US Patent & Trademark Office
Patent Public Search | Text View

United States Patent	12384772
Kind Code	B2
Date of Patent	August 12, 2025
Inventor(s)	Heiser; Ulrich et al.

Inhibitors

Abstract

Compounds of formula (I):
A-B-D-E
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof, wherein: A is monocyclic and bicyclic heteroaryl; B is alkyl, heteroalkyl, alkyl-amino, aryl, heteroaryl, cycloalkyl, heterocyclyl, or alkylene; D is aryl-amino, heteroaryl-amino, cycloalkyl-amino, heterocyclyl, heterocyclyl-amino, urea, thioamide, thiourea, sulfonamide, sulfoximine, or sulfamoyl; and E is aryl, heteroaryl, cycloalkyl, or heterocyclyl. These compounds of formula (I) are inhibitors of glutaminyl cyclase (QC, EC 2.3.2.5).

Inventors: **Heiser; Ulrich (Halle, DE), Hoffmann; Torsten (Halle, DE), Lues; Ingeborg (Seeheim-Jugenheim, DE), Meyer; Antje (Halle, DE)**

Applicant: **VIVORYON THERAPEUTICS N.V.** (Halle, DE)

Family ID: **58682483**

Assignee: **VIVORYON THERAPEUTICS N.V. (Halle, DE)**

Appl. No.: **17/737602**

Filed: **May 05, 2022**

Prior Publication Data

Document Identifier	Publication Date
US 20220274977 A1	Sep. 01, 2022

Foreign Application Priority Data

GB	1705263	Mar. 31, 2017

Related U.S. Application Data

division parent-doc US 16497040 US 11339152 WO PCT/EP2018/058391 20180403 child-doc US 17737602

Publication Classification

Int. Cl.: **C07D417/12** (20060101); **A61K45/06** (20060101); **C07D235/08** (20060101); **C07D249/14** (20060101); **C07D277/40** (20060101); **C07D285/135** (20060101); **C07D401/04** (20060101); **C07D401/12** (20060101); **C07D403/12** (20060101); **C07D417/04** (20060101)

U.S. Cl.:

CPC **C07D417/12** (20130101); **C07D235/08** (20130101); **C07D249/14** (20130101); **C07D277/40** (20130101); **C07D285/135** (20130101); **C07D401/04** (20130101); **C07D401/12** (20130101); **C07D403/12** (20130101); **C07D417/04** (20130101); A61K45/06 (20130101); C07B2200/13 (20130101)

Field of Classification Search

CPC: C07D (417/14); C07D (417/12); C07D (235/06); C07D (235/08); C07D (249/08); C07D (249/14); C07D (277/40); C07D (285/135); C07D (401/04); C07D (401/12); C07D (403/12); C07D (417/04); A61K (45/06); A61P (25/00); A61P (35/00); A61P (37/00); C07B (2200/13)

USPC: 548/138; 548/198

References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
5525604	12/1995	Lee et al.	N/A	N/A
2001/0031760	12/2000	Pamukcu et al.	N/A	N/A
2009/0048301	12/2008	Chen et al.	N/A	N/A
2011/0262388	12/2010	Heiser et al.	N/A	N/A
2013/0165458	12/2012	Huang et al.	N/A	N/A

FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
69408750	12/1997	DE	N/A
2008008375	12/2007	WO	N/A
2011029920	12/2010	WO	N/A
2011131748	12/2010	WO	N/A
2017025868	12/2016	WO	N/A

OTHER PUBLICATIONS

Jimenez-Sanchez, Maria et al.: “siRNA screen identifies QPCT as a druggable target for Huntington's disease”, Nature Chemical Biology, vol. 11, No. 5, 2, May 1, 2015 (May 1, 2015), pp. 347-354, XP055479437, Basingstoke, ISSN: 1552-4450, DOI: 10.1038jnchembio.1790 figure 3a. cited by applicant

Saulnier, Mark G. et al: “Nucleophilic Capture of the Imino-Quinone Methide Type Intermediates

Generated from 2-Aminothiazol-5-yl Carbinols", Organic Letters, vol. 11, No. 22, Nov. 19, 2009 (Nov. 19, 2009), pp. 5154-5157, XP055014692, ISSN: 1523-7060. DOI: 10.1021/ol902023g compounds 8, 9. cited by applicant
Ferrari, Stefania et al: "Virtual Screening Identification of Nonfolate Compounds, Including a CNS Drug, as Antiparasitic Agents Inhibiting Pteridine Reductase", Journal of Medicinal Chemistry, American Medical Society, vol. 1, 54, No. 1, Jan. 1, 2011 (Jan. 1, 2011). pp. 211-221, XP002643161, ISSN: 0022-2623, DOI: 10.1021/JM1010572 [retrieved on Dec. 2, 2010] p. 214; compounds 24b. 25b. cited by applicant
STEC Markian M. et al: "Structure-Activity Relationships of Phosphoinositide 3-Kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) Dual Inhibitors: Investigations of Various 6,5-Heterocycles to Improve Metabolic Stability", Journal of Chemistry, vol. 54, No. 14, Jul. 28, 2011 (Jul. 28, 2011), pp. 5174-5184, XP055258397, ISSN: 0022-2623, DOI: 10.1021jm2004442 compounds 15, 18. cited by applicant
Database Registry, 2014, RN 1609858-93-6, Retrieved from STN international [online]; retrieved on Feb. 3, 2022. cited by applicant
Database Registry, 2014, RN 1567371-28-1, Retrieved from STN international [online]; retrieved on Feb. 3, 2022. cited by applicant
Database Registry, 2010, RN 1211493-15-0, Retrieved from STN international [online]; retrieved on Feb. 3, 2022. cited by applicant
Database Registry, 2010, RN 1211492-61-3, Retrieved from STN international [online]; retrieved on Feb. 3, 2022. cited by applicant
Database Registry, 2010, RN 1211465-90-5, Retrieved from STN international [online]; retrieved on Feb. 3, 2022. cited by applicant
Database Registry, 2009, RN 1199216-00-6, Retrieved from STN international [online]; retrieved on Feb. 3, 2022. cited by applicant
Database Registry, 2004, RN 694497-92-2, Retrieved from STN international [online]; retrieved on Feb. 3, 2022. cited by applicant

---

Primary Examiner: Murray; Jeffrey H

Assistant Examiner: Burkett; Daniel John

Attorney, Agent or Firm: Olson & Cepuritis, Ltd.

Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) This application is a divisional of U.S. patent application Ser. No. 16/497,040, filed on Sep. 24, 2019, which is a continuation to PCT/EP2018/058391, filed on Apr. 3, 2018, which claims priority of British Patent Application No. 1705263.0, filed on Mar. 31, 2017, each of which is incorporated herein by reference.

SEQUENCE LISTING INCORPORATION
(1) Biological sequence information for this application is included in an ASCII text file, having the file name "eolf-seq1.txt" and a having file size of 12 KB, which is part of said PCT/EP2018/058391 and is incorporated herein by reference.
FIELD OF THE INVENTION
(2) The invention relates to novel heterocyclic derivatives as inhibitors of glutaminyl cyclase (QC, EC 2.3.2.5). QC catalyzes the intramolecular cyclization of N-terminal glutamine residues into pyroglutamic acid (5-oxo-prolyl, pGlu*) under liberation of ammonia and the intramolecular

cyclization of N-terminal glutamate residues into pyroglutamic acid under liberation of water.

BACKGROUND OF THE INVENTION

(3) Glutaminyl cyclase (QC, EC 2.3.2.5) catalyzes the intramolecular cyclization of N-terminal glutamine residues into pyroglutamic acid (pGlu*) liberating ammonia. A QC was first isolated by Messer from the latex of the tropical plant *Carica papaya* in 1963 (Messer, M. 1963 Nature 4874, 1299). 24 years later, a corresponding enzymatic activity was discovered in animal pituitary (Busby, W. H. J. et al. 1987 J Biol Chem 262, 8532-8536; Fischer. W. H. and Spiess, J. 1987 Proc Natl Acad Sci USA 84, 3628-3632). For the mammalian QC, the conversion of Gln into pGlu by QC could be shown for the precursors of TRH and GnRH (Busby, W. H. J. et al. 1987 J Biol Chem 262, 8532-8536; Fischer, W. H. and Spiess, J. 1987 Proc Natl Acad Sci USA 84, 3628-3632). In addition, initial localization experiments of QC revealed a co-localization with its putative products of catalysis in bovine pituitary, further improving the suggested function in peptide hormone synthesis (Bockers, T. M. et al. 1995 J Neuroendocrinol 7, 445-453). In contrast, the physiological function of the plant QC is less clear. In the case of the enzyme from *C. papaya*, a role in the plant defense against pathogenic microorganisms was suggested (El Moussaoui, A. et al. 2001 Cell Mol Life Sci 58, 556-570). Putative QCs from other plants were identified by sequence comparisons recently (Dahl, S. W. et al. 2000 Protein Expr Purif 20, 27-36). The physiological function of these enzymes, however, is still ambiguous.

(4) The QCs known from plants and animals show a strict specificity for L-Glutamine in the N-terminal position of the substrates and their kinetic behavior was found to obey the Michaelis-Menten equation (Pohl, T. et al. 1991 Proc Natl Acad Sci USA 88, 10059-10063; Consalvo, A. P. et al. 1988 Anal Biochem 175, 131-138; Gololobov, M. Y. et al. 1996 Biol Chem Hoppe Seyler 377, 395-398). A comparison of the primary structures of the QCs from *C. papaya* and that of the highly conserved QC from mammals, however, did not reveal any sequence homology (Dahl, S. W. et al. 2000 Protein Expr Purif 20, 27-36). Whereas the plant QCs appear to belong to a new enzyme family (Dahl, S. W. et al. 2000 Protein Expr Purif 20, 27-36), the mammalian QCs were found to have a pronounced sequence homology to bacterial aminopeptidases (Bateman, R. C. et al. 2001 Biochemistry 40, 11246-11250), leading to the conclusion that the QCs from plants and animals have different evolutionary origins.

(5) Recently, it was shown that recombinant human QC as well as QC-activity from brain extracts catalyze both, the N-terminal glutaminyl as well as glutamate cyclization. Most striking is the finding, that cyclase-catalyzed Glu.sub.1-conversion is favored around pH 6.0 while Gln.sub.1-conversion to pGlu-derivatives occurs with a pH-optimum of around 8.0. Since the formation of pGlu-Aβ-related peptides can be suppressed by inhibition of recombinant human QC and QC-activity from pig pituitary extracts, the enzyme QC is a target in drug development for treatment of Alzheimer's disease.

(6) Inhibitors of QC are e.g. described in WO 2004/098625, WO 2004/098591, WO 2005/039548, WO 2005/075436, WO 2008/055945, WO 2008/055947, WO 2008/055950, WO2008/065141, WO 2008/110523, WO 2008/128981, WO 2008/128982, WO 2008/128983, WO 2008/128984, WO 2008/128985, WO 2008/128986, WO 2008/128987, WO 2010/026212, WO 2011/029920, WO 2011/107530, WO 2011/110613, WO 2011/131748 and WO 2012/123563.

(7) EP 02 011 349.4 discloses polynucleotides encoding insect glutaminyl cyclase, as well as polypeptides encoded thereby and their use in methods of screening for agents that reduce glutaminyl cyclase activity. Such agents are useful as pesticides.

Definitions

(8) The terms “k.sub.i” or “K.sub.i” and “K.sub.D” are binding constants, which describe the binding of an inhibitor to and the subsequent release from an enzyme. Another measure is the “IC.sub.50” value, which reflects the inhibitor concentration, which at a given substrate concentration results in 50% enzyme activity.

(9) The term “DP IV-inhibitor” or “dipeptidyl peptidase IV inhibitor” is generally known to a

person skilled in the art and means enzyme inhibitors, which inhibit the catalytic activity of DP IV or DP IV-like enzymes.
(10) “DP IV-activity” is defined as the catalytic activity of dipeptidyl peptidase IV (DP IV) and DP IV-like enzymes. These enzymes are post-proline (to a lesser extent post-alanine, post-serine or post-glycine) cleaving serine proteases found in various tissues of the body of a mammal including kidney, liver, and intestine, where they remove dipeptides from the N-terminus of biologically active peptides with a high specificity when proline or alanine form the residues that are adjacent to the N-terminal amino acid in their sequence.
(11) The term “PEP-inhibitor” or “prolyl endopeptidase inhibitor” is generally known to a person skilled in the art and means enzyme inhibitors, which inhibit the catalytic activity of prolyl endopeptidase (PEP, prolyl oligopeptidase, POP).
(12) “PEP-activity” is defined as the catalytic activity of an endoprotease that is capable to hydrolyze post proline bonds in peptides or proteins where the proline is in amino acid position 3 or higher counted from the N-terminus of a peptide or protein substrate.
(13) The term ‘QC’ as used herein comprises glutaminyl cyclase (QC) and QC-like enzymes. QC and QC-like enzymes have identical or similar enzymatic activity, further defined as QC activity. In this regard, QC-like enzymes can fundamentally differ in their molecular structure from QC. Examples of QC-like enzymes are the glutaminyl-peptide cyclotransferase-like proteins (QPCTLs) from human (GenBank NM_017659), mouse (GenBank BC058181), *Macaca fascicularis* (GenBank AB168255), *Macaca* mulatta (GenBank XM_001110995), *Canis familiaris* (GenBank XM_541552), *Rattus norvegicus* (GenBank XM_001066591). *Mus musculus* (GenBank BC058181) and *Bos taurus* (GenBank BT026254).
(14) The term “QC activity” as used herein is defined as intramolecular cyclization of N-terminal glutamine residues into pyroglutamic acid (pGlu*) or of N-terminal L-homoglutamine or L-β-homoglutamine to a cyclic pyro-homoglutamine derivative under liberation of ammonia. See therefore schemes 1 and 2.
(15) ##STR00001##
(16) ##STR00002##
(17) The term “EC” as used herein comprises the activity of QC and QC-like enzymes as glutamate cyclase (EC), further defined as EC activity.
(18) The term “EC activity” as used herein is defined as intramolecular cyclization of N-terminal glutamate residues into pyroglutamic acid (pGlu*) by QC. See therefore scheme 3.
(19) ##STR00003##
(20) The term “QC-inhibitor” “glutaminyl cyclase inhibitor” is generally known to a person skilled in the art and means enzyme inhibitors, which inhibit the catalytic activity of glutaminyl cyclase (QC) or its glutamyl cyclase (EC) activity.
(21) Potency of QC Inhibition
(22) In light of the correlation with QC inhibition, in preferred embodiments, the subject method and medical use utilize an agent with an IC.sub.50 for QC inhibition of 10 μM or less, more preferably of 1 μM or less, even more preferably of 0.1 μM or less or 0.01 μM or less, or most preferably 0.001 μM or less. Indeed, inhibitors with K; values in the lower micromolar, preferably the nanomolar and even more preferably the picomolar range are contemplated. Thus, while the active agents are described herein, for convenience, as “QC inhibitors”, it will be understood that such nomenclature is not intending to limit the subject of the invention to a particular mechanism of action.
(23) Molecular Weight of QC Inhibitors
(24) In general, the QC inhibitors of the subject method or medical use will be small molecules, e.g., with molecular weights of 500 g/mole or less, 400 g/mole or less, preferably of 350 g/mole or less, and even more preferably of 300 g/mole or less and even of 250 g/mole or less.
(25) The term “subject” as used herein, refers to an animal, preferably a mammal, most preferably

a human, who has been the object of treatment, observation or experiment.
(26) The term “therapeutically effective amount” as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.
(27) As used herein, the term “pharmaceutically acceptable” embraces both human and veterinary use: For example the term “pharmaceutically acceptable” embraces a veterinarily acceptable compound or a compound acceptable in human medicine and health care.
(28) Throughout the description and the claims the expression “alkyl”, unless specifically limited, denotes a C.sub.1-12alkyl group, suitably a C.sub.1-6 alkyl group, e.g. C.sub.1-6 alkyl group, e.g. C.sub.1-4 alkyl group. Alkyl groups may be straight chain or branched. Suitable alkyl groups include, for example, methyl, ethyl, propyl (e.g. n-propyl and isopropyl), butyl (e.g. n-butyl, iso-butyl, sec-butyl and tert-butyl), pentyl (e.g. n-pentyl), hexyl (e.g. n-hexyl), heptyl (e.g. n-heptyl) and octyl (e.g. n-octyl). The expression “alk”, for example in the expressions “alkoxy”, “haloalkyl” and “thioalkyl” should be interpreted in accordance with the definition of “alkyl”. Exemplary alkoxy groups include methoxy, ethoxy, propoxy (e.g. n-propoxy), butoxy (e.g. n-butoxy), pentoxy (e.g. n-pentoxy), hexoxy (e.g. n-hexoxy), heptoxy (e.g. n-heptoxy) and octoxy (e.g. n-octoxy). Exemplary thioalkyl groups include methylthio-. Exemplary haloalkyl groups include fluoroalkyl e.g. CF.sub.3.
(29) The expression “alkylene” denotes a chain of formula —(CH.sub.2).sub.n— wherein n is an integer e.g. 1-5, unless specifically limited.
(30) The expression “cycloalkyl”, unless specifically limited, denotes a C.sub.3-10 cycloalkyl group (i.e. 3 to 10 ring carbon atoms), more suitably a C.sub.3-8 cycloalkyl group, e.g. a C.sub.3-8 cycloalkyl group. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. A most suitable number of ring carbon atoms is three to six.
(31) The expression “heterocyclyl”, unless specifically limited, refers to a carbocyclyl group wherein one or more (e.g. 1, 2 or 3) ring atoms are replaced by heteroatoms selected from N, S and O. A specific example of a heterocyclyl group is a cycloalkyl group (e.g. cyclopentyl or more particularly cyclohexyl) wherein one or more (e.g. 1, 2 or 3, particularly 1 or 2, especially 1) ring atoms are replaced by heteroatoms selected from N, S or O. Exemplary heterocyclyl groups containing one hetero atom include pyrrolidine, tetrahydrofuran and piperidine, and exemplary heterocyclyl groups containing two hetero atoms include morpholine, piperazine, dioxolane and dioxane. A further specific example of a heterocyclyl group is a cycloalkenyl group (e.g. a cyclohexenyl group) wherein one or more (e.g. 1, 2 or 3, particularly 1 or 2, especially 1) ring atoms are replaced by heteroatoms selected from N, S and O. An example of such a group is dihydropyranyl (e.g. 3,4-dihydro-2H-pyran-2-yl-).
(32) The expression “aryl”, unless specifically limited, denotes a C.sub.6-12 aryl group, suitably a C.sub.6-10 aryl group, more suitably a C.sub.6-8 aryl group. Aryl groups will contain at least one aromatic ring (e.g. one, two or three rings). An example of a typical aryl group with one aromatic ring is phenyl. An example of a typical aryl group with two aromatic rings is naphthyl.
(33) The expression “heteroaryl”, unless specifically limited, denotes an aryl residue, wherein one or more (e.g. 1, 2, 3, or 4, suitably 1, 2 or 3) ring atoms are replaced by heteroatoms selected from N, S and O, or else a 5-membered aromatic ring containing one or more (e.g. 1, 2, 3, or 4, suitably 1, 2 or 3) ring atoms selected from N, S and O. Exemplary monocyclic heteroaryl groups having one heteroatom include: five membered rings (e.g. pyrrole, furan, thiophene); and six membered rings (e.g. pyridine, such as pyridin-2-yl, pyridin-3-yl and pyridin-4-yl). Exemplary monocyclic heteroaryl groups having two heteroatoms include: five membered rings (e.g. pyrazole, oxazole, isoxazole, thiazole, isothiazole, imidazole, such as imidazol-1-yl, imidazol-2-yl imidazol-4-yl); six membered rings (e.g. pyridazine, pyrimidine, pyrazine). Exemplary monocyclic heteroaryl groups

having three heteroatoms include: 1,2,3-triazole and 1,2,4-triazole. Exemplary monocyclic heteroaryl groups having four heteroatoms include tetrazole. Exemplary bicyclic heteroaryl groups include: indole (e.g. indol-6-yl), benzofuran, benzthiophene, quinoline, isoquinoline, indazole, benzimidazole, benzthiazole, quinazoline and purine.
(34) The expression “-alkylaryl”, unless specifically limited, denotes an aryl residue which is connected via an alkylene moiety e.g. a C.sub.1-4alkylene moiety.
(35) The expression “-alkylheteroaryl”, unless specifically limited, denotes a heteroaryl residue which is connected via an alkylene moiety e.g. a C.sub.1-4alkylene moiety.
(36) The term “halogen” or “halo” comprises fluorine (F), chlorine (Cl) and bromine (Br).
(37) The term “amino” refers to the group —NH.sub.2.
(38) When benzimidazolyl is shown as benzimidazol-5-yl, which is represented as:
(39) ##STR00004##
(40) the person skilled in the art will appreciate that benzimidazol-6-yl, which is represented as:
(41) ##STR00005##
(42) is an equivalent structure. As employed herein, the two forms of benzimidazolyl are covered by the term “benzimidazol-5-yl”.
(43) Stereoisomers:
(44) All possible stereoisomers of the claimed compounds are included in the present invention.
(45) Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.
(46) Preparation and Isolation of Stereoisomers:
(47) Where the processes for the preparation of the compounds according to the invention give rise to a mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their components enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (−)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.
(48) Pharmaceutically Acceptable Salts:
(49) In view of the close relationship between the free compounds and the compounds in the form of their salts or solvates, whenever a compound is referred to in this context, a corresponding salt, solvate or polymorph is also intended, provided such is possible or appropriate under the circumstances.
(50) Salts and solvates of the compounds of formula (I) and physiologically functional derivatives thereof which are suitable for use in medicine are those wherein the counter-ion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds and their pharmaceutically acceptable salts and solvates.
(51) Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulfuric, nitric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulfamic, sulfanilic, succinic, oxalic, fumaric, maleic, malic, mandelic, glutamic, aspartic, oxaloacetic, methanesulfonic, ethanesulfonic, arylsulfonic (for example p-toluenesulfonic, benzenesulfonic, naphthalenesulfonic or naphthalenedisulfonic),

salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic), isethionic acids, perchloric, propionic, glycolic, hydroxyethanesulfonic, pamoic, cyclohexanesulfamic, salicylic, saccharinic and trifluoroacetic acid. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

(52) All pharmaceutically acceptable acid addition salt forms of the compounds of the present invention are intended to be embraced by the scope of this invention.

