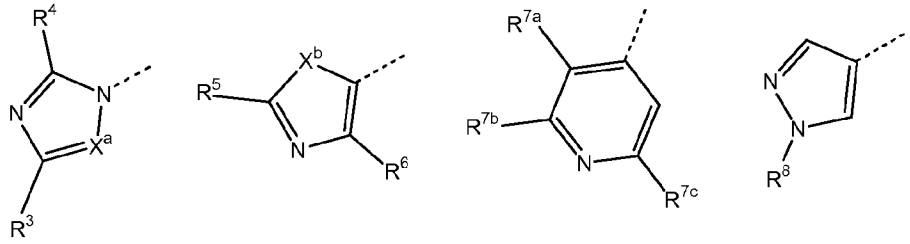
each R^{12a}, R^{12b} and R^{12c} independently is hydrogen or C_{1-4}alkyl;

each R^{13a}, R^{13b} and R^{13c} independently is hydrogen, or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and cycloC_{3-7}alkyl;

or a pharmaceutically acceptable addition salt or a solvate thereof.

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

Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3a), or (a-4)



(a-1) (a-2) (a-3a) (a-4);

R^3 is C_{1-4}alkyl;

R^4, R^5, R^6, and R^8 each independently are hydrogen or C_{1-4}alkyl optionally substituted with one or more halo substituents;

R^{7a} is hydrogen, halo, or C_{1-4}alkyl;

R^{7b} and R^{7c} each independently are hydrogen, halo, cyano, C_{1-4}alkyloxy, cycloC_{3-7}alkyl, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

X^a is CH or N;

X^b is O or S;

A^1 is CR^9 or N; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

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

provided that maximum two of A^1, A^2, A^3 and A^4 are N;

L^1 is O, carbonyl, NR^{10}, NH–(C=O), or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is cycloC_{3-7}alkyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-

1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 1,2-dihydropyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,2-dihydropyridinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, C_{1-4}alkylcarbonyl, oxo, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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, $NR^{11b}R^{12b}$, morpholinyl, C_{1-4}alkyloxy substituted with one or more halo substituents, and C_{1-4}alkyl optionally substituted with one or more halo substituents; or a 5- or 6-membered heteroaryl selected from the group consisting of furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl, wherein said 5- or 6-membered heteroaryl may be substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, $NR^{11c}R^{12c}$, morpholinyl, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

each R^{11a}, R^{11b}, and R^{11c} independently is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

each R^{12a}, R^{12b}, and R^{12c} independently is hydrogen or C_{1-4}alkyl;

each R^{13a}, R^{13b}, and R^{13c} independently is hydrogen, or C_{1-4}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and cycloC_{3-7}alkyl;

or a pharmaceutically acceptable addition salt or a solvate thereof.

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

Het^1 is a heterocycle, having formula (a-1), (a-2), or (a-3);

R^3 is C_{1-4}alkyl;

R^4 is hydrogen;

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

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

R^{7a} is hydrogen or C_{1-4}alkyl;

R^{7b} is hydrogen, C_{1-4}alkyloxy, or C_{1-4}alkyl optionally substituted with one or more halo substituents;

R^{7c} is hydrogen or C_{1-4}alkyl;

X^a is CH or N;

X^b is O;

A^1 is CR^9; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy;

A^2 is CH or N;

A^3 and A^4 are CH;

L^1 is carbonyl, NR^{10}, NH-(C=O) or (C=O)-NH; wherein R^{10} is hydrogen or C_{1-4}alkyl;

R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of $NR^{11a}R^{12a}$, 1-pyrrolidinyl, and C_{1-6}alkyloxy;

L^2 represents a direct bond; O; NR^{13a}; or C_{1-3}alkanediyl;

R^2 is pyrrolidinyl; piperidinyl; morpholinyl; piperazinyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-2(1H)-isoquinolinyl; 2-oxo-5-(trifluoromethyl)-1(2*H*)-pyridinyl; or Ar;

wherein pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, and hexahydro-1H-1,4-diazepin-1-yl, may be substituted with one or more substituents each independently selected from the group consisting of cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

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

each R^{11a} independently is hydrogen or C_{1-4}alkyl;

each R^{12a} independently is hydrogen or C_{1-4}alkyl;

R^{13a} is hydrogen;

or a pharmaceutically acceptable addition salt or a solvate thereof.