(53) Polymorph Crystal Forms:

(54) Furthermore, some of the crystalline forms of the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e. hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention. The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

(55) Prodrugs:

(56) The present invention further includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible in vivo into the desired therapeutically active compound. Thus, in these cases, the methods of treatment of the present invention, the term “administering” shall encompass the treatment of the various disorders described with prodrug versions of one or more of the claimed compounds, but which converts to the above specified compound in vivo after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in “Design of Prodrugs”, ed. H. Bundgaard, Elsevier, 1985.

(57) Protective Groups:

(58) During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis. John Wiley & Sons, 1991, fully incorporated herein by reference. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

(59) As used herein, the term “composition” is intended to encompass a product comprising the claimed compounds in the therapeutically effective amounts, as well as any product which results, directly or indirectly, from combinations of the claimed compounds.

(60) Carriers and Additives for Galenic Formulations:

(61) Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives may advantageously include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like.

(62) Carriers, which can be added to the mixture, include necessary and inert pharmaceutical excipients, including, but not limited to, suitable binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, coatings, disintegrating agents, dyes and coloring agents.

(63) Soluble polymers as targetable drug carriers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamide-phenol, or

polyethyleneoxidepolyllysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polyactic acid, polyepsilon caprolactone, polyhydroxy butyeric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

(64) Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or betalactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

(65) Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

DESCRIPTION OF THE INVENTION

(66) According to the invention there is provided a compound of formula (I):

A-B-D-E (I)

or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof, wherein: A is selected from monocyclic and bicyclic heteroaryl, which may independently substituted by alkyl or amino; B is selected from alkyl, heteroalkyl, alkyl-amino, aryl, heteroaryl, cycloalkyl, heterocyclyl and alkylene, wherein said groups may independently be substituted by alkyl; D is selected from aryl-amino, heteroaryl-amino, cycloalkyl-amino, heterocyclyl, heterocyclyl-amino, urea, thioamide, thiourea, sulfonamide and sulfoximine, wherein said aryl, heteroaryl, cycloalkyl and heterocyclyl groups may independently be substituted with one or more substituents; In another embodiment, D is sulfamoyl; E is selected from aryl, heteroaryl, cycloalkyl, heterocyclyl, wherein said aryl, heteroaryl, cycloalkyl and heterocyclyl groups may independently be substituted with one or more substituents.

(67) In a preferred embodiment, there is provided a compound of formula (I) with the provisos that i) when B is alkyl or heteroalkyl, then D may not be sulfonamide; and ii) the compound of formula (I) is not a compound selected from:

(68) ##STR00006##

(69) Compounds of proviso i) are known from the CAS Registry Database without any functional definition and are selected from

(70) TABLE-US-00001 Compound Chemical Name CAS No. A Benzenesulfonamide, N-[3-(5-amino-1,3,4-thiadiazol-2- 1211493-15-0 yl)propyl]-4-chloro- B Benzenesulfonamide, N-[3-(5-amino-1,3,4-thiadiazol-2- 1211465-90-5 yl)propyl]-4-bromo- C Benzenesulfonamide, N-[3-(5-amino-1,3,4-thiadiazol-2- 1199216-00-6 yl)propyl]-4-methyl- D Benzenesulfonamide, 4-(1,1-dimethylethyl)-N-[3-(4- 2128710-23-4 methyl-4H-1,2,4-triazol-3-yl)propyl]- E Benzenesulfonamide, N-[3-(5-amino-1,3,4-thiadiazol-2- 1211492-68-0 yl)propyl]-4-fluoro- F Benzenesulfonamide, N-[3-(5-amino-1,3,4-thiadiazol-2- 1211492-61-3 yl)propyl]-4-methoxy- G Benzenesulfonamide, N-[2-[(5-amino-1,3,4-thiadiazol-2- 694497-92-2 yl)thio]ethyl]-4-methyl- H Benzenesulfonamide, 4-methyl-N-[2-[(4-methyl-4H- 329266-08-2 1,2,4-triazol-3-yl)thio]ethyl]- (CA INDEX NAME) I Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1798221-00-7 4-(1-methylethoxy)- J Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1798220-92-4 4-chloro- K Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1798183-20-6 4-ethoxy- L Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1798182-87-2 4-fluoro-3-methyl- M Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1795649-47-6 4-(1,1-dimethylethyl)- N Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1795648-73-5 4-(1-methylethyl)- O Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1795648-65-5 4-ethyl- P Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1795648-57-5 3,4-dimethyl- Q Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1795648-51-9 4-methyl- R Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1795588-58-7 4-fluoro- S Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1790918-17-0 3,4-dimethoxy- T

Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1790918-11-4 4-methoxy-3-methyl- U
Benzenesulfonamide, N-(1H-benzimidazol-6-ylmethyl)- 1787494-28-3 4-methoxy-
(71) In a preferred embodiment according tp proviso i), the compound of formula (I) is not a compound selected from compounds A to U.
(72) Compound V of proviso ii) is known from CAS Registry with CAS No. 2117405-13-5 without functional definition. Compound W of proviso ii) is known from CAS Registry with CAS No. 1090606-68-0 without functional definition. Compound W of proviso ii) is known from CAS Registry with CAS No. 2093539-54-7 without functional definition.
(73) When A is a monocyclic heteroaryl, A is preferably selected from thiadiazolyl, such as 1,3,4-thiadiazolyl, thiazolyl and triazolyl, such as 1,2,4-triazolyl. In one embodiment of the invention, said monocyclic heteroaryl is substituted by amino or methyl. In another embodiment, said monocyclic heteroaryl is unsubstituted.
(74) When cycloalkyl and heterocyclyl are substituted, they are typically substituted by 1 or 2 substituents (e.g. 1 substituent). Typically the substituent is C.sub.1-6 alkyl (i.e. methyl) or halogen (i.e. chlorine or fluorine). More typically cycloalkyl and heterocyclyl groups are unsubstituted.
(75) When aryl and heteroaryl are substituted, they are typically substituted by 1, 2 or 3 (e.g. 1 or 2) substituents. Substituents for aryl and heteroaryl are selected from C.sub.1-6alkyl (e.g. methyl), C.sub.2-6alkenyl (e.g. buten-3-yl), C.sub.2-6alkynyl (e.g. butyn-3-yl), C.sub.1-4 haloalkyl (e.g. fluoromethyl, trifluoromethyl), —C.sub.1-6thioalkyl (e.g. —S-methyl), —SOC.sub.1-4alkyl (e.g. —SOmethyl), —SO.sub.2C.sub.1-4alkyl (e.g. —SO.sub.2methyl), C.sub.1-6alkoxy- (e.g. methoxy, ethoxy), —O—C.sub.3-8cycloalkyl (e.g. —O-cyclopentyl or —O-cyclohexyl), C.sub.3-8cycloalkyl (e.g. cyclopropyl, cyclohexyl), —SO.sub.2C.sub.3-8cycloalkyl (e.g. —SO.sub.2cyclohexyl), —SOC.sub.3-8cycloalkyl (e.g. —SOcyclopropyl), —O-aryl (e.g. —O-phenyl) C.sub.3-8alkenyloxy- (e.g. —O-buten-2-yl), C.sub.3-8alkynyloxy- (e.g. —O-buten-2-yl), —C(O)C.sub.1-6alkyl (e.g. —C(O)ethyl), —C(O)OC.sub.1-6alkyl (e.g. —C(O)O-methyl), C.sub.1-6alkoxy-C.sub.1-6alkyl- (e.g. methoxy-ethyl-), nitro, halogen (e.g. fluoro, chloro, bromo), cyano, hydroxyl, —C(O)OH, —NH.sub.2, —NHC.sub.1-4alkyl (e.g. —NHmethyl), —N(C.sub.1-4alkyl)(C.sub.1-4alkyl) (e.g. —N(methyl).sub.2), —C(O)N(C.sub.1-4alkyl)(C.sub.1-4alkyl) (e.g. —C(O)N(methyl).sub.2), —C(O)NH.sub.2, —C(O)NH(C.sub.1-4alkyl) (e.g. —C(O)NHmethyl), —C(O)NH(C.sub.3-10cycloalkyl) (e.g. —C(O)NHcyclopropyl). More typically, substituents will be selected from C.sub.1-6alkyl (e.g. methyl), C.sub.1-6haloalkyl (e.g. C.sub.1-6fluoroalkyl, e.g. CF.sub.3), C.sub.1-6alkoxy (e.g. OMe), halogen and hydroxy.
(76) When E represents aryl, said aryl suitably represents optionally substituted phenyl. Exemplary substituted phenyl groups for E include 2-bromophenyl, 2-bromo-4-fluorophenyl-, 2-bromo-5-fluorophenyl-, 2-fluoro-5-bromophenyl, 2-chlorophenyl-, 2-fluorophenyl-, 3-chlorophenyl-, 3-bromophenyl-, 3-fluorophenyl-, 4-chlorophenyl-, 4-fluorophenyl-, 4-bromophenyl-, 4-bromo-2-fluorophenyl, 2-chloro-3,6-difluorophenyl), 2,3-dichlorophenyl-, 2,3-difluorophenyl-, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,4-dichlorophenyl-, 2,4-difluorophenyl-, 2,4,6-trifluorophenyl-, 2,5-dichlorophenyl-, 2,6-dichlorophenyl-, 2,6-difluorophenyl-, 3,4-dichlorophenyl-, 3,4-difluorophenyl-, 3,5-difluorophenyl-, 2,4,5-trifluorophenyl-, 3,4,5-trifluorophenyl-, 2,4-dimethylphenyl-, 3-methylphenyl-, 3,4-dimethylphenyl-, 4-methylphenyl-, 4-isopropylphenyl-, 4-tert-butylphenyl-, 2,4,6-trimethylphenyl-, 2-isopropyl-6-methylphenyl-, 2-(trifluoromethyl)phenyl-, 4-(trifluoromethyl)phenyl-. 2,4-bis(trifluoromethyl)phenyl-, 3,5-bis(trifluoromethyl)phenyl-, 2-methoxyphenyl-, 2,4-dimethoxyphenyl-, 2,6-dimethoxyphenyl-, 3-methoxyphenyl-, 4-methoxyphenyl-, 4-ethoxyphenyl-, 4-propoxyphenyl-, 4-butoxyphenyl-, 4-pentoxyphenyl-, 4-isopropyloxyphenyl-, 3-(cyclopentyloxy)-4-methoxyphenyl-, 3,4,5-trimethoxyphenyl-, 3,4-dimethoxyphenyl-, 3,5-dimethoxyphenyl-, 4-tetrafluoroethyloxyphenyl, 4-cyanophenyl-, 4-thiomethylphenyl- and 4-dimethylaminophenyl. Alternatively, E may represent unsubstituted phenyl-. Further exemplary substituted phenyl groups include 2,3-difluoro-4-methylphenyl. 2-fluoro-5-(trifluoromethyl)phenyl-, 2-hydroxy-3-methoxyphenyl-, 2-hydroxy-5-

methylphenyl-, 3-fluoro-4-(trifluoromethyl)phenyl-, 3-fluoro-5-(trifluoromethyl)phenyl-, 2-fluoro-4-(trifluoromethyl)phenyl-, 2-fluoro-3-(methyl)phenyl-, 3-fluoro-4-(methoxy)phenyl-, 3-hydroxy-4-methoxyphenyl-, 4-chloro-3-(trifluoromethyl)phenyl-, 4-chloro-3-methylphenyl, 4-bromo-4-ethylphenyl, 2,3,5,6-tetrafluoro-4-(methyl)phenyl-, 2,6-difluoro-4-(methoxy)phenyl- and 2-fluoro-4,5-(dimethoxy)phenyl-.
(77) When E represents optionally substituted heteroaryl, examples include pyridinyl (e.g. pyridin-2-yl and pyridin-4-yl) and pyrimidinyl. Specific substituents that may be mentioned are one or more e.g. 1, 2 or 3 groups selected from halogen, hydroxyl, alkyl (e.g. methyl) and alkoxy- (e.g. methoxy-). An example substituted ring is 1-oxy-pyridin-4-yl-.
(78) In a more preferred embodiment, when A is a monocyclic heteroaryl, A is selected from
(79) ##STR00007##
(80) In a most preferred embodiment, when A is a monocyclic heteroaryl, A is
(81) ##STR00008##
(82) In a further a most preferred embodiment, when A is a monocyclic heteroaryl, A is
(83) ##STR00009##
(84) In yet a most preferred embodiment, when A is a monocyclic heteroaryl, A is
(85) ##STR00010##
(86) When A is a bicyclic heteroaryl, A is preferably selected from benzimidazole and imidazopyridine, such as imidazo[1,2-a]pyridine.
(87) In a more preferred embodiment, when A is a bicyclic heteroaryl, A is selected from
(88) ##STR00011##
(89) In a most preferred embodiment, when A is a bicyclic heteroaryl, A is
(90) ##STR00012##
(91) In a further a most preferred embodiment, when A is a bicyclic heteroaryl. A is
(92) ##STR00013##
(93) In yet a most preferred embodiment, when A is a bicyclic heteroaryl, A is
(94) ##STR00014##
(95) In a preferred embodiment, B is selected from C.sub.3-5-heteroalkyl, phenyl, C.sub.5-C.sub.6-heterocyclyl and C.sub.1-5 alkylene, wherein said C.sub.1-5 alkylene group may independently be substituted by alkyl.
(96) More preferably, B is selected from
(97) ##STR00015##
wherein X.sub.1 is alkyl, N, O or S, preferably methyl or S; and n is an integer selected from 1 and 2;
(98) ##STR00016##
wherein o is 0 or 1; and p is 0 or 1; and
(99) ##STR00017##
wherein R.sub.1 is hydrogen or alkyl and q is 0, 1 or 2.
(100) In a most preferred embodiment, B is
(101) ##STR00018##
wherein X.sub.1 and n are as defined above.
(102) In a further most preferred embodiment, B is
(103) ##STR00019##
wherein o is as defined above.
(104) In yet a most preferred embodiment, B is
(105) ##STR00020##
wherein R.sub.1 and p are as defined above.
(106) In a preferred embodiment, D is a group selected from
(107) ##STR00021##
wherein R is absent or is hydrogen; or R forms together with the nitrogen atom a heterocyclic ring

of group B; R.sub.2 is hydrogen, alkyl or cycloalkyl; Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are independently selected from CH, N, S and O.
(108) When D is
(109) ##STR00022##
R is preferably absent and R.sub.2 is preferably hydrogen or alkyl.
(110) When D is
(111) ##STR00023##
(112) R is preferably hydrogen.
(113) In a further embodiment, D is
(114) ##STR00024##
wherein R is hydrogen or alkyl.
(115) In a further preferred embodiment, when D is one of the above groups, R forms together with the nitrogen, to which it is attached, a heterocyclic ring of group B. More preferably, said heterocyclic ring, which is formed by the NR group, is selected from piperidine, pyrrolidine, tetrahydrofuran, morpholine, piperazine, dioxolane and dioxane. Most preferably, when D is one of the above groups, R forms together with the nitrogen, to which it is attached, a piperidine ring having the structure
(116) ##STR00025##
When D is
(117) ##STR00026##
(118) Y.sub.1 to Y.sub.4 are preferably CH or N.
(119) In a more preferred embodiment, all of Y.sub.1 to Y.sub.4 are CH.
(120) Even more preferably, one of Y.sub.1 to Y.sub.4 is N. and the other three are CH.
(121) In a further more preferred embodiment, two of Y.sub.1 to Y.sub.4 are N and the other two are CH.
(122) Yet more preferably, three of Y.sub.1, to Y.sub.4 are N and the other one is CH.
(123) Still more preferably, all of Y.sub.1 to Y.sub.4 are N.
(124) When Y.sub.4 is CH, Y.sub.4 may be substituted or unsubstituted.
(125) In a preferred embodiment, Y.sub.4 is CH and is unsubstituted.
(126) In another preferred embodiment, Y.sub.4 is CH and is substituted.
(127) When Y.sub.4 is CH and is substituted, Y.sub.4 is preferably substituted with halogen or alkyl, most preferably with fluorine or methyl.
(128) E is preferably
(129) ##STR00027##
wherein Y.sub.5 is C; Y.sub.6-Y.sub.10 are independently selected from CH, N or O, and R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 are independently selected from hydrogen, halogen, alkyl, O-alkyl.
(130) In a preferred embodiment, Y.sub.8-Y.sub.10 are independently selected from CH and N.
(131) In a preferred embodiment, R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 are independently selected from hydrogen, halogen and O-alkyl.
(132) In a further preferred embodiment, R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 are independently selected from O-phenyl and O-cycloalkyl.
(133) When R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 independently are halogen, R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 are preferably fluorine or chlorine, most preferably fluorine.
(134) When R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 independently are O-alkyl, R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 are O—C.sub.1-4alkyl, preferably methoxy, ethoxy, propoxy or butoxy, more preferably methoxy or propoxy.
(135) When R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 independently are O-alkyl, R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 are more most preferably methoxy.
(136) R.sub.3, R.sub.4, R.sub.5, R.sub.6, and R.sub.7 may independently be substituted or

unsubstituted. Preferably, up to three of R.sub.3-R.sub.7 are substituted and the other ones are hydrogen.
(137) In a most preferred embodiment, E represents a pyridine ring, wherein one of Y.sub.6-Y.sub.10 is N and the other ones are CH.
(138) In another most preferred embodiment, E represents a pyridine ring, wherein two of Y.sub.6-Y.sub.10 are N and the other ones are CH.
(139) Said pyrimidine ring may optionally be substituted with halo or alkyl, preferably fluorine and methoxy.
(140) In a specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (IIa) or formula (IIb):
(141) ##STR00028##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein Z is selected from CH and N; X.sub.1 is selected from alkyl, N, O, S, preferably from CH.sub.2 and S; n is 1 or 2; Y.sub.1 to Y.sub.4 and Y.sub.6 to Y.sub.10 are independently selected from CH, N, S and O, preferably from CH and N, Y.sub.5 is C; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(142) In a preferred embodiment, Z is CH.
(143) In another preferred embodiment, Z is N.
(144) Most preferably, X.sub.1 is CH.sub.2.
(145) Further most preferably, X.sub.1 is S.
(146) Most preferably, n is 1.
(147) Preferably, one, two, three or all four of Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are N.
(148) In more preferred embodiments, Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is N and Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.2 are N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is CH, Y.sub.2 is N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are N and Y.sub.2 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are CH and Y.sub.2 and Y.sub.4 are N; or Y.sub.1 and Y.sub.2 are CH and Y.sub.3 and Y.sub.4 are N; or Y.sub.1, Y.sub.2 and Y.sub.3 are CH and Y.sub.4 is N.
(149) Preferably one or two of Y.sub.6 to Y.sub.10 are N and the other of Y.sub.6 to Y.sub.10 are CH.
(150) In more preferred embodiments,
(151) Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N and Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7, Y.sub.8, Y.sub.9 are CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N, Y.sub.8 is CH, Y.sub.9 is N and Y.sub.10 is CH; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 is CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7 and Y.sub.8 are CH, Y.sub.9 is N and Y.sub.10 is CH; or R.sub.5 is preferably hydrogen, fluorine or methoxy.
(152) R.sub.6 is preferably hydrogen or methoxy.
(153) More preferably, R.sub.5 and R.sub.6 are both hydrogen; or R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(154) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (IIIa) or formula (IIIb):
(155) ##STR00029##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein X.sub.1 is selected from alkyl, N, O, S; n is 1 or 2; Y.sub.1 to Y.sub.4 and Y.sub.6 to

Y.sub.10 are independently selected from CH, N, S and O, preferably from CH and N, Y.sub.5 is C; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(156) Most preferably, X.sub.1 is CH.sub.2.
(157) Further most preferably, X.sub.1 is S.
(158) Most preferably, n is 1.
(159) Preferably, one, two, three or all four of Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are N.
(160) In more preferred embodiments, Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is N and Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.2 are N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is CH, Y.sub.2 is N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are N and Y.sub.2 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are CH and Y.sub.2 and Y.sub.4 are N; or Y.sub.1 and Y.sub.2 are CH and Y.sub.3 and Y.sub.4 are N; or Y.sub.1, Y.sub.2 and Y.sub.3 are CH and Y.sub.4 is N.
(161) Preferably one or two of Y.sub.6 to Y.sub.10 are N and the other of Y.sub.6 to Y.sub.10 are CH.
(162) In more preferred embodiments. Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N and Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7, Y.sub.8, Y.sub.9 are CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N, Y.sub.8 is CH, Y.sub.9 is N and Y.sub.10 is CH; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 is CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7 and Y.sub.8 are CH, Y.sub.9 is N and Y.sub.10 is CH; or R.sub.5 is preferably hydrogen, fluorine or methoxy.
(163) R6 is preferably hydrogen or methoxy.
(164) More preferably, R.sub.5 and R.sub.6 are both hydrogen; or R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(165) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (IVa) or formula (IVb):
(166) ##STR00030##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein Z is selected from CH and N; is 0 or 1; p is 0 or 1; Y.sub.1 to Y.sub.4 and Y.sub.6 to Y.sub.10 are independently selected from CH, N, S and O, preferably from CH and N, Y.sub.5 is C; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy. In a further embodiment, R.sub.5 is O-phenyl; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(167) In a preferred embodiment, Z is CH.
(168) In another preferred embodiment, Z is N.
(169) Most preferably, o is 0.
(170) Most preferably, p is 0.
(171) In a further most preferred embodiment, p is 1.
(172) Preferably, one, two, three or all four of Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are N.
(173) In more preferred embodiments, Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is N and Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.2 are N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is CH, Y.sub.2 is N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are N and Y.sub.2 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are CH and Y.sub.2 and Y.sub.4 are N; or Y.sub.1 and Y.sub.2 are CH and Y.sub.3 and Y.sub.4 are N; or Y.sub.1, Y.sub.2 and Y.sub.3 are CH and Y.sub.4 is N.
(174) Preferably one or two of Y.sub.6 to Y.sub.10 are N and the other of Y.sub.6 to Y.sub.10 are

CH.
(175) In more preferred embodiments, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N and Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7, Y.sub.8, Y.sub.9 are CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N, Y.sub.8 is CH, Y.sub.9 is N and Y.sub.10 is CH; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 is CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7 and Y.sub.8 are CH, Y.sub.9 is N and Y.sub.10 is CH; or R.sub.5 is preferably hydrogen, fluorine or methoxy.
(176) Further preferably, R.sub.5 is propoxy or O-phenyl.
(177) R.sub.6 is preferably hydrogen or methoxy.
(178) More preferably, R.sub.5 and R.sub.6 are both hydrogen; or R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 is methoxy and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy; or R.sub.5 is propoxy and R.sub.6 is hydrogen; or R.sub.5 is O-phenyl and R.sub.6 is hydrogen; or.
(179) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (Va) or formula (Vb):
(180) ##STR00031##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein o is 0 or 1; p is 0 or 1; Y.sub.1 to Y.sub.4 and Y.sub.6 to Y.sub.10 are independently selected from CH, N, S and O, preferably from CH and N, Y.sub.5 is C; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy. In a further embodiment, R.sub.5 is O-phenyl; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(181) In a preferred embodiment, Z is CH.
(182) In another preferred embodiment, Z is N.
(183) Most preferably, o is 0.
(184) Most preferably, p is 0.
(185) In a further most preferred embodiment, p is 1.
(186) Preferably, one, two, three or all four of Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are N.
(187) In more preferred embodiments, Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is N and Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.2 are N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is CH, Y.sub.2 is N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are N and Y.sub.2 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are CH and Y.sub.2 and Y.sub.4 are N; or Y.sub.1 and Y.sub.2 are CH and Y.sub.3 and Y.sub.4 are N; or Y.sub.1 and Y.sub.2 are CH; Y.sub.3 is N and Y.sub.4 is CH, or Y.sub.1, Y.sub.2 and Y.sub.3 are CH and Y.sub.4 is N.
(188) Preferably one or two of Y.sub.6 to Y.sub.10 are N and the other of Y.sub.6 to Y.sub.10 are CH.
(189) In more preferred embodiments. Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N and Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N and Ye, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7, Y.sub.8, Y.sub.9 are CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N, Y.sub.8 is CH, Y.sub.9 is N and Y.sub.10 is CH; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 is CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7 and Y.sub.8 are CH, Y.sub.9 is N and Y.sub.10 is CH; or R.sub.5 is preferably hydrogen, fluorine or methoxy.
(190) R.sub.6 is preferably hydrogen or methoxy.
(191) More preferably, R.sub.5 and R.sub.6 are both hydrogen; or R.sub.5 is fluorine and R.sub.6 is

hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(192) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (VI):
(193) ##STR00032##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein Z is selected from CH and N; X.sub.1 is selected from alkyl, N, O, S, preferably from CH.sub.2 or S; n is 1 or 2; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(194) In a preferred embodiment, Z is CH.
(195) In another preferred embodiment, Z is N.
(196) Most preferably, X.sub.1 is CH.sub.2.
(197) Further most preferably, X.sub.1 is S.
(198) Most preferably, n is 1.
(199) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(200) R.sub.6 is preferably hydrogen or methoxy.
(201) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(202) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (VII):
(203) ##STR00033##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein Z is selected from CH and N; X.sub.1 is selected from alkyl, N, O, S, preferably from CH.sub.2 or S; n is 1 or 2; R.sub.2 is selected from alkyl and cycloalkyl, preferably from methyl and cyclopropyl; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(204) In a preferred embodiment, Z is CH.
(205) In another preferred embodiment, Z is N.
(206) Most preferably, X.sub.1 is CH.sub.2.
(207) Further most preferably, X.sub.1 is S.
(208) Most preferably, n is 1.
(209) In a preferred embodiment, R.sub.2 is methyl.
(210) In a further preferred embodiment, R.sub.2 is cyclopropyl.
(211) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(212) R.sub.6 is preferably hydrogen or methoxy.
(213) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(214) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (VIII):
(215) ##STR00034##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein X.sub.1 is selected from alkyl, N, O, S, preferably from CH.sub.2 or S; n is 1 or 2; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(216) Most preferably, X.sub.1 is CH.sub.2.
(217) Further most preferably, X.sub.1 is S.

(218) Most preferably, n is 1.
(219) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(220) R.sub.6 is preferably hydrogen or methoxy.
(221) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(222) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (IX):
(223) ##STR00035##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein X.sub.1 is selected from alkyl, N, O, S, preferably from CH.sub.2 or S; n is 1 or 2; R.sub.2 is selected from alkyl and cycloalkyl, preferably from methyl and cyclopropyl; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(224) Most preferably, X.sub.1 is CH.sub.2.
(225) Further most preferably, X.sub.1 is S.
(226) Most preferably, n is 1.
(227) In a preferred embodiment, R.sub.2 is methyl.
(228) In a further preferred embodiment, R.sub.2 is cyclopropyl.
(229) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(230) R.sub.6 is preferably hydrogen or methoxy.
(231) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(232) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (X):
(233) ##STR00036##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein is 0 or 1; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(234) Most preferably, o is 0.
(235) Most preferably, p is 0.
(236) Even most preferably, p is 1.
(237) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(238) R.sub.6 is preferably hydrogen or methoxy.
(239) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(240) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XI):
(241) ##STR00037##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein o is 0 or 1; R.sub.2 is selected from alkyl and cycloalkyl, preferably from methyl and cyclopropyl; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(242) Most preferably, o is 0.
(243) Most preferably, p is 0.
(244) Even most preferably, p is 1.

(245) In a preferred embodiment, R.sub.2 is methyl.
(246) In a further preferred embodiment, R.sub.2 is cyclopropyl.
(247) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(248) R6 is preferably hydrogen or methoxy.
(249) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(250) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XIIa) or formula (XIIb):
(251) ##STR00038##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein Z is selected from CH and N; Y.sub.1 to Y.sub.4 and Y.sub.6 to Y.sub.10 are independently selected from CH, N, S and O, preferably from CH and N, Y.sub.5 is C; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(252) In a preferred embodiment, Z is CH.
(253) In another preferred embodiment, Z is N.
(254) Preferably, one, two, three or all four of Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are N.
(255) In more preferred embodiments, Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is N and Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.2 are N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is CH, Y.sub.2 is N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are N and Y.sub.2 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are CH and Y.sub.2 and Y.sub.4 are N; or Y.sub.1 and Y.sub.2 are CH and Y.sub.3 and Y.sub.4 are N; or Y.sub.1, Y.sub.2 and Y.sub.3 are CH and Y.sub.4 is N.
(256) Preferably one or two of Y.sub.6 to Y.sub.10 are N and the other of Y.sub.6 to Y.sub.10 are CH.
(257) In more preferred embodiments, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N and Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7, Y.sub.8, Y.sub.9 are CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N, Y.sub.8 is CH, Y.sub.9 is N and Y.sub.10 is CH; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 is CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7 and Y.sub.8 are CH, Y.sub.9 is N and Y.sub.10 is CH; or R.sub.5 is preferably hydrogen, fluorine or methoxy.
(258) R.sub.6 is preferably hydrogen or methoxy.
(259) More preferably, R.sub.5 and R.sub.6 are both hydrogen; or R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(260) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XIII):
(261) ##STR00039##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein Z is selected from CH and N; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(262) In a preferred embodiment, Z is CH.
(263) In another preferred embodiment, Z is N.
(264) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(265) R.sub.6 is preferably hydrogen or methoxy.
(266) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both

methoxy.
(267) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XIV):
(268) ##STR00040##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(269) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(270) R.sub.6 is preferably hydrogen or methoxy.
(271) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(272) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XVa) or formula (XVb):
(273) ##STR00041##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein Y.sub.1 to Y.sub.4 and Y.sub.6 to Y.sub.10 are independently selected from CH, N, S and O, preferably from CH and N, Y.sub.5 is C; R.sub.5 is selected from halogen, alkyl, O-alkyl, O-phenyl and O-cycloalkyl, preferably from halogen, O—C.sub.1-4alkyl, O-phenyl and O-cycloalkyl. In a more preferred embodiment, R.sub.5 is fluorine or chlorine, most preferably fluorine. In another more preferred embodiment, R.sub.5 is O—C.sub.1-4alkyl, such as methoxy, ethoxy, propoxy or butoxy, most preferably methoxy, propoxy or propan-2-yloxy. In another more preferred embodiment, R.sub.5 is O-phenyl. In another more preferred embodiment, R.sub.5 is O-cycloalkyl, most preferably O-cyclohexyl. R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(274) Preferably, one, two, three or all four of Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are N.
(275) In more preferred embodiments, Y.sub.1, Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is N and Y.sub.2, Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.2 are N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 is CH, Y.sub.2 is N and Y.sub.3 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are N and Y.sub.2 and Y.sub.4 are CH; or Y.sub.1 and Y.sub.3 are CH and Y.sub.2 and Y.sub.4 are N; or Y.sub.1 and Y.sub.2 are CH and Y.sub.3 and Y.sub.4 are N; or Y.sub.1 is N, Y.sub.2 and Y.sub.3 are CH and Y.sub.4 is N; or Y.sub.1, Y.sub.2 and Y.sub.3 are CH and Y.sub.4 is N.
(276) When Y.sub.4 is CH, Y.sub.4 may be substituted or unsubstituted.
(277) In a preferred embodiment, Y.sub.4 is CH and is unsubstituted.
(278) In another preferred embodiment, Y.sub.4 is CH and is substituted.
(279) When Y.sub.4 is CH and is substituted. Y.sub.4 is preferably substituted with halogen or alkyl, most preferably with fluorine or methyl.
(280) Preferably one or two of Y.sub.6 to Y.sub.10 are N and the other of Y.sub.6 to Y.sub.10 are CH.
(281) In more preferred embodiments, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N and Y.sub.7, Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7, Y.sub.8, Y.sub.9 are CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are N and Y.sub.8, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is CH, Y.sub.7 is N, Y.sub.8 is CH, Y.sub.9 is N and Y.sub.10 is CH; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 is CH and Y.sub.10 is N; or Y.sub.6 and Y.sub.7 are CH, Y.sub.8 is N, Y.sub.9 and Y.sub.10 are CH; or Y.sub.6 is N, Y.sub.7 and Y.sub.8 are CH, Y.sub.9 is N and Y.sub.10 is CH; or R.sub.5 is preferably hydrogen, fluorine or methoxy.
(282) R.sub.6 is preferably hydrogen or methoxy.

(283) More preferably, R.sub.5 and R.sub.6 are both hydrogen; or R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(284) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XVI):
(285) ##STR00042##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(286) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(287) R6 is preferably hydrogen or methoxy.
(288) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(289) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XVII):
(290) ##STR00043##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein R.sub.2 is selected from alkyl and cycloalkyl, preferably from methyl and cyclopropyl; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(291) In a preferred embodiment, R.sub.2 is methyl.
(292) In a further preferred embodiment, R.sub.2 is cyclopropyl.
(293) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(294) R6 is preferably hydrogen or methoxy.
(295) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(296) In a further specifically preferred embodiment, there is provided a compound of formula (I), which is a compound of formula (XVIII):
(297) ##STR00044##
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof,
wherein X.sub.1 is selected from alkyl, N, O, S, preferably from CH.sub.2 or S; n is 1 or 2; R.sub.5 is selected from halogen, alkyl and O-alkyl, preferably from fluorine and methoxy; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl, preferably from hydrogen and methoxy.
(298) Most preferably, X.sub.1 is CH.sub.2.
(299) Further most preferably, X.sub.1 is S.
(300) Most preferably, n is 1.
(301) R.sub.5 is preferably hydrogen, fluorine or methoxy.
(302) R.sub.6 is preferably hydrogen or methoxy.
(303) More preferably, R.sub.5 is fluorine and R.sub.6 is hydrogen; or R.sub.5 and R.sub.6 are both methoxy.
(304) In one embodiment, the compound of formula (I) is a compound according to any one of examples 1 to 1323 or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers.
(305) In a preferred embodiment, the compound of formula (I) is a compound selected from: 5-[3-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)propyl]-1,3,4-thiadiazol-2-amine; 5-{[2-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)ethyl]sulfanyl}-1,3,4-thiadiazol-2-amine; 5-{[2-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl)amino)ethyl]sulfanyl}-1,3,4-thiadiazol-2-amine; 4′-fluoro-N-[3-(4-methyl-4H-

1,2,4-triazol-3-yl)propyl]-[1,1′-biphenyl]-2-amine; 3′,4′-dimethoxy-N-[3-(4-methyl-4H-1,2,4-triazol-3-yl)propyl]-[1,1′-biphenyl]-2-amine; 5-[4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)phenyl]-1,3,4-thiadiazol-2-amine; 5-(4-{[2-(3,4-dimethoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-amine; 5-(4-{[2-(4-methoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-amine; N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-methoxyphenyl)pyridin-2-amine; N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-methoxyphenyl)pyridin-4-amine; N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(3,4-dimethoxyphenyl)pyridin-4-amine; N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-fluorophenyl)pyridin-2-amine; N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-fluorophenyl)pyrazin-2-amine; 5-(4-{[2-(4-phenoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-amine; 5-(4-{[2-(4-propoxyphenyl)phenyl]amino)phenyl)-1,3,4-thiadiazol-2-amine; 5-[4-({2-[4-(propan-2-yloxy)phenyl]phenyl}amino)phenyl]-1,3,4-thiadiazol-2-amine; 4′-fluoro-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]-[1,1′-biphenyl]-2-amine; 3′,4′-dimethoxy-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]-[1,1′-biphenyl]-2-amine; N-[2-(4-methoxyphenyl)phenyl]-4-(4-methyl-4H-1,2,4-triazol-3-yl)aniline: 2-(4-methoxyphenyl)-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]pyridin-3-amine; 2-(4-fluorophenyl)-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]pyridin-3-amine; 4-(4-methyl-4H-1,2,4-triazol-3-yl)-N-[2-(4-phenoxyphenyl)phenyl]aniline; 3-(3,4-dimethoxyphenyl)-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]pyridin-4-amine; N-[3-(5-amino-1,3,4-thiadiazol-2-yl)propyl]-4-fluorobenzene-1-sulfonamide; N-{2-[(5-amino-1,3,4-thiadiazol-2-yl)sulfanyl]ethyl}-4-fluorobenzene-1-sulfonamide; 5-(3-{[(4-fluorophenyl)(methyl)oxo-λω-sulfanylidene]amino}propyl)-1,3,4-thiadiazol-2-amine; 4-fluoro-N-[3-(4-methyl-4H-1,2,4-triazol-3-yl)propyl]benzene-1-sulfonamide; 4-fluoro-N-{2-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]ethyl}benzene-1-sulfonamide; [(3,4-dimethoxyphenyl)sulfamoyl]({2-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]ethyl})amine; N-[4-(2-amino-1,3-thiazol-5-yl)phenyl]-4-fluorobenzene-1-sulfonamide; N-[4-(2-amino-1,3-thiazol-5-yl)phenyl]-3,4-dimethoxybenzene-1-sulfonamide; 5-(1-{4′-fluoro-[1,1′-biphenyl]-2-yl}piperidin-4-yl)-1,3,4-thiadiazol-2-amine; 5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3-thiazol-2-amine; 5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3,4-thiadiazol-2-amine; 1-(4-fluorobenzenesulfonyl)-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine; N-[(1H-1,3-benzodiazol-5-yl)methyl]-4′-fluoro-[1,1′-biphenyl]-2-amine; N-[(1H-1,3-benzodiazol-5-yl)methyl]-3′,4′-dimethoxy-[1,1′-biphenyl]-2-amine: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)pyridin-3-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyridin-4-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-4-(4-methoxyphenyl)pyridin-3-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-5-(4-methoxyphenyl)pyrimidin-4-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-4-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-fluorophenyl)pyridin-3-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-fluorophenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-fluorophenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-phenoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(cyclohexyloxy)phenyl]aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-propoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(propan-2-yloxy)phenyl]aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)-3-methylaniline: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-methylaniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-chlorophenyl)-3-fluoroaniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-fluoroaniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-fluoro-2-(4-fluorophenyl)aniline; N-[(1H-1,3-benzodiazol-5-yl)methyl]-4-fluorobenzene-1-sulfonamide; and [(1H-1,3-benzodiazol-5-yl)methyl][(4-

fluorophenyl)(methyl)oxo-λω-sulfanylidene]amine;
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers.

(306) In a more preferred embodiment, the compound of formula (I) is a compound selected from: 5-(1-{4′-fluoro-[1,1′-biphenyl]-2-yl}piperidin-4-yl)-1,3,4-thiadiazol-2-amine; N-[(1H-1,3-benzodiazol-5-yl)methyl]-4′-fluoro-[1,1′-biphenyl]-2-amine; N-[(1H-1,3-benzodiazol-5-yl)methyl]-3′,4′-dimethoxy-[1,1′-biphenyl]-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)pyridin-3-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyridin-4-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-4-(4-methoxyphenyl)pyridin-3-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-5-(4-methoxyphenyl)pyrimidin-4-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-4-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyrazin-2-amine: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-fluorophenyl)pyridin-3-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-fluorophenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-fluorophenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-phenoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(cyclohexyloxy)phenyl]aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-propoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(propan-2-yloxy)phenyl]aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)-3-methylaniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-methylaniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-chlorophenyl)-3-fluoroaniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-fluoroaniline: N-(1H-1,3-benzodiazol-5-ylmethyl)-3-fluoro-2-(4-fluorophenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)-3-methylaniline: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-methylaniline; and N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-fluoroaniline;
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers.

(307) In an evenly preferred embodiment, the compound of formula (I) is a compound selected from: 5-(1-{4′-fluoro-[1,1′-biphenyl]-2-yl}piperidin-4-yl)-1,3,4-thiadiazol-2-amine; N-[(1H-1,3-benzodiazol-5-yl)methyl]-4′-fluoro-[1,1′-biphenyl]-2-amine: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-4-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-phenoxyphenyl)aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(cyclohexyloxy)phenyl]aniline: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(propan-2-yloxy)phenyl]aniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)-3-methylaniline: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-methylaniline; and N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-fluoroaniline;
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers.