4. The compound according to claim 1, wherein

R^1 is cycloC_{3-7}alkyl; C_{2-6}alkenyl; or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, $NR^{11a}R^{12a}$, cycloC_{3-7}alkyl, and C_{1-6}alkyloxy;

wherein each cycloC_{3-7}alkyl may be substituted with one or more substitents each independently selected from the group consisting of halo, C_{1-4}alkyloxy, cyano, and C_{1-4}alkyl optionally substituted with one or more halo substituents;

L^2 represents a direct bond; C_{2-6}alkenediyl; carbonyl; O; S; $S(=O)_p$; NR^{13a}; NR^{13b}-C_{1-3}alkanediyl; C_{1-3}alkanediyl-NR^{13c}; C_{1-3}alkanediyl optionally substituted with one or more halo substituents; or C_{1-3}alkanediyl wherein two geminal hydrogen atoms may be replaced by C_{2-6}alkanediyl;

p represents 1 or 2;

R^2 is pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydropyranyl; morpholinyl; piperazinyl; cycloC_{3-7}alkyl; hexahydro-1H-1,4-diazepin-1-yl; 1,3-dihydro-2H-isoindol-2-yl; 2,3-dihydro-1H-indol-1-yl; 3,4-dihydro-1(2H)-quinolinyl; 3,4-dihydro-2(1H)-isoquinolinyl; 2-oxo-5-(trifluoromethyl)-1(2*H*)-pyridinyl; indanyl; 1,3-benzodioxolyl; or Ar;

wherein pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, cycloC_{3-7}alkyl, hexahydro-1H-1,4-diazepin-1-yl, 1,3-dihydro-2H-isoindol-2-yl, 2,3-dihydro-1H-indol-1-yl, 3,4-dihydro-1(2H)-quinolinyl, 3,4-dihydro-2(1H)-isoquinolinyl, indanyl and 1,3-benzodioxolyl may be substituted with one or more substituents each independently selected from the group consisting of C_{2-6}alkenyl, cycloC_{3-7}alkyl, C_{1-4}alkylcarbonyl, hydroxyl, halo, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, Ar, and C_{1-4}alkyl optionally substituted with one or more halo substituents.

5. The compound according to claim 1 wherein Het^1 is a heterocycle, having formula (a-1), (a-2) or (a-3).

6. The compound according to claim 1 wherein A^1 is CR^9; wherein R^9 is hydrogen, halo, or C_{1-4}alkyloxy; A^2 is CH or N; and A^3 and A^4 are CH.

7. The compound according to claim 1 wherein L^1 is NH.

8. The compound according to claim 1 wherein Het^1 is a heterocycle, having formula (a-1), (a-2), (a-3a), or (a-4).

9. The compound according to claim 1 wherein the compound is 5-(2-chlorophenoxy)-N-[3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine,

N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine .2.2HCl .2.7H_2O,
5-(2-chlorophenoxy)-N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-1H-1,2,4-triazol-3-amine .HCl .2.7H_2O,
N-[3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)-1-piperidinyl]-1H-1,2,4-triazol-3-amine,
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[2-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine .HCl .H_2O, or
N-[3-methoxy-4-(2-methyl-4-pyridinyl)phenyl]-1-(1-methylethyl)-5-[3-(trifluoromethyl)phenoxy]-1H-1,2,4-triazol-3-amine .HCl .1.5H_2O,
a stereoisomeric form thereof,
or a pharmaceutically acceptable addition salt or a solvate thereof.

10. 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 9.

11. A compound as defined in any one of claims 1 to 9 for use as a medicament.

12. A compound as defined in any one of claims 1 to 9 for use in 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, dementia pugilistica, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid.

13. The compound according to claim 12 wherein the disease is Alzheimer's disease.

14. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for the modulation of gamma-secretase activity.