(308) In a most preferred embodiment, the compound of formula (I) is a compound selected from: N-[(1H-1,3-benzodiazol-5-yl)methyl]-4′-fluoro-[1,1′-biphenyl]-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyrazin-2-amine; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)-3-methylaniline; N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-methylaniline; and

N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-fluoroaniline;
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers.
(309) In a further most preferred embodiment, the compound of formula (I) is: 5-(1-{4′-fluoro-[1,1′-biphenyl]-2-yl}piperidin-4-yl)-1,3,4-thiadiazol-2-amine;
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers.
(310) In a further most preferred embodiment, the compound of formula (I) is: N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-fluoroaniline;
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers.
Synthesis Methods
(311) The compounds of formula (I) of the present invention can be prepared by a method selected from synthesis methods A to R as described in the example section below. The invention thus further relates to synthesis methods A, B, C, D, E, F, G, H, I, K, L, M, N, O, P. Q and R.
(312) In a preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method A.
(313) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method B.
(314) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method C.
(315) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method D.
(316) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method E.
(317) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method F.
(318) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method G.
(319) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method H.
(320) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method 1.
(321) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method K.
(322) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method L.
(323) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method M.
(324) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method N.
(325) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method O.
(326) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method P.
(327) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method Q.
(328) In a further preferred embodiment, the compounds of formula (I) of the present invention are prepared according to synthesis method R.
(329) Therapeutic Uses

(330) Physiological substrates of QC (EC) in mammals are, e.g. amyloid beta-peptides (3-40), (3-42), (11-40 and (11-42), ABri, ADan, Gastrin, Neurotensin, FPP, CCL 2, CCL 7, CCL 8, CCL 16. CCL 18, Fractalkine, Orexin A, [Gln.sup.3]-glucagon(3-29), [Gln.sup.5]-substance P(5-11) and the peptide QYNAD. For further details see table 1. The compounds and/or combinations according to the present invention and pharmaceutical compositions comprising at least one inhibitor of QC (EC) are useful for the treatment of conditions that can be treated by modulation of QC activity.

(331) TABLE-US-00002 TABLE 1 Amino acid sequences of physiological active peptides with an N-terminal glutamine residue, which are prone to be cyclized to final pGlu Peptide Amino acid sequence Function Abeta(1-42) Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala Plays a role in neurodegeneration, e.g. in Alzheimer's Disease, Familial British Dementia, Familial Danish Dementia, Down Syndrome Abeta(1-40) Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val Plays a role in neurodegeneration, e.g. in Alzheimer's Disease, Familial British Dementia, Familial Danish Dementia, Down Syndrome Abeta(3-42) Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala Plays a role in neurodegeneration, e.g. in Alzheimer's Disease, Familial British Dementia, Familial Danish Dementia, Down Syndrome Abeta(3-40) Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val Plays a role in neurodegeneration, e.g. in Alzheimer's Disease, Familial British Dementia, Familial Danish Dementia, Down Syndrome Abeta(11-42) Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala Plays a role in neurodegeneration, e.g. in Alzheimer's Disease, Familial British Dementia, Familial Danish Dementia, Down Syndrome Abeta(11-40) Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val Plays a role in neurodegeneration, e.g. in Alzheimer's Disease, Familial British Dementia, Familial Danish Dementia, Down Syndrome ABri EASNCFAIRHFENKFAV Pyroglutamated form plays a role in Familial British Dementia ETLIC SRTVKKNIIEEN ADan EASNCFAIRHFENKFAV Pyroglutamated form plays a role in Familial Danish Dementia ETLIC FNLFLNSQEKHY Gastrin 17 QGPWLEEEEEAYGWMDF (amide) Gastrin stimulates the stomach mucosa to produce and secrete hydrochloric acid and the pancreas to secrete its digestive enzymes it siso stimulates smooth muscie contraction and increases blood circulation and water secretion in the stomach and intestine. Swiss-Prot: P01350 Neurotensin QLYENKPRRPYIL Neurotensin plays an endocrine or paracrine role in the regulation of fat metabolism, it causes contraction of smooth muscle. Swiss-Prot: P30990 FPP QEP amide A tripeptide related to thyrotrophin releasing hormone (TRH), is found in seminal plasma. Recent evidence obtained in vitro and in vivo showed that FPP plays an important role in regulating sperm fertility. TRH QHP amide TRH functions as a regulator of the biosynthesis of TSH in the anterior pituitary gland and as a neurotransmitter/neuromodulator in the central and peripheral nervous systems. Swiss-Prot: P20396 GnRH QHWSYGLRP(G) amide Stimulates the secretion of gonadotropins; it stimulates the secretion of both luteinizing and follicle-stimulating hormones. Swiss-Prot: P01148 CCL16 (small cytokine A16) QPKVPEWVNTPSTCCLKYYEKVLPRRLVVGYRKALNC HLPAIIFVTKRNREVCTNPN Shows chemotactic activity for lymphocytes and monocytes but not neutrophils. Aiso shows DDWVQEYIKD Swiss-Prot:

PNLPLLPTRN potent myelosuppressive 015467 LSTVKIITAK NGQPQLLNSQ activity, suppresses proliferation of myeloid progenitor cells. Recombinant SCYA16 shows chemotactic activity for monocytes and THP-1 monocytes, but not for resting lymphocytes and neutrophils, induces a calcium flux in THP-1 cells that were desensitized by prior expression to RANTES. CCL8 (small QPDSVSI PITCCFNVIN Chemotactic factor that attracts inducible RKIPIQRLES YTRITNIQCP monocytes, lymphocytes, Cytokine A8) KEAViFKTKR GKEVCADPKE basophils and eosinophils. May Swiss-Prot: RWVRDSMKHL DQIFQNLKP play a role in neopiasia and P80075 inflammatory host responses. This protein can bind heparin. CCL2 QPDAINA PVTCCYNFTN Chemotactic factor that attracts (MCP-1, small RKISVQRLAS YRRITSSKCP monocytes and basophils but inducible KEAVIFKTIV AKEICADPKQ not neutrophils or eosinophils. cytokine A2) KWVQDSMDHL DKQTQTPKT Augments monocyte anti-tumor Swiss-Prot: activity Has been implicated in P13500 the pathogenesis of diseases characterized by monocytic infiltrates, like psoriasis, rheumatoid arthritis or atherosclerosis. May be involved in the recruitment of monocytes into the arterial wall during the disease process of atherosclerosis. Binds to CCR2 and CCR4. CCL18 (small QVGTNKELC CLVYTSWQIP Chemotactic factor that attracts inducible QKFIVDYSET SPQCPKPGVI lymphocytes but not monocytes Cytokine A18) LLTKRGRQIC ADPNKKWVQK or granulocytes. May be Swiss-Prot: YISDLKLNA involved in B cell migration into P55774 B cell foliicles in lymph nodes. Attracts naive T lymphocytes toward dendritic cells and activated macrophages in lymph nodes, has chemotactic activity for naive T cells, CD4+ and CD8+ T cells and thus may play a role in both humoral and cell-mediated immunity responses. Fractalkine QHHGVT KCNITCSKMT The soluble form is chemotactic (neurotactin) SKIPVALLIH YQQNQASCGK for T celis and monocytes, but Swiss-Prot: RAIILETRQH RLFCADPKEQ not for neutrophils. The P78423 WVKDAMQHLD RQAAALTRNG membrane-bound form GTFEKQIGEV KPRTTPAAGG promotes adhesion of those MDESVVLEPE ATGESSSLEP leukocytes to endothelial cells. TPSSQEAQRA LGTSPELPTG May play a role in regulating VTGSSGTRLP PTPKAQDGGP leukocyte adhesion and VGTELFRVPP VSTAATWQSS migration processes at the APHQPGPSLW AEAKTSEAPS endothelium binds to CX3CR1. TQDPSTQAST ASSPAPEENA PSEGQRVWGQ GQSPRPENSL EREEMGPVPA HTDAFQDWGP GSMAHVSVVP VSSEGTPSRE PVASGSWTPK AEEPIHATMD PGRLGVLITP VPDAGAATRR QAVGLLAFLG LLFCLGVAMF TYQSLQGCPR KMAGEMAEGL RYIPRSCGSN SYVLVPV CCL7 (small QPVGINT STTCCYRFIN Chemotactic factor that attracts inducible KKIPKQRLES YRRTTSSHCP monocytes and eosinophils, but cytokine A7) REAVIFKTKL DKEICADPTQ not neutrophils. Augments Swiss-Prot: KWVQDFMKHL DKKTQTPKL monocyte anti-tumor activity. P80098 Also induces the release of gelatinase B. This protein can bind heparin. Binds to CCR1, CCR2 and CCR3. Orexin A QPLPDCCRQK TCSCRLYELL Neuropeptide that plays a (Hypocretin-1) HGAGNHAAGI LTL significant role in the regulation Swiss-Prot of food intake and sleep- 043612 wakefulness, possibly by coordinating the complex behavioral and physiologic responses of these complementary homeostatic functions. It plays also a broader role in the homeostatic regulation of energy metabolism, autonomic function, hormonal balance and the regulation of body fluids. Orexin-A binds to both OX1R and OX2R with a high affinity. Substance P RPK PQQFFGLM Belongs to the tachykinins. Tachykinins are active peptides which excite neurons, evoke behavioral responses, are potent vasodilators and secretagogues. and contract (directly or indirectly) many smooth muscles. QYNAD Gln-Tyr-Asn-Ala-Asp Acts on voltage-gated sodium channels.

(332) Glutamate is found in positions 3, 11 and 22 of the amyloid fi-peptide. Among them the mutation from glutamic acid (E) to glutamine (0) in position 22 (corresponding to amyloid precursor protein APP 693, Swissprot P05067) has been described as the so called Dutch type cerebroarterial amyloidosis mutation.
(333) The β-amyloid peptides with a pyroglutamic acid residue in position 3, 11 and/or 22 have been described to be more cytotoxic and hydrophobic than the amyloid β-peptides 1-40(42/43) (Saido T. C. 2000 Medical Hypotheses 54(3): 427-429).
(334) The multiple N-terminal variations, e.g. Abeta(3-40), Abeta(3-42), Abeta(11-40) and Abeta (11-42) can be generated by the β-secretase enzyme β-site amyloid precursor protein-cleaving enzyme (BACE) at different sites (Huse J. T. et al. 2002 J. Biol. Chem. 277 (18): 16278-16284), and/or by aminopeptidase or dipeptidylaminopeptidase processing from the full length peptides Abeta(1-40) and Abeta(1-42). In all cases, cyclization of the then N-terminal occurring glutamic acid residue is catalyzed by QC.
(335) Transepithelial transducing cells, particularly the gastrin (G) cell, co-ordinate gastric acid secretion with the arrival of food in the stomach. Recent work showed that multiple active products are generated from the gastrin precursor, and that there are multiple control points in gastrin biosynthesis. Biosynthetic precursors and intermediates (progastrin and Gly-gastrins) are putative growth factors; their products, the amidated gastrins, regulate epithelial cell proliferation, the differentiation of acid-producing parietal cells and histamine-secreting enterochromaffin-like (ECL) cells, and the expression of genes associated with histamine synthesis and storage in ECL cells, as well as acutely stimulating acid secretion. Gastrin also stimulates the production of members of the epidermal growth factor (EGF) family, which in turn inhibit parietal cell function but stimulate the growth of surface epithelial cells. Plasma gastrin concentrations are elevated in subjects with *Helicobacter pylori*, who are known to have increased risk of duodenal ulcer disease and gastric cancer (Dockray, G. J. 1999 J Physiol 15 315-324).
(336) The peptide hormone gastrin, released from antral G cells, is known to stimulate the synthesis and release of histamine from ECL cells in the oxyntic mucosa via CCK-2 receptors. The mobilized histamine induces acid secretion by binding to the H(2) receptors located on parietal cells. Recent studies suggest that gastrin, in both its fully amidated and less processed forms (progastrin and glycine-extended gastrin), is also a growth factor for the gastrointestinal tract. It has been established that the major trophic effect of amidated gastrin is for the oxyntic mucosa of stomach, where it causes increased proliferation of gastric stem cells and ECL cells, resulting in increased parietal and ECL cell mass. On the other hand, the major trophic target of the less processed gastrin (e.g. glycine-extended gastrin) appears to be the colonic mucosa (Koh, T. J. and Chen, D. 2000 Regul Pept 9337-44).
(337) Neurotensin (NT) is a neuropeptide implicated in the pathophysiology of schizophrenia that specifically modulates neurotransmitter systems previously demonstrated to be misregulated in this disorder. Clinical studies in which cerebrospinal fluid (CSF) NT concentrations have been measured revealed a subset of schizophrenic patients with decreased CSF NT concentrations that are restored by effective antipsychotic drug treatment. Considerable evidence also exists concordant with the involvement of NT systems in the mechanism of action of antipsychotic drugs. The behavioral and biochemical effects of centrally administered NT remarkably resemble those of systemically administered antipsychotic drugs, and antipsychotic drugs increase NT neurotransmission. This concatenation of findings led to the hypothesis that NT functions as an endogenous antipsychotic. Moreover, typical and atypical antipsychotic drugs differentially alter NT neurotransmission in nigrostriatal and mesolimbic dopamine terminal regions, and these effects are predictive of side effect liability and efficacy, respectively (Binder, E. B. et al. 2001 Biol Psychiatry 50 856-872).
(338) Fertilization promoting peptide (FPP), a tripeptide related to thyrotrophin releasing hormone (TRH), is found in seminal plasma. Recent evidence obtained in vitro and in vivo showed that FPP

plays an important role in regulating sperm fertility. Specifically, FPP initially stimulates nonfertilizing (uncapacitated) spermatozoa to “switch on” and become fertile more quickly, but then arrests capacitation so that spermatozoa do not undergo spontaneous acrosome loss and therefore do not lose fertilizing potential. These responses are mimicked, and indeed augmented, by adenosine, known to regulate the adenylyl cyclase (AC)/cAMP signal transduction pathway. Both FPP and adenosine have been shown to stimulate cAMP production in uncapacitated cells but inhibit it in capacitated cells, with FPP receptors somehow interacting with adenosine receptors and G proteins to achieve regulation of AC. These events affect the tyrosine phosphorylation state of various proteins, some being important in the initial “switching on”, others possibly being involved in the acrosome reaction itself. Calcitonin and angiotensin II, also found in seminal plasma, have similar effects in vitro on uncapacitated spermatozoa and can augment responses to FPP. These molecules have similar effects in vivo, affecting fertility by stimulating and then maintaining fertilizing potential. Either reductions in the availability of FPP, adenosine, calcitonin, and angiotensin II or defects in their receptors contribute to male infertility (Fraser. L. R. and Adeoya-Osiguwa. S. A. 2001 Vitam Horm 63, 1-28).

(339) CCL2 (MCP-1), CCL7, CCL8, CCL16, CCL18 and fractalkine play an important role in pathophysiological conditions, such as suppression of proliferation of myeloid progenitor cells, neoplasia, inflammatory host responses, cancer, psoriasis, rheumatoid arthritis, atherosclerosis, vasculitis, humoral and cell-mediated immunity responses, leukocyte adhesion and migration processes at the endothelium, inflammatory bowel disease, restenosis, pulmonary fibrosis, pulmonary hypertention, liver fibrosis, liver cirrhosis, nephrosclerosis, ventricular remodeling, heart failure, arteriopathy after organ transplantations and failure of vein grafts.

(340) A number of studies have underlined in particular the crucial role of MCP-1 for the development of atherosclerosis (Gu, L., et al., (1998) *Mol. Cell* 2, 275-281; Gosling, J., et al., (1999) *J Clin. Invest* 103, 773-778); rheumatoid arthritis (Gong, J. H., et al., (1997) *J Exp. Med* 186, 131-137; Ogata, H., et al., (1997) *J Pathol.* 182, 106-114); pancreatitis (Bhatia. M., et al., (2005) *Am. J Physiol Gastrointest. Liver Physiol* 288, G1259-G1265); Alzheimer's disease (Yamamoto, M., et al., (2005) *Am. J Pathol.* 166, 1475-1485); lung fibrosis (Inoshima, I., et al., (2004) *Am. J Physiol Lung Cell Mol. Physiol* 286, L1038-L1044); renal fibrosis (Wada. T., et al., (2004) *J Am. Soc. Nephrol.* 15, 940-948), and graft rejection (Saiura, A., et al., (2004) *Arterioscler. Thromb. Vasc. Biol.* 24, 1886-1890). Furthermore, MCP-1 might also play a role in gestosis (Katabuchi, H., et al., (2003) *Med Electron Microsc.* 36, 253-262), as a paracrine factor in tumor development (Ohta, M., et al., (2003) *Int. J Oncol.* 22, 773-778; Li, S., et al., (2005) *J Exp. Med* 202, 617-624), neuropathic pain (White, F. A., et al., (2005) *Proc. Natl. Acad. Sci. U.S.A*) and AIDS (Park, I. W., Wang, J. F., and Groopman, J. E. (2001) *Blood* 97, 352-358; Coll, B., et al., (2006) *Cytokine* 34, 51-55).

(341) MCP-1 levels are increased in CSF of AD patients and patients showing mild cognitive impairment (MCI) (Galimberti, D., et al., (2006) *Arch. Neurol.* 63, 538-543). Furthermore. MCP-1 shows an increased level in serum of patients with MCI and early AD (Clerici, F., et al., (2006) *Neurobiol. Aging* 27, 1763-1768).

(342) Several cytotoxic T lymphocyte peptide-based vaccines against hepatitis B, human immunodeficiency virus and melanoma were recently studied in clinical trials. One interesting melanoma vaccine candidate alone or in combination with other tumor antigens, is the decapeptide ELA. This peptide is a Melan-A/MART-1 antigen immunodominant peptide analog, with an N-terminal glutamic acid. It has been reported that the amino group and gamma-carboxylic group of glutamic acids, as well as the amino group and gamma-carboxamide group of glutamines, condense easily to form pyroglutamic derivatives. To overcome this stability problem, several peptides of pharmaceutical interest have been developed with a pyroglutamic acid instead of N-terminal glutamine or glutamic acid, without loss of pharmacological properties. Unfortunately compared with ELA, the pyroglutamic acid derivative (PyrELA) and also the N-terminal acetyl-capped

derivative (AcELA) failed to elicit cytotoxic T lymphocyte (CTL) activity. Despite the apparent minor modifications introduced in PyrELA and AcELA, these two derivatives probably have lower affinity than ELA for the specific class I major histocompatibility complex. Consequently, in order to conserve full activity of ELA, the formation of PyrELA must be avoided (Beck A. et al. 2001, J Pept Res 57(6):528-38.).

(343) Orexin A is a neuropeptide that plays a significant role in the regulation of food intake and sleep-wakefulness, possibly by coordinating the complex behavioral and physiologic responses of these complementary homeostatic functions. It plays also a role in the homeostatic regulation of energy metabolism, autonomic function, hormonal balance and the regulation of body fluids.

(344) Recently, increased levels of the pentapeptide QYNAD were identified in the cerebrospinal fluid (CSF) of patients suffering from multiple sclerosis or Guillain-Barré syndrome compared to healthy individuals (Brinkmeier H. et al. 2000, Nature Medicine 6, 808-811). There is a big controversy in the literature about the mechanism of action of the pentapeptide Gin-Tyr-Asn-Ala-Asp (QYNAD), especially its efficacy to interact with and block sodium channels resulting in the promotion of axonal dysfunction, which are involved in inflammatory autoimmune diseases of the central nervous system. But recently, it could be demonstrated that not QYNAD, but its cyclized, pyroglutamated form, pEYNAD, is the active form, which blocks sodium channels resulting in the promotion of axonal dysfunction. Sodium channels are expressed at high density in myelinated axons and play an obligatory role in conducting action potentials along axons within the mammalian brain and spinal cord. Therefore, it is speculated that they are involved in several aspects of the pathophysiology of inflammatory autoimmune diseases, especially multiple sclerosis, the Guillain-Barré syndrome and chronic inflammatory demyelinizing polyradiculoneuropathy.

(345) Furthermore. QYNAD is a substrate of the enzyme glutaminyl cyclase (QC, EC 2.3.2.5), which is also present in the brain of mammals, especially in human brain. Glutaminyl cyclase catalyzes effectively the formation of pEYNAD from its precursor QYNAD.

(346) Accordingly, the present invention provides the use of the compounds of formula (I) for the preparation of a medicament for the prevention or alleviation or treatment of a disease selected from the group consisting of mild cognitive impairment, Alzheimer's disease, Familial British Dementia, Familial Danish Dementia, neurodegeneration in Down Syndrome, Huntington's disease, Kennedy's disease, ulcer disease, duodenal cancer with or w/o *Helicobacter pylori* infections, colorectal cancer, Zolliger-Ellison syndrome, gastric cancer with or without *Helicobacter pylori* infections, pathogenic psychotic conditions, schizophrenia, infertility, neoplasia, inflammatory host responses, cancer, malign metastasis, melanoma, psoriasis, rheumatoid arthritis, atherosclerosis, pancreatitis, restenosis, impaired humoral and cell-mediated immune responses, leukocyte adhesion and migration processes in the endothelium, impaired food intake, impaired sleep-wakefulness, impaired homeostatic regulation of energy metabolism, impaired autonomic function, impaired hormonal balance or impaired regulation of body fluids, multiple sclerosis, the Guillain-Barré syndrome and chronic inflammatory demyelinizing polyradiculoneuropathy.

(347) Furthermore, by administration of a compound according to the present invention to a mammal it can be possible to stimulate the proliferation of myeloid progenitor cells.

(348) In addition, the administration of a QC inhibitor according to the present invention can lead to suppression of male fertility.

(349) In a preferred embodiment, the present invention provides the use of inhibitors of QC (EC) activity in combination with other agents, especially for the treatment of neuronal diseases, artherosclerosis and multiple sclerosis.

(350) The present invention also provides a method of treatment of the aforementioned diseases comprising the administration of a therapeutically active amount of at least one compound of formula (I) to a mammal, preferably a human.

(351) Most preferably, said method and corresponding uses are for the treatment of a disease selected from the group consisting of mild cognitive impairment, Alzheimer's disease, Familial British Dementia, Familial Danish Dementia, neurodegeneration in Down Syndrome, Parkinson's disease and Chorea Huntington, comprising the administration of a therapeutically active amount of at least one compound of formula (I) to a mammal, preferably a human.
(352) Even preferably, the present invention provides a method of treatment and corresponding uses for the treatment of rheumatoid arthritis, atherosclerosis, pancreatitis and restenosis.
(353) Pharmaceutical Combinations
(354) In a preferred embodiment, the present invention provides a composition, preferably a pharmaceutical composition, comprising at least one QC inhibitor optionally in combination with at least one other agent selected from the group consisting of nootropic agents, neuroprotectants, antiparkinsonian drugs, amyloid protein deposition inhibitors, beta amyloid synthesis inhibitors, antidepressants, anxiolytic drugs, antipsychotic drugs and anti-multiple sclerosis drugs.
(355) Most preferably, said QC inhibitor is a compound of formula (I) of the present invention.
(356) More specifically, the aforementioned other agent is selected from the group consisting of beta-amyloid antibodies, vaccines, cysteine protease inhibitors, PEP-inhibitors, LiCl, acetylcholinesterase (AChE) inhibitors, PIMT enhancers, inhibitors of beta secretases, inhibitors of gamma secretases, inhibitors of aminopeptidases, preferably inhibitors of dipeptidyl peptidases, most preferably DP IV inhibitors; inhibitors of neutral endopeptidase, inhibitors of Phosphodiesterase-4 (PDE-4), TNFalpha inhibitors, muscarinic M1 receptor antagonists, NMDA receptor antagonists, sigma-1 receptor inhibitors, histamine H3 antagonists, immunomodulatory agents, immunosuppressive agents, MCP-1 antagonists or an agent selected from the group consisting of antegren (natalizumab), Neurelan (fampridine-SR), campath (alemtuzumab), IR 208. NBI 5788/MSP 771 (tiplimotide), paclitaxel, Anergix.MS (AG 284), SH636, Differin (CD 271, adapalene), BAY 361677 (interleukin-4), matrix-metalloproteinase-inhibitors (e.g. BB 76163), interferon-tau (trophoblastin) and SAIK-MS.
(357) Furthermore, the other agent may be, for example, an anti-anxiety drug or antidepressant selected from the group consisting of (a) Benzodiazepines, e.g. alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, fludiazepam, loflazepate, lorazepam, methaqualone, oxazepam, prazepam, tranxene, (b) Selective serotonin re-uptake inhibitors (SSRI's), e.g. citalopram, fluoxetine, fluvoxamine, escitalopram, sertraline, paroxetine, (c) Tricyclic antidepressants, e.g. amitryptiline, clomipramine, desipramine, doxepin, imipramine (d) Monoamine oxidase (MAO) inhibitors, (e) Azapirones, e.g. buspirone, tandopsirone, (f) Serotonin-norepinephrine reuptake inhibitors (SNRI's), e.g. venlafaxine, duloxetine, (g) Mirtazapine, (h) Norepinephrine reuptake inhibitors (NRI's), e.g. reboxetine, (i) Bupropione, (j) Nefazodone, (k) beta-blockers. (l) NPY-receptor ligands: NPY agonists or antagonists.
(358) In a further embodiment, the other agent may be, for example, an anti-multiple sclerosis drug selected from the group consisting of a) dihydroorotate dehydrogenase inhibitors, e.g. SC-12267, teriflunomide, MNA-715, HMR-1279 (syn. to HMR-1715, MNA-279), b) autoimmune suppressant, e.g. laquinimod, c) paclitaxel, d) antibodies, e.g. AGT-1, anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) monoclonal antibody, Nogo receptor modulators, ABT-874, alemtuzumab (CAMPATH), anti-OX40 antibody, CNTO-1275, DN-1921, natalizumab (syn. to AN-100226, Antegren, VLA-4 Mab), daclizumab (syn. to Zenepax, Ro-34-7375, SMART anti-Tac), J-695, priliximab (syn. to Centara, CEN-000029, cM-T412), MRA, Dantes, anti-IL-12-antibody, e) peptide nucleic acid (PNA) preparations, e.g. reticulose, f) interferon alpha, e.g. Alfaferone, human alpha interferon (syn. to Omniferon, Alpha Leukoferon), g) interferon beta, e.g. Frone, interferon beta-1a like Avonex, Betron (Rebif), interferon beta analogs, interferon beta-transferrin fusion protein, recombinant interferon beta-1b like Betaseron, h) interferon tau, i) peptides, e.g. AT-008, AnergiX.MS, Immunokine (alpha-Immunokine-NNSO3), cyclic peptides like ZD-7349, j) therapeutic enzymes, e.g. soluble CD8 (sCD8), k) multiple sclerosis-specific autoantigen-encoding

plasmid and cytokine-encoding plasmid, e.g. BHT-3009; l) inhibitor of TNF-alpha, e.g. BLX-1002, thalidomide, SH-636, m) TNF antagonists, e.g. solimastat, lenercept (syn. to RO-45-2081. Tenefuse), onercept (sTNFR1), CC-1069, n) TNF alpha, e.g. etanercept (syn. to Enbrel, TNR-001) o) CD28 antagonists, e.g. abatacept, p) Lck tyrosine kinase inhibitors, q) cathepsin K inhibitors, r) analogs of the neuron-targeting membrane transporter protein taurine and the plant-derived calpain inhibitor leupeptin, e.g. Neurodur, s) chemokine receptor-1 (CCR1) antagonist, e.g. BX-471, t) CCR2 antagonists, u) AMPA receptor antagonists, e.g. ER-167288-01 and ER-099487, E-2007, talampanel, v) potassium channel blockers, e.g. fampridine, w) tosyl-proline-phenylalanine small-molecule antagonists of the VLA-4NCAM interaction. e.g. TBC-3342, x) cell adhesion molecule inhibitors, e.g. TBC-772, y) antisense oligonucleotides, e.g. EN-101, z) antagonists of free immunoglobulin light chain (IgLC) binding to mast cell receptors, e.g. F-991, aa) apoptosis inducing antigens, e.g. Apogen MS, bb) alpha-2 adrenoceptor agonist. e.g. tizanidine (syn. to Zanaflex, Temelin, Sirdalvo, Sirdalud, Mionidine), cc) copolymer of L-tyrosine, L-lysine, L-glutamic acid and L-alanine, e.g. glatiramer acetate (syn. to Copaxone, COP-1, copolymer-1), dd) topoisomerase II modulators, e.g. mitoxantrone hydrochloride, ee) adenosine deaminase inhibitor, e.g. cladribine (syn. to Leustatin, Mylinax, RWJ-26251), ff) interleukin-10, e.g. ilodecakin (syn. to Tenovil, Sch-52000, CSIF), gg) interleukin-12 antagonists, e.g. lisofylline (syn. to CT-1501R, LSF, lysofylline), hh) Ethanaminum, e.g. SRI-62-834 (syn. to CRC-8605, NSC-614383), ii) immunomodulators, e.g. SAIK-MS, PNU-156804, alpha-fetoprotein peptide (AFP), IPDS. jj) retinoid receptor agonists, e.g. adapalene (syn. to Differin, CD-271), kk) TGF-beta, e.g. GDF-1 (growth and differentiation factor 1), ii) TGF-beta-2, e.g. BetaKine, mm) MMP inhibitors, e.g. glycomed, nn) phosphodiesterase 4 (PDE4) inhibitors, e.g. RPR-122818, oo) purine nucleoside phosphorylase inhibitors, e.g. 9-(3-pyridylmethyl)-9-deazaguanine, peldesine (syn. to BCX-34. TO-200), mm) alpha-4/beta-1 integrin antagonists, e.g. ISIS-104278, qq) antisense alpha4 integrin (CD49d), e.g. ISIS-17044, ISIS-27104, rr) cytokine-inducing agents, e.g. nucleosides, ICN-17261, ss) cytokine inhibitors, tt) heat shock protein vaccines, e.g. HSPPC-96, uu) neuregulin growth factors, e.g. GGF-2 (syn. to neuregulin, glial growth factor 2), vv) cathepsin S—inhibitors, ww) bropirimine analogs, e.g. PNU-56169. PNU-63693, xx) Monocyte chemoattractant protein-1 inhibitors, e.g. benzimidazoles like MCP-1 inhibitors, LKS-1456, PD-064036, PD-064126, PD-084486, PD-172084, PD-172386.

(359) Further, the present invention provides pharmaceutical compositions e.g. for parenteral, enteral or oral administration, comprising at least one QC inhibitor, optionally in combination with at least one of the other aforementioned agents.

(360) These combinations provide a particularly beneficial effect. Such combinations are therefore shown to be effective and useful for the treatment of the aforementioned diseases. Accordingly, the invention provides a method for the treatment of these conditions.

(361) The method comprises either co-administration of at least one QC inhibitor and at least one of the other agents or the sequential administration thereof.

(362) Co-administration includes administration of a formulation, which comprises at least one QC inhibitor and at least one of the other agents or the essentially simultaneous administration of separate formulations of each agent.

(363) Beta-amyloid antibodies and compositions containing the same are described, e.g. in WO/2009/065054, WO/2009/056490, WO/2009/053696, WO/2009/033743, WO/2007/113172, WO/2007/022416, WO 2006/137354, WO 2006/118959, WO 2006/103116, WO 2006/095041, WO 2006/081171, WO 2006/066233, WO 2006/066171, WO 2006/066089, WO 2006/066049, WO 2006/055178, WO 2006/046644, WO 2006/039470, WO 2006/036291, WO 2006/026408, WO 2006/016644, WO 2006/014638, WO 2006/014478, WO 2006/008661, WO 2005/123775, WO 2005/120571, WO 2005/105998, WO 2005/081872, WO 2005/080435, WO 2005/028511, WO 2005/025616, WO 2005/025516, WO 2005/023858, WO 2005/018424, WO 2005/011599, WO 2005/000193, WO 2004/108895, WO 2004/098631, WO 2004/080419, WO 2004/071408,

WO 2004/069182, WO 2004/067561, WO 2004/044204, WO 2004/032868, WO 2004/031400, WO 2004/029630, WO 2004/029629, WO 2004/024770, WO 2004/024090, WO 2003/104437, WO 2003/089460, WO 2003/086310, WO 2003/077858, WO 2003/074081, WO 2003/070760, WO 2003/063760, WO 2003/055514, WO 2003/051374, WO 2003/048204, WO 2003/045128, WO 2003/040183, WO 2003/039467, WO 2003/016466, WO 2003/015691, WO 2003/014162, WO 2003/012141, WO 2002/088307, WO 2002/088306, WO 2002/074240, WO 2002/046237, WO 2002/046222, WO 2002/041842, WO 2001/062801, WO 2001/012598, WO 2000/077178, WO 2000/072880, WO 2000/063250, WO 1999/060024, WO 1999/027944, WO 1998/044955, WO 1996/025435, WO 1994/017197, WO 1990/014840, WO 1990/012871, WO 1990/012870, WO 1989/006242.

(364) The beta-amyloid antibodies may be selected from, for example, polyclonal, monoclonal, chimenic or humanized antibodies. Furthermore, said antibodies may be useful to develop active and passive immune therapies, i.e. vaccines and monoclonal antibodies.

(365) Suitable examples of beta-amyloid antibodies are ACU-5A5, huC091 (Acumen/Merck); PF-4360365, RI-1014, RI-1219, RI-409, RN-1219 (Rinat Neuroscience Corp (Pfizer Inc)); the nanobody therapeutics of Ablynx/Boehringer Ingelheim; beta-amyloid-specific humanized monoclonal antibodies of Intellect Neurosciences/IBL; m266, m266.2 (Eli Lilly & Co.); AAB-02 (Elan); bapineuzumab (Elan); BAN-2401 (Bioarctic Neuroscience AB); ABP-102 (Abiogen Pharma SpA); BA-27, BC-05 (Takeda); R-1450 (Roche); ESBA-212 (ESBATech AG); AZD-3102 (AstraZeneca) and beta-amyloid antibodies of Mindset BioPharmaceuticals Inc.

(366) Especially preferred are antibodies, which recognize the N-terminus of the Aβ peptide. A suitable antibody, which recognizes the Aβ-N-Terminus is, for example Acl-24 (AC Immune SA).

(367) Monoclonal antibodies against beta-amyloid peptide are disclosed in WO 2007/068412, WO/2008/156621 and WO/2010/012004. Respective chimeric and humanized antibodies are disclosed in WO 2008/011348 and WO/2008/060364. Vaccine composition for treating an amyloid-associated disease is disclosed in WO/2002/096937, WO/2005/014041, WO 2007/068411. WO/2007/097251, WO/2009/029272, WO/2009/054537, WO/2009/090650 WO/2009/095857, WO/2010/016912, WO/2010/011947, WO/2010/011999, WO/2010/044464.

(368) Suitable vaccines for treating an amyloid-associated disease are, e.g. Affitopes AD-01 and AD-02 (GlaxoSmithKline), ACC-01 and ACC-02 (Elan/Wyeth), CAD-106 (Novartis/Cytos Biotechnology),

(369) Suitable cysteine protease inhibitors are inhibitors of cathepsin B. Inhibitors of cathepsin B and compositions containing such inhibitors are described, e.g. in WO/2008/077109, WO/2007/038772, WO 2006/060473, WO 2006/042103, WO 2006/039807, WO 2006/021413, WO 2006/021409, WO 2005/097103, WO 2005/007199, WO2004/084830, WO 2004/078908, WO 2004/026851, WO 2002/094881, WO 2002/027418, WO 2002/021509, WO 1998/046559, WO 1996/021655.

(370) Examples of suitable PIMT enhancers are 10-aminoaliphatyl-dibenz[b f] oxepines described in WO 98/15647 and WO 03/057204, respectively. Further useful according to the present invention are modulators of PIMT activity described in WO 2004/039773.

(371) Inhibitors of beta secretase and compositions containing such inhibitors are described. e.g. in WO/2010/094242, WO/2010/058333, WO/2010/021680, WO12009/108550, WO/2009/042694, WO/2008/054698, WO/2007/051333, WO/2007/021793, WO/2007/019080, WO/2007/019078, WO/2007/011810, WO03/059346, WO2006/099352, WO2006/078576, WO2006/060109, WO2006/057983, WO2006/057945, WO2006/055434, WO2006/044497, WO2006/034296, WO2006/034277, WO2006/029850. WO2006/026204, WO2006/014944, WO2006/014762, WO2006/002004, U.S. Pat. No. 7,109,217, WO2005/113484, WO2005/103043, WO2005/103020, WO2005/065195, WO2005/051914, WO2005/044830, WO2005/032471, WO2005/018545, WO2005/004803, WO2005/004802, WO2004/062625, WO2004/043916, WO2004/013098, WO03/099202, WO03/043987, WO03/039454, U.S. Pat. No. 6,562,783, WO02/098849 and

WO02/096897.
(372) Suitable examples of beta secretase inhibitors for the purpose of the present invention are WY-25105 (Wyeth); Posiphen, (+)-phenserine (TorreyPines/NIH); LSN-2434074, LY-2070275, LY-2070273, LY-2070102 (Eli Lilly & Co.); PNU-159775A, PNU-178025A, PNU-17820A, PNU-33312. PNU-38773, PNU-90530 (Elan/Pfizer); KMI-370, KMI-358, kmi-008 (Kyoto University): OM-99-2, OM-003 (Athenagen Inc.); AZ-12304146 (AstraZeneca/Astex); GW-840736X (GlaxoSmithKline plc.), DNP-004089 (De Novo Pharmaceuticals Ltd.) and CT-21166 (CoMentis Inc.).
(373) Inhibitors of gamma secretase and compositions containing such inhibitors are described, e.g. in WO/2010/090954, WO/2009/011851, WO/2009/008980, WO/2008/147800, WO/2007/084595, WO2005/008250, WO2006/004880, U.S. Pat. Nos. 7,122,675, 7,030,239, 6,992,081, 6,982,264, WO2005/097768, WO2005/028440, WO2004/101562, U.S. Pat. Nos. 6,756,511, 6,683,091, WO03/066592, WO03/014075, WO03/013527, WO02/36555, WO01/53255, U.S. Pat. Nos. 7,109,217, 7,101,895, 7,049,296, 7,034,182. U.S. Pat. No. 6,984,626. WO2005/040126, WO2005/030731, WO2005/014553, U.S. Pat. No. 6,890,956, EP 1334085, EP 1263774, WO2004/101538, WO2004/00958, WO2004/089911, WO2004/073630, WO2004/069826, WO2004/039370, WO2004/031139, WO2004/031137, U.S. Pat. Nos. 6,713,276, 6,686,449, WO03/091278, U.S. Pat. Nos. 6,649,196, 6,448,229, WO01/77144 and WO01/66564.
(374) Suitable gamma secretase inhibitors for the purpose of the present invention are GSI-953, WAY-GSI-A, WAY-GSI-B (Wyeth); MK-0752, MRK-560, L-852505, L-685-458, L-852631, L-852646 (Merck & Co. Inc.); LY-450139, LY-411575, AN-37124 (Eli Lilly & Co.); BMS-299897. BMS-433796 (Bristol-Myers Squibb Co.); E-2012 (Eisai Co. Ltd.); EHT-0206, EHT-206 (ExonHit Therapeutics SA); NGX-555 (TorreyPines Therapeutics Inc.) and Semagacestat (Eli Lilly).
(375) DP IV-inhibitors and compositions containing such inhibitors are described, e.g. in U.S. Pat. Nos. 6,011,155; 6,107,317; 6,110,949; 6,124,305; 6,172,081; WO99/61431, WO99/67278, WO99/67279, DE19834591, WO97/40832, WO95/15309, WO98/19998, WO00/07617, WO99/38501, WO99/46272, WO99/38501, WO01/68603. WO01/40180, WO01/81337, WO01/81304, WO01/55105, WO02/02560, WO01/34594, WO02/38541, WO02/083128, WO03/072556, WO03/002593, WO03/000250, WO03/000180, WO03/000181, EP1258476, WO03/002553, WO03/002531, WO03/002530, WO03/004496, WO03/004498, WO03/024942, WO03/024965, WO03/033524, WO03/035057, WO03/035067, WO03/037327, WO03/040174, WO03/045977. WO03/055881, WO03/057144, WO03/057666, WO03/068748, WO03/068757, WO03/082817, WO03/101449, WO03/101958, WO03/104229, WO03/74500, WO2004/007446, WO2004/007468, WO2004/018467, WO2004/018468, WO2004/018469, WO2004/026822, WO2004/032836, WO2004/033455, WO2004/037169, WO2004/041795, WO2004/043940, WO2004/048352, WO2004/050022, WO2004/052850, WO2004/058266. WO2004/064778, WO2004/069162, WO2004/071454, WO2004/076433, WO2004/076434, WO2004/087053, WO2004/089362, WO2004/099185, WO2004/103276, WO2004/103993, WO2004/108730, WO2004/110436, WO2004/111041, WO2004/112701, WO2005/000846, WO2005/000848, WO2005/011581, WO2005/016911, WO2005/023762, WO2005/025554, WO2005/026148, WO2005/030751, WO2005/033106, WO2005/037828, WO2005/040095, WO2005/044195, WO2005/047297, WO2005/051950, WO2005/056003, WO2005/056013, WO2005/058849, WO2005/075426, WO2005/082348, WO2005/085246, WO2005/087235. WO2005/095339, WO2005/095343, WO2005/095381, WO2005/108382, WO2005/113510, WO2005/116014, WO2005/116029, WO2005/118555, WO2005/120494, WO2005/121089, WO2005/121131, WO2005/123685, WO2006/995613: WO20061009886; WO2006/013104; WO2006/017292; WO2006/019965; WO2006/020017; WO2006/023750; WO2006/039325; WO2006/041976; WO2006/047248; WO2006/058064; WO2006/058628; WO2006/066747; WO2006/066770 and WO2006/068978.
(376) Suitable DP IV-inhibitors for the purpose of the present invention are for example Sitagliptin,

des-fluoro-sitagliptin (Merck & Co. Inc.); vildagliptin, DPP-728, SDZ-272-070 (Novartis); ABT-279. ABT-341 (Abbott Laboratories); denagliptin, TA-6666 (GlaxoSmithKline plc.); SYR-322 (Takeda San Diego Inc.); talabostat (Point Therapeutics Inc.); Ro-0730699, R-1499, R-1438 (Roche Holding AG); FE-999011 (Ferring Pharmaceuticals); TS-021 (Taisho Pharmaceutical Co. Ltd.); GRC-8200 (Glenmark Pharmaceuticals Ltd.); ALS-2-0426 (Alantos Pharmaceuticals Holding Inc.); ARI-2243 (Arisaph Pharmaceuticals Inc.); SSR-162369 (Sanofi-Synthelabo); MP-513 (Mitsubishi Pharma Corp.); DP-893, CP-867534-01 (Pfizer Inc.); TSL-225, TMC-2A (Tanabe Seiyaku Co. Ltd.); PHX-1149 (Phenomenix Corp.); saxagliptin (Bristol-Myers Squibb Co.); PSN-9301 ((OSI) Prosidion), S-40755 (Servier); KRP-104 (ActivX Biosciences Inc.); sulphostin (Zaidan Hojin); KR-62436 (Korea Research Institute of Chemical Technology); P32/98 (Probiodrug AG); BI-A, BI-B (Boehringer Ingelheim Corp.); SK-0403 (Sanwa Kagaku Kenkyusho Co. Ltd.); and NNC-72-2138 (Novo Nordisk A/S).

(377) Other preferred DP IV-inhibitors are (i) dipeptide-like compounds, disclosed in WO 99/61431, e.g. N-valyl prolyl, O-benzoyl hydroxylamine, alanyl pyrrolidine, isoleucyl thiazolidine like L-allo-isoleucyl thiazolidine, L-threo-isoleucyl pyrrolidine and salts thereof, especially the fumaric salts, and L-allo-isoleucyl pyrrolidine and salts thereof; (ii) peptide structures, disclosed in WO 03/002593. e.g. tripeptides; (iii) peptidylketones, disclosed in WO 03/033524; (vi) substituted aminoketones, disclosed in WO 03/040174; (v) topically active DP IV-inhibitors, disclosed in WO 01/14318; (vi) prodrugs of DP IV-inhibitors, disclosed in WO 99/67278 and WO 99/67279; and (v) glutaminyl based DP IV-inhibitors, disclosed in WO 03/072556 and WO 2004/099134.

(378) Suitable beta amyloid synthesis inhibitors for the purpose of the present invention are for example Bisnorcymserine (Axonyx Inc.); (R)-flurbiprofen (MCP-7869; Flurizan) (Myriad Genetics); nitroflurbiprofen (NicOx); BGC-20-0406 (Sankyo Co. Ltd.) and BGC-20-0466 (BTG plc.), RQ-00000009 (RaQualia Pharma Inc).

(379) Suitable amyloid protein deposition inhibitors for the purpose of the present invention are for example SP-233 (Samaritan Pharmaceuticals); AZD-103 (Ellipsis Neurotherapeutics Inc.); AAB-001 (Bapineuzumab), AAB-002, ACC-001 (Elan Corp plc.); Colostrinin (ReGen Therapeutics plc.); Tramiprosate (Neurochem); AdPEDI-(amyloid-beta1-6)11) (Vaxin Inc.); MPI-127585, MPI-423948 (Mayo Foundation); SP-08 (Georgetown University); ACU-5A5 (Acumen/Merck); Transthyretin (State University of New York); PTI-777, DP-74, DP 68, Exebryl (ProteoTech Inc.); m266 (Eli Lilly & Co.); EGb-761 (Dr. Willmar Schwabe GmbH); SPI-014 (Satori Pharmaceuticals Inc.); ALS-633, ALS-499 (Advanced Life Sciences Inc.); AGT-160 (ArmaGen Technologies Inc.); TAK-070 (Takeda Pharmaceutical Co. Ltd.); CHF-5022, CHF-5074. CHF-5096 and CHF-5105 (Chiesi Farmaceutici SpA.), SEN-1176 and SEN-1329 (Senexis Ltd.), AGT-160 (ArmaGen Technologies), Davunetide (Allon Therapeutics), ELND-005 (Elan Corp/Transition Therapeutics) and nilvadipine (Archer Pharmaceuticals).

(380) Suitable PDE-4 inhibitors for the purpose of the present invention are for example Doxofylline (Instituto Biologico Chemioterapica ABC SpA.); idudilast eye drops, tipelukast, ibudilast (Kyorin Pharmaceutical Co. Ltd.); theophylline (Elan Corp.); cilomilast (GlaxoSmithKline plc.); Atopik (Barrier Therapeutics Inc.); tofimilast, CI-1044, PD-189659, CP-220629, PDE 4d inhibitor BHN (Pfizer Inc.); arofylline, LAS-37779 (Almirall Prodesfarma SA.); roflumilast, hydroxypumafentrine (Altana AG), tetomilast (Otska Pharmaceutical Co. Ltd.); tipelukast, ibudilast (Kyorin Pharmaceutical), CC-10004 (Celgene Corp.); HT-0712, IPL-4088 (Inflazyme Pharmaceuticals Ltd.); MEM-1414, MEM-1917 (Memory Pharmaceuticals Corp.); oglemilast, GRC-4039 (Glenmark Pharmaceuticals Ltd.); AWD-12-281, ELB-353, ELB-526 (Elbion AG); EHT-0202 (ExonHit Therapeutics SA.); ND-1251 (Neuro3d SA.); 4AZA-PDE4 (4 AZA Bioscience NV.); AVE-8112 (Sanofi-Aventis); CR-3465 (Rottapharm SpA.); GP-0203, NCS-613 (Centre National de la Recherche Scientifique); KF-19514 (Kyowa Hakko Kogyo Co. Ltd.); ONO-6126 (Ono Pharmaceutical Co. Ltd.); OS-0217 (Dainippon Pharmaceutical Co. Ltd.); IBFB-130011, IBFB-150007, IBFB-130020, IBFB-140301 (IBFB Pharma GmbH); IC-485 (ICOS Corp.);

RBx-14016 and RBx-11082 (Ranbaxy Laboratories Ltd.). A preferred PDE-4-inhibitor is Rolipram.
(381) MAO inhibitors and compositions containing such inhibitors are described, e.g. in WO2006/091988, WO2005/007614, WO2004/089351, WO01/26656, WO01/12176, WO99/57120, WO99/57119, WO99/13878, WO98/40102, WO98/01157. WO96/20946, WO94/07890 and WO92/21333.
(382) Suitable MAO-inhibitors for the purpose of the present invention are for example Linezolid (Pharmacia Corp.); RWJ-416457 (RW Johnson Pharmaceutical Research Institute); budipine (Altana AG); GPX-325 (BioResearch Ireland); isocarboxazid; phenelzine; tranylcypromine; indantadol (Chiesi Farmaceutici SpA.); moclobemide (Roche Holding AG); SL-25.1131 (Sanofi-Synthelabo); CX-1370 (Burroughs Wellcome Co.); CX-157 (Krenitsky Pharmaceuticals Inc.); desoxypeganine (HF Arzneimittelforschung GmbH & Co. KG); bifemelane (Mitsubishi-Tokyo Pharmaceuticals Inc.); RS-1636 (Sankyo Co. Ltd.); esuprone (BASF AG); rasagiline (Teva Pharmaceutical Industries Ltd.); ladostigil (Hebrew University of Jerusalem); safinamide (Pfizer), NW-1048 (Newron Pharmaceuticals SpA.), EVT-302 (Evotec).
(383) Suitable histamine H3 antagonists for the purpose of the present invention are, e.g. ABT-239, ABT-834 (Abbott Laboratories); 3874-Hi (Aventis Pharma); UCL-2173 (Berlin Free University). UCL-1470 (BioProjet, Societe Civile de Recherche); DWP-302 (Daewoong Pharmaceutical Co Ltd); GSK-189254A, GSK-207040A (GlaxoSmithKline Inc.); cipralisant, GT-2203 (Gliatech Inc.); Ciproxifan (INSERM), 1S,2S-2-(2-Aminoethyl)-1-(1H-imidazol-4-yl)cyclopropane (Hokkaido University); JNJ-17216498, JNJ-5207852 (Johnson & Johnson); NNC-0038-0000-1049 (Novo Nordisk A/S); and Sch-79687 (Schering-Plough).
(384) PEP inhibitors and compositions containing such inhibitors are described, e.g. in JP 01042465, JP 03031298, JP 04208299, WO 00/71144, U.S. Pat. No. 5,847,155; JP 09040693, JP 10077300, JP 05331072, JP 05015314, WO 95/15310, WO 93/00361, EP 0556482, JP 06234693, JP 01068396. EP 0709373, U.S. Pat. Nos. 5,965,556, 5,756,763, 6,121,311, JP 63264454, JP 64000069, JP 63162672, EP 0268190, EP 0277588, EP 0275482, U.S. Pat. Nos. 4,977,180, 5,091,406, 4,983,624, 5,112,847, 5,100,904, 5,254,550, 5,262,431, 5,340,832, 4,956,380, EP 0303434, JP 03056486, JP 01143897, JP 1226880, EP 0280956. U.S. Pat. No. 4,857,537, EP 0461677, EP 0345428, JP 02275858, U.S. Pat. No. 5,506,256, JP 06192298, EP 0618193, JP 03255080, EP 0468469, U.S. Pat. No. 5,118,811, JP 05025125, WO 9313065, JP 05201970, WO 9412474, EP 0670309, EP 0451547, JP 06339390, U.S. Pat. No. 5,073,549. U.S. Pat. No. 4,999,349, EP 0268281, U.S. Pat. No. 4,743,616. EP 0232849. EP 0224272, JP 62114978, JP 62114957, U.S. Pat. Nos. 4,757,083, 4,810,721, 5,198,458, 4,826,870, EP 0201742, EP 0201741, U.S. Pat. No. 4,873,342, EP 0172458, JP 61037764, EP 0201743, U.S. Pat. No. 4,772,587. EP 0372484, U.S. Pat. No. 5,028,604, WO 91/18877, JP 04009367, JP 04235162, U.S. Pat. No. 5,407,950, WO 95/01352, JP 01250370, JP 02207070, U.S. Pat. No. 5,221,752, EP 0468339, JP 04211648, WO 99/46272, WO 2006/058720 and PCT/EP2006/061428.
(385) Suitable prolyl endopeptidase inhibitors for the purpose of the present invention are, e.g. Fmoc-Ala-Pyrr-CN, Z-Phe-Pro-Benzothiazole (Probiodrug), Z-321 (Zeria Pharmaceutical Co Ltd.); ONO-1603 (Ono Pharmaceutical Co Ltd); JTP-4819 (Japan Tobacco Inc.) and S-17092 (Servier).
(386) Other suitable compounds that can be used according to the present invention in combination with QC-inhibitors are NPY, an NPY mimetic or an NPY agonist or antagonist or a ligand of the NPY receptors.
(387) Preferred according to the present invention are antagonists of the NPY receptors.
(388) Suitable ligands or antagonists of the NPY receptors are 3a,4,5,9b-tetrahydro-1h-benz[e]indol-2-yl amine-derived compounds as disclosed in WO 00/68197.
(389) NPY receptor antagonists which may be mentioned include those disclosed in European patent applications EP 0 614 911, EP 0 747 357, EP 0 747 356 and EP 0 747 378; international patent applications WO 94/17035, WO 97/19911, WO 97/19913, WO 96/12489, WO 97/19914, WO 96/22305, WO 96/40660, WO 96/12490, WO 97/09308, WO 97/20820, WO 97/20821, WO

97/20822, WO 97/20823, WO 97/19682, WO 97/25041, WO 97/34843, WO 97/46250, WO 98/03492, WO 98/03493, WO 98/03494 and WO 98/07420: WO 00/30674, U.S. Pat. Nos. 5,552,411, 5,663,192 and 5,567,714; 6,114,336, Japanese patent application JP 09157253; international patent applications WO 94/00486, WO 93/12139, WO 95/00161 and WO 99/15498; U.S. Pat. No. 5,328,899; German patent application DE 393 97 97; European patent applications EP 355 794 and EP 355 793; and Japanese patent applications JP 06116284 and JP 07267988. Preferred NPY antagonists include those compounds that are specifically disclosed in these patent documents. More preferred compounds include amino acid and non-peptide-based NPY antagonists. Amino acid and non-peptide-based NPY antagonists which may be mentioned include those disclosed in European patent applications EP 0 614 911, EP 0 747 357, EP 0 747 356 and EP 0 747 378; international patent applications WO 94/17035, WO 97/19911, WO 97/19913, WO 96/12489, WO 97/19914, WO 96/22305, WO 96/40660, WO 96/12490, WO 97/09308, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 97/19682, WO 97/25041, WO 97/34843, WO 97/46250, WO 98/03492, WO 98/03493, WO 98/03494, WO 98/07420 and WO 99/15498; U.S. Pat. Nos. 5,552,411, 5,663,192 and 5,567,714; and Japanese patent application JP 09157253. Preferred amino acid and non-peptide-based NPY antagonists include those compounds that are specifically disclosed in these patent documents.

(390) Particularly preferred compounds include amino acid-based NPY antagonists. Amino acid-based compounds, which may be mentioned include those disclosed in international patent applications WO 94/17035, WO 97/19911, WO 97/19913, WO 97/19914 or, preferably, WO 99/15498. Preferred amino acid-based NPY antagonists include those that are specifically disclosed in these patent documents, for example BIBP3226 and, especially, (R)-N2-(diphenylacetyl)-(R)-N-[1-(4-hydroxy-phenyl) ethyl] arginine amide (Example 4 of international patent application WO 99/15498).

(391) M1 receptor agonists and compositions containing such inhibitors are described, e.g. in WO2004/087158, WO91/10664.

(392) Suitable M1 receptor antagonists for the purpose of the present invention are for example CDD-0102 (Cognitive Pharmaceuticals); Cevimeline (Evoxac) (Snow Brand Milk Products Co. Ltd.); NGX-267 (TorreyPines Therapeutics); sabcomeline (GlaxoSmithKline); alvameline (H Lundbeck A/S); LY-593093 (Eli Lilly & Co.); VRTX-3 (Vertex Pharmaceuticals Inc.); WAY-132983 (Wyeth), CI-101 7/(PD-151832) (Pfizer Inc.) and MCD-386 (Mitridion Inc.).

(393) Acetylcholinesterase inhibitors and compositions containing such inhibitors are described, e.g. in WO2006/071274, WO2006/070394, WO2006/040688, WO2005/092009, WO2005/079789, WO2005/039580, WO2005/027975, WO2004/084884, WO2004/037234, WO2004/032929, WO03/101458, WO03/091220, WO03/082820, WO03/020289, WO02/32412, WO01/85145, WO01/78728, WO01/66096, WO00/02549, WO01/00215, WO00/15205, WO00/23057, WO00/33840, WO00/30446, WO00/23057. WO00/15205, WO00/09483, WO00/07600, WO00/02549, WO99/47131, WO99/07359, WO98/30243, WO97/38993, WO97/13754, WO94/29255, WO94/20476, WO94/19356, WO93/03034 and WO92/19238.

(394) Suitable acetylcholinesterase inhibitors for the purpose of the present invention are for example Donepezil (Eisai Co. Ltd.); rivastigmine (Novartis AG); (−)-phenseine (TorreyPines Therapeutics); ladostigil (Hebrew University of Jerusalem); huperzine A (Mayo Foundation); galantamine (Johnson & Johnson); Memoquin (Universita di Bologna); SP-004 (Samaritan Pharmaceuticals Inc.); BGC-20-1259 (Sankyo Co. Ltd.); physostigmine (Forest Laboratories Inc.); NP-0361 (Neuropharma SA); ZT-1 (Debiopharm); tacrine (Wamer-Lambert Co.); metrifonate (Bayer Corp.). INM-176 (Whanin), huperzine A (Neuro-Hitech/Xel Pharmaceutical), mimopezil (Debiopharm) and Dimebon (Medivation/Pfizer).

(395) NMDA receptor antagonists and compositions containing such inhibitors are described, e.g. in WO2006/094674, WO2006/058236, WO2006/058059, WO2006/010965, WO2005/000216, WO2005/102390, WO2005/079779, WO2005/079756, WO2005/072705, WO2005/070429,

WO2005/055996, WO2005/035522, WO2005/009421, WO2005/000216. WO2004/092189, WO2004/039371, WO2004/028522, WO2004/009062, WO03/010159, WO02/072542, WO02/34718, WO01/98262, WO01/94321. WO01/92204, WO01/81295, WO01/32640, WO01/10833, WO01/10831, WO00/56711, WO00/29023, WO00/00197, WO99/53922, WO99/48891, WO99/45963, WO99/01416, WO99/07413, WO99/01416. WO98/50075, WO98/50044, WO98/10757, WO98/05337, WO97/32873, WO97/23216, WO97/23215, WO97/23214, WO96/14318. WO96/08485. WO95/31986, WO95/26352, WO95/26350, WO95/26349, WO95/26342, WO95/12594, WO95/02602, WO95/02601, WO94/20109, WO94/13641, WO94/09016 and WO93/25534.

(396) Suitable NMDA receptor antagonists for the purpose of the present invention are for example Memantine (Merz & Co. GmbH); topiramate (Johnson & Johnson); AVP-923 (Neurodex) (Center for Neurologic Study); EN-3231 (Endo Pharmaceuticals Holdings Inc.); neramexane (MRZ-2/579) (Merz and Forest); CNS-5161 (CeNeS Pharmaceuticals Inc.); dexanabinol (HU-211; Sinnabidol; PA-50211) (Pharmos); EpiCept NP-1 (Dalhousie University); indantadol (V-3381; CNP-3381) (Vemalis); perzinfotel (EAA-090, WAY-126090, EAA-129) (Wyeth); RGH-896 (Gedeon Richter Ltd.); traxoprodil (CP-101606), besonprodil (PD-196860, CI-1041) (Pfizer Inc.); CGX-1007 (Cognetix Inc.); delucemine (NPS-1506) (NPS Pharmaceuticals Inc.); EVT-101 (Roche Holding AG); acamprosate (Synchroneuron LLC.); CR-3991, CR-2249, CR-3394 (Rottapharm SpA.); AV-101 (4-CI-kynurenine (4-CI-KYN)), 7-chloro-kynurenic acid (7-CI-KYNA) (VistaGen); NPS-1407 (NPS Pharmaceuticals Inc.); YT-1006 (Yaupon Therapeutics Inc.); ED-1812 (Sosei R&D Ltd.); himantane (hydrochloride N-2-(adamantly)-hexamethylen-imine) (RAMS); Lancicemine (AR-R-15896) (AstraZeneca); EVT-102, Ro-25-6981 and Ro-63-1908 (Hoffmann-La Roche AG/Evotec), neramexane (Merz).

(397) Furthermore, the present invention relates to combination therapies useful for the treatment of atherosclerosis, restenosis or arthritis, administering a QC inhibitor in combination with another therapeutic agent selected from the group consisting of inhibitors of the angiotensin converting enzyme (ACE); angiotensin II receptor blockers; diuretics; calcium channel blockers (CCB); beta-blockers; platelet aggregation inhibitors; cholesterol absorption modulators; HMG-Co-A reductase inhibitors; high density lipoprotein (HDL) increasing compounds; renin inhibitors; IL-6 inhibitors; antiinflammatory corticosteroids; antiproliferative agents; nitric oxide donors; inhibitors of extracellular matrix synthesis; growth factor or cytokine signal transduction inhibitors; MCP-1 antagonists and tyrosine kinase inhibitors providing beneficial or synergistic therapeutic effects over each monotherapy component alone.

(398) Angiotensin II receptor blockers are understood to be those active agents that bind to the AT1-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the blockade of the AT1 receptor, these antagonists can, e.g. be employed as antihypertensive agents.

(399) Suitable angiotensin II receptor blockers which may be employed in the combination of the present invention include AT.sub.1 receptor antagonists having differing structural features, preferred are those with non-peptidic structures. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (EP 443983), losartan (EP 253310), candesartan (EP 459136), eprosartan (EP 403159), irbesartan (EP 454511), olmesartan (EP 503785), tasosartan (EP 539086), telmisartan (EP 522314), the compound with the designation E-41 77 of the formula

(400) ##STR00045##

(401) the compound with the designation SC-52458 of the following formula

(402) ##STR00046##

(403) and the compound with the designation the compound ZD-8731 of the formula

(404) ##STR00047##

(405) or, in each case, a pharmaceutically acceptable salt thereof.

(406) Preferred AT1-receptor antagonists are those agents that have been approved and reached the market, most preferred is valsartan, or a pharmaceutically acceptable salt thereof.
(407) The interruption of the enzymatic degradation of angiotensin to angiotensin II with ACE inhibitors is a successful variant for the regulation of blood pressure and thus also makes available a therapeutic method for the treatment of hypertension.
(408) A suitable ACE inhibitor to be employed in the combination of the present invention is, e.g. a compound selected from the group consisting alacepril, benazepril, benazeprilat; captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril and trandolapril, or in each case, a pharmaceutically acceptable salt thereof.
(409) Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.
(410) A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. The most preferred diuretic is hydrochlorothiazide. A diuretic furthermore comprises a potassium sparing diuretic such as amiloride or triameterine, or a pharmaceutically acceptable saft thereof.
(411) The class of CCBs essentially comprises dihydropyridines (DHPs) and non-DHPs, such as diltiazem-type and verapamil-type CCBs.
(412) A CCB useful in said combination is preferably a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof. All these CCBs are therapeutically used, e.g. as anti-hypertensive, anti-angina pectoris or anti-arrhythmic drugs.
(413) Preferred CCBs comprise amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine and verapamil or, e.g. dependent on the specific CCB, a pharmaceutically acceptable salt thereof. Especially preferred as DHP is amlodipine or a pharmaceutically acceptable salt thereof, especially the besylate. An especially preferred representative of non-DHPs is verapamil or a pharmaceutically acceptable salt, especially the hydrochloride, thereof.
(414) Beta-blockers suitable for use in the present invention include beta-adrenergic blocking agents (beta-blockers), which compete with epinephrine for beta-adrenergic receptors and interfere with the action of epinephrine. Preferably, the beta-blockers are selective for the beta-adrenergic receptor as compared to the alpha-adrenergic receptors, and so do not have a significant alpha-blocking effect. Suitable beta-blockers include compounds selected from acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol and timolol. Where the beta-blocker is an acid or base or otherwise capable of forming pharmaceutically acceptable salts or prodrugs, these forms are considered to be encompassed herein, and it is understood that the compounds may be administered in free form or in the form of a pharmaceutically acceptable salt or a prodrug, such as a physiologically hydrolyzable and acceptable ester. For example, metoprolol is suitably administered as its tartrate salt, propranolol is suitably administered as the hydrochloride salt, and so forth.
(415) Platelet aggregation inhibitors include PLAVIX® (clopidogrel bisulfate), PLETAL® (cilostazol) and aspirin.
(416) Cholesterol absorption modulators include ZETIA® (ezetimibe) and KT6-971 (Kotobuki Pharmaceutical Co. Japan).
(417) HMG-Co-A reductase inhibitors (also called beta-hydroxy-beta-methylglutaryl-co-enzyme-A reductase inhibitors or statins) are understood to be those active agents which may be used to lower

lipid levels including cholesterol in blood.
(418) The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds, which are selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, or in each case, a pharmaceutically acceptable salt thereof.
(419) Preferred HMG-Co-A reductase inhibitors are those agents, which have been marketed, most preferred is atorvastatin, pitavastatin or simvastatin, or a pharmaceutically acceptable salt thereof.
(420) HDL-increasing compounds include, but are not limited to, cholesterol ester transfer protein (CETP) inhibitors. Examples of CETP inhibitors include JTT705 disclosed in Example 26 of U.S. Pat. No. 6,426,365 issued Jul. 30, 2002, and pharmaceutically acceptable salts thereof.
(421) Inhibition of interleukin 6 mediated inflammation may be achieved indirectly through regulation of endogenous cholesterol synthesis and isoprenoid depletion or by direct inhibition of the signal transduction pathway utilizing interleukin-6 inhibitor/antibody, interleukin-6 receptor inhibitor/antibody, interleukin-6 antisense oligonucleotide (ASON), gp130 protein inhibitor/antibody, tyrosine kinase inhibitors/antibodies, serne/threonine kinase inhibitors/antibodies, mitogen-activated protein (MAP) kinase inhibitors/antibodies, phosphatidylinositol 3-kinase (PI3K) inhibitors/antibodies, Nuclear factor kappaB (NF-κB) inhibitors/antibodies, IκB kinase (IKK) inhibitors/antibodies, activator protein-1 (AP-1) inhibitors/antibodies, STAT transcription factors inhibitors/antibodies, altered IL-6, partial peptides of IL-6 or IL-6 receptor, or SOCS (suppressors of cytokine signaling) protein, PPAR gamma and/or PPAR beta/delta activators/ligands or a functional fragment thereof.
(422) A suitable antiinflammatory corticosteroid is dexamethasone.
(423) Suitable antiproliferative agents are cladribine, rapamycin, vincristine and taxol.
(424) A suitable inhibitor of extracellular matrix synthesis is halofuginone.
(425) A suitable growth factor or cytokine signal transduction inhibitor is, e.g. the ras inhibitor R115777.
(426) A suitable tyrosine kinase inhibitor is tyrphostin.
(427) Suitable renin inhibitors are described, e.g. in WO 2006/116435. A preferred renin inhibitor is aliskiren, preferably in the form of the hemi-fumarate salt thereof.
(428) MCP-1 antagonists may, e.g. be selected from anti-MCP-1 antibodies, preferably monoclonal or humanized monoclonal antibodies, MCP-1 expression inhibitors, CCR2-antagonists, TNF-alpha inhibitors, VCAM-1 gene expression inhibitors and anti-C5a monoclonal antibodies.
(429) MCP-1 antagonists and compositions containing such inhibitors are described, e.g. in WO02/070509, WO02/081463, WO02/060900, US2006/670364, US2006/677365, WO2006/097624, US2006/316449, WO2004/056727, WO03/053368, WO00/198289, WO00/157226, WO00/046195, WO00/046196, WO00/046199, WO00/046198, WO00/046197, WO99/046991, WO99/007351, WO98/006703, WO97/012615, WO2005/105133, WO03/037376, WO2006/125202, WO2006/085961, WO2004/024921, WO2006/074265.
(430) Suitable MCP-1 antagonists are, for instance, C-243 (Telik Inc.); NOX-E36 (Noxxon Pharma AG); AP-761 (Actimis Pharmaceuticals Inc.); ABN-912, NIBR-177 (Novartis AG); CC-11006 (Celgene Corp.); SSR-150106 (Sanofi-Aventis); MLN-1202 (Millenium Pharmaceuticals Inc.); AGI-1067, AGIX-4207, AGI-1096 (AtherioGenics Inc.); PRS-211095, PRS-211092 (Pharmos Corp.); anti-C5a monoclonal antibodies, e.g. neutrazumab (G2 Therapies Ltd.); AZD-6942 (AstraZeneca plc.); 2-mercaptoimidazoles (Johnson & Johnson); TEI-E00526, TEI-6122 (Deltagen); RS-504393 (Roche Holding AG); SB-282241, SB-380732, ADR-7 (GlaxoSmithKline); anti-MCP-1 monoclonal antibodies (Johnson & Johnson).
(431) Combinations of QC-inhibitors with MCP-1 antagonists may be useful for the treatment of inflammatory diseases in general, including neurodegenerative diseases.
(432) Combinations of QC-inhibitors with MCP-1 antagonists are preferred for the treatment of Alzheimer's disease.

(433) Most preferably the QC inhibitor is combined with one or more compounds selected from the following group:
(434) PF-4360365, m266, bapineuzumab, R-1450, Posiphen, (+)-phenserine, MK-0752, LY-450139, E-2012, (R)-flurbiprofen, AZD-103, AAB-001 (Bapineuzumab), Tramiprosate, EGb-761, TAK-070, Doxofylline, theophylline, cilomilast, tofimilast, roflumilast, tetomilast, tipelukast, ibudilast, HT-0712, MEM-1414, oglemilast, Linezolid, budipine, isocarboxazid, phenelzine, tranylcypromine, indantadol, moclobemide, rasagiline, ladostigil, safinamide, ABT-239, ABT-834, GSK-189254A, Ciproxifan, JNJ-17216498, Fmoc-Ala-Pyrr-CN, Z-Phe-Pro-Benzothiazole, Z-321, ONO-1603, JTP-4819, S-17092, BIBP3226; (R)-N2-(diphenylacetyl)-(R)-N-[1-(4-hydroxyphenyl) ethyl] arginine amide, Cevimeline, sabcomeline, (PD-151832), Donepezil, rivastigmine, (−)-phenserine, ladostigil, galantamine, tacrine, metrifonate, Memantine, topiramate, AVP-923, EN-3231, neramexane, valsartan, benazepril, enalapril, hydrochlorothiazide, amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, verapamil, amlodipine, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol, PLAVIX® (clopidogrel bisulfate), PLETAL® (cilostazol), aspirin, ZETIA® (ezetimibe) and KT6-971, statins, atorvastatin, pitavastatin or simvastatin; dexamethasone, ciadribine, rapamycin, vincristine, taxol, aliskiren, C-243, ABN-912, SSR-150106. MLN-1202 and betaferon.
(435) In particular, the following combinations are considered: a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with Atorvastatin for the treatment and/or prevention of artherosclerosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with immunosuppressive agents, preferably rapamycin for the prevention and/or treatment of restenosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with immunosuppressive agents, preferably paclitaxel for the prevention and/or treatment of restenosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with AChE inhibitors, preferably Donepezil, for the prevention and/or treatment of Alzheimer's disease, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with interferones, preferably Aronex, for the prevention and/or treatment of multiple sclerosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with interferones, preferably betaferon, for the prevention and/or treatment of multiple sclerosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with interferones, preferably Rebif, for the prevention and/or treatment of multiple sclerosis a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with Copaxone, for the prevention and/or treatment of multiple sclerosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with dexamethasone, for the prevention and/or treatment of restenosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with dexamethasone, for the prevention and/or treatment of atherosclerosis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with dexamethasone, for the prevention and/or treatment of rheumatid arthritis, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with HMG-Co-A-reductase inhibitors, for the prevention and/or treatment of restenosis, wherein the HMG-Co-A-reductase inhibitor is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and

simvastatin, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with HMG-Co-A reductase inhibitors, for the prevention and/or treatment of atherosclerosis wherein the HMG-Co-A-reductase inhibitor is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with HMG-Co-A reductase inhibitors, for the prevention and/or treatment of rheumatoid arthritis wherein the HMG-Co-A-reductase inhibitor is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with amyloid-beta antibodies for the prevention and/or treatment of mild cognitive impairment, wherein the amyloid-beta antibody is Acl-24, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with amyloid-beta antibodies for the prevention and/or treatment of Alzheimer's disease, wherein the amyloid-beta antibody is Acl-24, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with amyloid-beta antibodies for the prevention and/or treatment of neurodegeneration in Down Syndrome, wherein the amyloid-beta antibody is Acl-24, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with beta-secretase inhibitors for the prevention and/or treatment of mild cognitive impairment, wherein the beta-secretase inhibitor is selected from WY-25105, GW-840736X and CTS-21166, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with beta-secretase inhibitors for the prevention and/or treatment of Alzheimer's disease, wherein the beta-secretase inhibitor is selected from WY-25105, GW-840736X and CTS-21166, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with beta-secretase inhibitors for the prevention and/or treatment of neurodegeneration in Down Syndrome, wherein the beta-secretase inhibitor is selected from WY-25105, GW-840736X and CTS-21166, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with gamma-secretase inhibitors for the prevention and/or treatment of mild cognitive impairment, wherein the gamma-secretase inhibitor is selected from LY-450139, LY-411575 and AN-37124, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with gamma-secretase inhibitors for the prevention and/or treatment of Alzheimer's disease, wherein the gamma-secretase inhibitor is selected from LY-450139, LY-411575 and AN-37124, a QC inhibitor, preferably a QC inhibitor of formula (I), more preferably a QC inhibitor selected from any one of examples 1 to 1323, in combination with gamma-secretase inhibitors for the prevention and/or treatment of neurodegeneration in Down Syndrome, wherein the gamma-secretase inhibitor is selected from LY-450139, LY-411575 and AN-37124.

(436) Such a combination therapy is in particular useful for AD, FAD, FDD and neurodegeneration in Down syndrome as well as atherosclerosis, rheumatoid arthritis, restenosis and pancreatitis.

(437) Such combination therapies might result in a better therapeutic effect (less proliferation as well as less inflammation, a stimulus for proliferation) than would occur with either agent alone.

(438) With regard to the specific combination of inhibitors of QC and further compounds it is referred in particular to WO 2004/098625 in this regard, which is incorporated herein by reference.

(439) Pharmaceutical Compositions

(440) To prepare the pharmaceutical compositions of this invention, at least one compound of formula (I) optionally in combination with at least one of the other aforementioned agents can be used as the active ingredient(s). The active ingredient(s) is intimately admixed with a

pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included.

(441) Injectable suspensions may also prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient(s) necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.03 mg to 100 mg/kg (preferred 0.1-30 mg/kg) and may be given at a dosage of from about 0.1-300 mg/kg per day (preferred 1-50 mg/kg per day) of each active ingredient or combination thereof. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

(442) Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble saft of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of each active ingredient or combinations thereof of the present invention.

(443) The tablets or pills of the compositions of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

(444) This liquid forms in which the compositions of the present invention may be incorporated for

administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

(445) The pharmaceutical composition may contain between about 0.01 mg and 100 mg, preferably about 5 to 50 mg, of each compound, and may be constituted into any form suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

(446) Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

(447) For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or betalactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

(448) The liquid forms in suitable flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

(449) The compounds or combinations of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

(450) Compounds or combinations of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamid-ephenol, or polyethyl eneoxidepolyllysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polyactic acid, polyepsilon caprolactone, polyhydroxy butyeric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

(451) Compounds or combinations of this invention may be administered in any of the foregoing

compositions and according to dosage regimens established in the art whenever treatment of the addressed disorders is required.
(452) The daily dosage of the products may be varied over a wide range from 0.01 to 1.000 mg per mammal per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of each active ingredient or combinations thereof for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.1 mg/kg to about 300 mg/kg of body weight per day. Preferably, the range is from about 1 to about 50 mg/kg of body weight per day. The compounds or combinations may be administered on a regimen of 1 to 4 times per day.
(453) Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.
(454) In a further aspect, the invention also provides a process for preparing a pharmaceutical composition comprising at least one compound of formula (I), optionally in combination with at least one of the other aforementioned agents and a pharmaceutically acceptable carrier.
(455) The compositions are preferably in a unit dosage form in an amount appropriate for the relevant daily dosage.
(456) Suitable dosages, including especially unit dosages, of the compounds of the present invention include the known dosages including unit doses for these compounds as described or referred to in reference text such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

Description

EXAMPLES
(1) In a further embodiment, the present invention provides compounds of formula (IIa) and (IIb), wherein X.sub.1, n, Z, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 1 to 265:
(2) ##STR00048##
(3) TABLE-US-00003 Comp X.sub.1 n Z Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 1 CH.sub.2 1 CH CH CH CH CH C CH CH CH CH CH H H 2 CH.sub.2 1 N CH CH CH CH C CH CH CH CH CH H H 3 S 1 N CH CH CH CH C CH CH CH CH CH H H 4 CH.sub.2 1 CH CH CH CH CH C N CH CH CH CH H H 5 CH.sub.2 1 N CH CH CH CH C N CH CH CH CH H H 6 S 1 N CH CH CH CH C N CH CH CH CH H H 7 CH.sub.2 1 CH CH CH CH CH C CH N CH CH CH H H 8 CH.sub.2 1 N CH CH CH CH C CH N CH CH CH H H 9 S 1 N CH CH CH CH C CH N CH CH CH H H 10 CH.sub.2 1 CH CH CH CH CH C N CH CH CH N H H 11 CH.sub.2 1 N CH CH CH CH C N CH CH CH N H H 12 S 1 N CH CH CH CH C N CH CH CH N H H 13 CH.sub.2 1 CH CH CH CH CH C N N CH CH CH H H 14 CH.sub.2 1 N CH CH CH CH C N N CH CH CH H H 15 S 1 N CH CH CH CH C N N CH CH CH H H 16 CH.sub.2 1 CH CH CH CH CH C CH N CH N CH H absent 17 CH.sub.2 1 N CH CH CH CH C CH N CH N CH H 18 S 1 N CH CH CH CH C CH N CH N CH H 19 CH2 1 CH CH CH CH CH C CH CH N CH N absent H 20 CH2 1 N CH CH CH CH C CH CH N CH N H 21 S 1 N CH CH CH CH C CH CH N CH N H 22 1 C CH CH CH CH H H 23 CH.sub.2 1 CH CH CH CH CH C CH CH N CH CH absent H 24 CH.sub.2 1 N CH CH CH CH C CH CH N CH CH H 25 S 1 N

CH CH CH CH C CH CH N CH CH H 26 CH.sub.2 1 CH N CH CH CH C CH CH CH CH CH H H 27 CH.sub.2 1 N N CH CH CH C CH CH CH CH CH H H 28 S 1 N N CH CH CH C CH CH CH CH CH H H 29 CH.sub.2 1 CH N CH CH CH C N CH CH CH CH H H 30 CH.sub.2 1 N N CH CH CH C N CH CH CH CH H H 31 S 1 N N CH CH CH C N CH CH CH CH H H 32 CH.sub.2 1 CH N CH CH CH C CH N CH CH CH H H 33 CH.sub.2 1 N N CH CH CH C CH N CH CH CH H H 34 S 1 N N CH CH CH C CH N CH CH CH H H 35 CH.sub.2 1 CH N CH CH CH C N CH CH CH N H H 36 CH.sub.2 1 N N CH CH CH C N CH CH CH N H H 37 S 1 N N CH CH CH C N CH CH CH N H H 38 CH.sub.2 1 CH N CH CH CH C CH CH N CH N absent H 39 CH.sub.2 1 N N CH CH CH C CH CH N CH N H 40 S 1 N N CH CH CH C CH CH N CH N H 41 CH.sub.2 1 CH N CH CH CH C N CH CH CH CH H H 42 CH.sub.2 1 N N CH CH CH C N CH CH CH CH H H 43 S 1 N N CH CH CH C N CH CH CH CH H H 44 CH.sub.2 1 CH N N CH CH C CH CH N CH N absent H 45 CH.sub.2 1 N N N CH CH C CH CH N CH N H 46 S 1 N N N CH CH C CH CH N CH N H 47 CH.sub.2 1 CH N N CH CH C CH CH CH CH CH H H 48 CH.sub.2 1 N N N CH CH C CH CH CH CH CH H H 49 S 1 N N N CH CH C CH CH CH CH CH H H 50 CH.sub.2 1 CH CH N CH CH C CH CH CH CH CH H H 51 CH.sub.2 1 N CH N CH CH C CH CH CH CH CH H H 52 S 1 N CH N CH CH C CH CH CH CH CH H H 53 CH.sub.2 1 CH CH N CH CH C N CH CH CH CH H H 54 CH.sub.2 1 N CH N CH CH C N CH CH CH CH H H 55 S 1 N CH N CH CH C N CH CH CH CH H H 56 CH.sub.2 1 CH CH N CH CH C CH N CH CH CH H H 57 CH.sub.2 1 N CH N CH CH C CH N CH CH CH H H 58 S 1 N CH N CH CH C CH N CH CH CH H H 59 CH.sub.2 1 CH CH N CH CH C CH N CH N CH H absent 60 CH.sub.2 1 N CH N CH CH C CH N CH N CH H 61 S 1 N CH N CH CH C CH N CH N CH H 62 CH.sub.2 1 CH CH N CH CH C N CH CH N CH H H 63 CH.sub.2 1 N CH N CH CH C N CH CH N CH H H 64 S 1 N CH N CH CH C N CH CH N CH H H 65 CH.sub.2 1 CH CH N CH CH C CH CH N CH N absent H 66 CH.sub.2 1 N CH N CH CH C CH CH N CH N H 67 S 1 N CH N CH CH C CH CH N CH N H 68 CH.sub.2 1 CH CH N CH CH C CH CH N CH CH absent H 69 CH.sub.2 1 N CH N CH CH C CH CH N CH CH H 70 S 1 N CH N CH CH C CH CH N CH CH H 71 CH.sub.2 1 CH N CH N CH C CH CH CH CH CH H H 72 CH.sub.2 1 N N CH N CH C CH CH CH CH CH H H 73 S 1 N N CH N CH C CH CH CH CH CH H H 74 CH.sub.2 1 CH N CH N CH C N CH CH CH CH H H 75 CH.sub.2 1 N N CH N CH C N CH CH CH CH H H 76 S 1 N N CH N CH C N CH CH CH CH H H 77 CH.sub.2 1 CH N CH N CH C CH N CH CH CH H H 78 CH.sub.2 1 N N CH N CH C CH N CH CH CH H H 79 S 1 N N CH N CH C CH N CH CH CH H H 80 CH.sub.2 1 CH CH N CH N C CH CH CH CH CH H H 81 CH.sub.2 1 N CH N CH N C CH CH CH CH CH H H 82 S 1 N CH N CH N C CH CH CH CH CH H H 83 CH.sub.2 1 CH CH CH N N C CH CH CH CH CH H H 84 CH.sub.2 1 N CH CH N N C CH CH CH CH CH H H 85 S 1 N CH CH N N C CH CH CH CH CH H H 86 CH.sub.2 1 CH CH CH CH N C CH CH CH CH CH H H 87 CH.sub.2 1 N CH CH CH N C CH CH CH CH CH H H 88 S 1 N CH CH CH N C CH CH CH CH CH H H 89 CH.sub.2 1 CH CH CH CH N C CH CH N CH CH absent H 90 CH.sub.2 1 N CH CH CH N C CH CH N CH CH H 91 S 1 N CH CH CH N C CH CH N CH CH H 92 CH.sub.2 1 CH CH CH CH CH C CH CH CH CH CH F H 93 CH.sub.2 1 N CH CH CH CH C CH CH CH CH CH F H 94 S 1 N CH CH CH CH C CH CH CH CH CH F H 95 CH.sub.2 1 CH CH CH CH CH C N CH CH CH CH F H 96 CH.sub.2 1 N CH CH CH CH C N CH CH CH CH F H 97 S 1 N CH CH CH CH C N CH CH CH CH F H 98 CH.sub.2 1 CH CH CH CH CH C CH N CH CH CH F H 99 CH.sub.2 1 N CH CH CH CH C CH N CH CH CH F H 100 S 1 N CH CH CH CH C CH N CH CH CH F H 101 CH.sub.2 1 CH CH CH CH CH C N CH CH CH N F H 102 CH.sub.2 1 N CH CH CH CH C N CH CH CH N F H 103 S 1 N CH CH CH CH C N CH CH CH N F H 104 CH.sub.2 1 CH CH CH CH CH C N N CH CH CH F H 105 CH.sub.2 1 N CH CH CH CH C N N CH CH CH F H 106 S 1 N CH CH CH CH C N N CH CH CH F H 107 CH.sub.2 1 CH CH CH CH CH C CH N CH N CH F absent 108 CH.sub.2 1 N CH CH CH CH C CH N CH N CH F 109 S 1 N CH CH CH CH C CH N CH N CH F 110 CH.sub.2 1 CH CH CH CH CH C CH CH N CH N absent 111 CH.sub.2 1 N CH CH CH CH C CH CH N CH N 112 S 1 N CH CH CH CH C CH CH

N CH N 113 CH.sub.2 1 CH CH CH CH CH C CH CH N CH CH absent H 114 CH.sub.2 1 N CH CH CH CH C CH CH N CH CH H 115 S 1 N CH CH CH CH C CH CH N CH CH H 116 CH.sub.2 1 CH N CH CH CH C CH CH CH CH CH F H 117 CH.sub.2 1 N N CH CH CH C CH CH CH CH CH F H 118 S 1 N N CH CH CH C CH CH CH CH CH F H 119 CH.sub.2 1 CH N CH CH CH C N CH CH CH CH F H 120 CH.sub.2 1 N N CH CH CH C N CH CH CH CH F H 121 S 1 N N CH CH CH C N CH CH CH CH F H 122 CH.sub.2 1 CH N CH CH CH C CH N CH CH CH F H 123 CH.sub.2 1 N N CH CH CH C CH N CH CH CH F H 124 S 1 N N CH CH CH C CH N CH CH CH F H 125 CH.sub.2 1 CH N CH CH CH C N CH CH CH F H 126 CH.sub.2 1 N N CH CH CH C N CH CH CH F H 127 S 1 N N CH CH CH C N CH CH CH F H 128 CH.sub.2 1 CH N CH CH CH C CH CH N CH N absent H 129 CH.sub.2 1 N N CH CH CH C CH CH N CH N H 130 S 1 N N CH CH CH C CH CH N CH N H 131 CH.sub.2 1 CH N N CH CH C CH CH CH CH CH F H 132 CH.sub.2 1 N N N CH CH C CH CH CH CH CH F H 133 S 1 N N N CH CH C CH CH CH CH CH F H 134 CH.sub.2 1 CH N N CH CH C CH CH N CH N absent H 135 CH.sub.2 1 N N N CH CH C CH CH N CH N H 136 S 1 N N N CH CH C CH CH N CH N H 137 CH.sub.2 1 CH CH N CH CH C CH CH CH CH CH F H 138 CH.sub.2 1 N CH N CH CH C CH CH CH CH CH F H 139 S 1 N CH N CH CH C CH CH CH CH CH F H 140 CH.sub.2 1 CH CH N CH CH C N CH CH CH CH F H 141 CH.sub.2 1 N CH N CH CH C N CH CH CH CH F H 142 S 1 N CH N CH CH C N CH CH CH CH F H 143 CH.sub.2 1 CH CH N CH CH C CH N CH CH CH F H 144 CH.sub.2 1 N CH N CH CH C CH N CH CH CH F H 145 S 1 N CH N CH CH C CH N CH CH CH F H 146 CH.sub.2 1 CH CH N CH CH C CH N CH N CH F absent 147 CH.sub.2 1 N CH N CH CH C CH N CH N CH F 148 S 1 N CH N CH CH C CH N CH N CH F 149 CH.sub.2 1 CH CH N CH CH C N CH CH N CH F absent 150 CH.sub.2 1 N CH N CH CH C N CH CH N CH F 151 S 1 N CH N CH CH C N CH CH N CH F 152 CH.sub.2 1 CH CH N CH CH C CH CH N CH N absent H 153 CH.sub.2 1 N CH N CH CH C CH CH N CH N H 154 S 1 N CH N CH CH C CH CH N CH N H 155 CH.sub.2 1 CH N CH N CH C CH CH CH CH CH F H 156 CH.sub.2 1 N N CH N CH C CH CH CH CH CH F H 157 S 1 N N CH N CH C CH CH CH CH CH F H 158 CH.sub.2 1 CH N CH N CH C N CH CH CH CH F H 159 CH.sub.2 1 N N CH N CH C N CH CH CH CH F H 160 S 1 N N CH N CH C N CH CH CH CH F H 161 CH.sub.2 1 CH N CH N CH C CH N CH CH CH F H 162 CH.sub.2 1 N N CH N CH C CH N CH CH CH F H 163 S 1 N N CH N CH C CH N CH CH CH F H 164 CH.sub.2 1 CH CH N CH N C CH CH CH CH CH F H 165 CH.sub.2 1 N CH N CH N C CH CH CH CH CH F H 166 S 1 N CH N CH N C CH CH CH CH CH F H 167 CH.sub.2 1 CH CH CH N N C CH CH CH CH CH F H 168 CH.sub.2 1 N CH CH N N C CH CH CH CH CH F H 169 S 1 N CH CH N N C CH CH CH CH CH F H 170 CH.sub.2 1 CH CH CH CH N C CH CH CH CH CH F H 171 CH.sub.2 1 N CH CH CH N C CH CH CH CH CH F H 172 S 1 N CH CH CH N C CH CH CH CH CH F H 173 CH.sub.2 1 CH CH CH CH N C CH N CH CH CH F H 174 CH.sub.2 1 N CH CH CH N C CH N CH CH CH F H 175 S 1 N CH CH CH N C CH N CH CH CH F H 176 CH.sub.2 1 CH CH CH CH CH C CH CH CH CH CH OMe OMe 177 CH.sub.2 1 N CH CH CH CH C CH CH CH CH CH OMe OMe 178 S 1 N CH CH CH CH C CH CH CH CH CH OMe OMe 179 CH.sub.2 1 CH CH CH CH CH C N CH CH CH CH OMe OMe 180 CH.sub.2 1 N CH CH CH CH C N CH CH CH CH OMe OMe 181 S 1 N CH CH CH CH C N CH CH CH CH OMe OMe 182 CH.sub.2 1 CH CH CH CH CH C CH N CH CH CH OMe OMe 183 CH.sub.2 1 N CH CH CH CH C CH N CH CH CH OMe OMe 184 S 1 N CH CH CH CH C CH N CH CH CH OMe OMe 185 CH.sub.2 1 CH CH CH CH CH C N CH CH CH N OMe OMe 186 CH.sub.2 1 N CH CH CH CH C N CH CH CH N OMe OMe 187 S 1 N CH CH CH CH C N CH CH CH N OMe OMe 188 CH.sub.2 1 CH CH CH CH CH C N N CH CH CH OMe OMe 189 CH.sub.2 1 N CH CH CH CH C N N CH CH CH OMe OMe 190 S 1 N CH CH CH CH C N N CH CH CH OMe OMe 191 CH.sub.2 1 CH CH CH CH CH C CH N CH N CH OMe absent 192 CH.sub.2 1 N CH CH CH CH C CH N CH N CH OMe 193 S 1 N CH CH CH CH C CH N CH N CH OMe 194 CH.sub.2 1 CH CH CH CH CH C CH CH N CH N absent OMe 195 CH.sub.2 1 N CH CH CH CH C CH CH N CH N OMe 196 S 1 N CH CH CH CH C CH CH N CH

N OMe 197 CH.sub.2 1 CH CH CH CH CH C CH CH N CH CH absent OMe 198 CH.sub.2 1 N CH CH CH CH C CH CH N CH CH OMe 199 S 1 N N CH CH CH C CH CH N CH CH OMe 200 CH.sub.2 1 CH N CH CH CH C CH CH CH CH CH OMe OMe 201 CH.sub.2 1 N N CH CH CH C CH CH CH CH CH OMe OMe 202 S 1 N N CH CH CH C CH CH CH CH CH OMe OMe 203 CH.sub.2 1 CH N CH CH CH C N N CH CH CH OMe OMe 204 CH2 1 N N CH CH CH C N CH CH CH CH OMe OMe 205 S 1 N N CH CH CH C N CH CH CH CH OMe OMe 206 CH.sub.2 1 CH N CH CH CH C CH N CH CH CH OMe OMe 207 CH.sub.2 1 N N CH CH CH C CH N CH CH CH OMe OMe 208 S 1 N N CH CH CH C CH N CH CH CH OMe OMe 209 CH.sub.2 1 CH N CH CH CH C N CH CH CH N OMe OMe 210 CH.sub.2 1 N N CH CH CH C N CH CH CH N OMe OMe 211 S 1 N N CH CH CH C N CH CH CH N OMe OMe 212 CH.sub.2 1 CH N CH CH CH C CH CH N CH N absent OMe 213 CH.sub.2 1 N N CH CH CH C CH CH N CH N OMe 214 S 1 N N CH CH CH C CH CH N CH N OMe 215 CH.sub.2 1 CH N CH CH CH C N CH CH CH CH OMe OMe 216 CH.sub.2 1 N N CH CH CH C N CH CH CH CH OMe OMe 217 S 1 N N CH CH CH C N CH CH CH CH OMe OMe 218 CH.sub.2 1 CH N N CH CH C CH CH N CH N absent OMe 219 CH.sub.2 1 N N N CH CH C CH CH N CH N OMe 220 S 1 N N N CH CH C CH CH N CH N OMe 221 CH.sub.2 1 CH N N CH CH C CH CH CH CH CH OMe OMe 222 CH.sub.2 1 N N N CH CH C CH CH CH CH CH OMe OMe 223 S 1 N N N CH CH C CH CH CH CH CH OMe OMe 224 CH.sub.2 1 CH CH N CH CH C CH CH CH CH CH OMe OMe 225 CH.sub.2 1 N CH N CH CH C CH CH CH CH CH OMe OMe 226 S 1 N CH N CH CH C CH CH CH CH CH OMe OMe 227 CH.sub.2 1 CH CH N CH CH C N CH CH CH CH OMe OMe 228 CH.sub.2 1 N CH N CH CH C N CH CH CH CH OMe OMe 229 S 1 N CH N CH CH C N CH CH CH CH OMe OMe 230 CH.sub.2 1 CH CH N CH CH C CH N CH CH CH OMe OMe 231 CH.sub.2 1 N CH N CH CH C CH N CH CH CH OMe OMe 232 S 1 N CH N CH CH C CH N CH CH CH OMe OMe 233 CH.sub.2 1 CH CH N CH CH C CH N CH N CH OMe absent 234 CH.sub.2 1 N CH N CH CH C CH N CH N CH OMe 235 S 1 N CH N CH CH C CH N CH N CH OMe 236 CH.sub.2 1 CH CH N CH CH C N CH CH N CH OMe OMe 237 CH.sub.2 1 N CH N CH CH C N CH CH N CH OMe OMe 238 S 1 N CH N CH CH C N CH CH N CH OMe OMe 239 CH.sub.2 1 CH CH N CH CH C CH CH N CH N absent OMe 240 CH.sub.2 1 N CH N CH CH C CH CH N CH N OMe 241 S 1 N CH N CH CH C CH CH N CH N OMe 242 CH.sub.2 1 CH CH N CH CH C CH CH N CH CH absent OMe 243 CH.sub.2 1 N CH N CH CH C CH CH N CH CH OMe 244 S 1 N CH N CH CH C CH CH N CH CH OMe 245 CH.sub.2 1 CH N CH N CH C CH CH CH CH CH CH OMe OMe 246 CH.sub.2 1 N N CH N CH C CH CH CH CH CH OMe OMe 247 S 1 N N CH N CH C CH CH CH CH CH OMe OMe 248 CH.sub.2 1 CH N CH N CH C N CH CH CH CH OMe OMe 249 CH.sub.2 1 N N CH N CH C N CH CH CH CH OMe OMe 250 S 1 N N CH N CH C N CH CH CH CH OMe OMe 251 CH.sub.2 1 CH N CH N CH C CH N CH CH CH OMe OMe 252 CH.sub.2 1 N N CH N CH C CH N CH CH CH OMe OMe 253 S 1 N N CH N CH C CH N CH CH CH OMe OMe 254 CH.sub.2 1 CH CH N CH N C CH CH CH CH CH OMe OMe 255 CH.sub.2 1 N CH N CH N C CH CH CH CH CH OMe OMe 256 S 1 N CH N CH N C CH CH CH CH CH OMe OMe 257 CH.sub.2 1 CH CH CH N N C CH CH CH CH CH OMe OMe 258 CH.sub.2 1 N CH CH N N C CH CH CH CH CH OMe OMe 259 S 1 N CH CH N N C CH CH CH CH CH OMe OMe 260 CH.sub.2 1 CH CH CH CH N C CH CH CH CH CH OMe OMe 261 CH.sub.2 1 N CH CH CH N C CH CH CH CH CH OMe OMe 262 S 1 N CH CH CH N C CH CH CH CH CH OMe OMe 263 CH.sub.2 1 CH CH CH CH N C CH CH N CH CH absent OMe 264 CH.sub.2 1 N CH CH CH N C CH CH N CH CH OMe 265 S 1 N CH CH CH N C CH CH N CH CH OMe

(4) In a further embodiment, the present invention provides compounds of formula (IIIa) and (IIIb), wherein X.sub.1, n, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 266 to 443:

(5) ##STR00049##

(6) TABLE-US-00004 Comp X.sub.1 n Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7

Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 266 CH.sub.2 1 CH CH CH CH C CH CH CH CH CH H H 267 S 1 CH CH CH CH C CH CH CH CH CH H H 268 CH.sub.2 1 CH CH CH CH C N CH CH CH CH H H 269 S 1 CH CH CH CH C N CH CH CH CH H H 270 CH.sub.2 1 CH CH CH CH C CH N CH CH CH H H 271 S 1 CH CH CH CH C CH N CH CH CH H H 272 CH.sub.2 1 CH CH CH CH C N CH CH CH N H H 273 S 1 CH CH CH CH C N CH CH CH N H H 274 CH.sub.2 1 CH CH CH CH C N N CH CH CH H H 275 S 1 CH CH CH CH C N N CH CH CH H H 276 CH.sub.2 1 CH CH CH CH C CH N CH N CH H absent 277 S 1 CH CH CH CH C CH N CH N CH H 278 CH.sub.2 1 CH CH CH CH C CH CH N CH N absent H 279 S 1 CH CH CH CH C CH CH N CH N H 280 CH.sub.2 1 CH CH CH CH C CH CH N CH CH absent H 281 S 1 CH CH CH CH C CH CH N CH CH H 282 CH.sub.2 1 N CH CH CH C CH CH CH CH CH H H 283 S 1 N CH CH CH C CH CH CH CH CH H H 284 CH.sub.2 1 N CH CH CH C N CH CH CH CH H H 285 S 1 N CH CH CH C N CH CH CH CH H H 286 CH.sub.2 1 N CH CH CH C CH N CH CH CH H H 287 CH.sub.2 1 N CH CH CH C CH N CH CH CH H H 288 S 1 N CH CH CH C CH N CH CH CH H H 289 CH.sub.2 1 N CH CH CH C N CH CH CH N H H 290 S 1 N CH CH CH C N CH CH CH N H H 291 CH.sub.2 1 N CH CH CH C CH CH N CH N absent H 292 S 1 N CH CH CH C CH CH N CH N H 293 CH.sub.2 1 N CH CH CH C N CH CH CH CH H H 294 S 1 N CH CH CH C N CH CH CH CH H H 295 CH.sub.2 1 N N CH CH C CH CH N CH N absent H 296 CH.sub.2 1 N N CH CH C CH CH N CH N H 297 S 1 N N CH CH C CH CH N CH N H 298 CH.sub.2 1 N N CH CH C CH CH CH CH CH H H 299 S 1 N N CH CH C CH CH CH CH CH H H 300 CH.sub.2 1 CH N CH CH C CH CH CH CH CH H H 301 S 1 CH N CH CH C CH CH CH CH CH H H 302 CH.sub.2 1 CH N CH CH C N CH CH CH CH H H 303 S 1 CH N CH CH C N CH CH CH CH H H 304 CH.sub.2 1 CH N CH CH C CH N CH CH CH H H 305 S 1 CH N CH CH C CH N CH CH CH H H 306 CH.sub.2 1 CH N CH CH C CH N CH N CH H absent 307 S 1 CH N CH CH C CH N CH N CH H 308 CH.sub.2 1 CH N CH CH C N CH CH N CH H H 309 S 1 CH N CH CH C N CH CH N CH H H 310 CH.sub.2 1 CH N CH CH C CH CH N CH N absent H 311 S 1 CH N CH CH C CH CH N CH N H 312 CH.sub.2 1 CH N CH CH C CH CH N CH CH absent H 313 S 1 CH N CH CH C CH CH N CH CH H 314 CH.sub.2 1 N CH N CH C CH CH CH CH CH H H 315 S 1 N CH N CH C CH CH CH CH CH H H 316 CH.sub.2 1 N CH N CH C N CH CH CH CH H H 317 S 1 N CH N CH C N CH CH CH CH H H 318 CH.sub.2 1 N CH N CH C CH N CH CH CH H H 319 S 1 N CH N CH C CH N CH CH CH H H 320 CH.sub.2 1 CH N CH N C CH CH CH CH CH H H 321 S 1 CH N CH N C CH CH CH CH CH H H 322 CH.sub.2 1 CH CH N N C CH CH CH CH CH H H 323 S 1 CH CH N N C CH CH CH CH CH H H 324 CH.sub.2 1 CH CH CH N C CH CH CH CH CH H H 325 S 1 CH CH CH N C CH CH CH CH CH H H 326 CH.sub.2 1 CH CH CH N C CH CH N CH CH absent H 327 S 1 CH CH CH N C CH CH N CH CH H 328 CH.sub.2 1 CH CH CH CH C CH CH CH CH CH F H 329 S 1 CH CH CH CH C CH CH CH CH CH F H 330 CH.sub.2 1 CH CH CH CH C N CH CH CH CH F H 331 S 1 CH CH CH CH C N CH CH CH CH F H 332 CH.sub.2 1 CH CH CH CH C CH N CH CH CH F H 333 S 1 CH CH CH CH C CH N CH CH CH F H 334 CH.sub.2 1 CH CH CH CH C N CH CH CH N F H 335 S 1 CH CH CH CH C N CH CH CH N F H 336 CH.sub.2 1 CH CH CH CH C N N CH CH CH F H 337 S 1 CH CH CH CH C N N CH CH CH F H 338 CH.sub.2 1 CH CH CH CH C CH N CH N CH F absent 339 S 1 CH CH CH CH C CH N CH N CH F 340 CH.sub.2 1 CH CH CH CH C CH CH N CH N absent 341 S 1 CH CH CH CH C CH CH N CH N 342 CH.sub.2 1 CH CH CH CH C CH CH N CH CH absent H 343 S 1 CH CH CH CH C CH CH N CH CH H 344 CH.sub.2 1 N CH CH CH C CH CH CH CH CH F H 345 S 1 N CH CH CH C CH CH CH CH CH F H 346 CH.sub.2 1 N CH CH CH C N CH CH CH CH F H 347 S 1 N CH CH CH C N CH CH CH CH F H 348 CH.sub.2 1 N CH CH CH C CH N CH CH CH F H 349 S 1 N CH CH CH C CH N CH CH CH F H 350 CH.sub.2 1 N CH CH CH C N CH CH CH N F H 351 S 1 N CH CH CH C N CH CH CH N F H 352 CH.sub.2 1 N CH CH CH C CH CH N CH N absent H 353 S 1 N CH CH CH C CH CH N CH N H 354 CH.sub.2 1 N N CH CH C CH CH CH CH CH F H 355 S 1 N N CH CH C CH CH CH CH CH F H 356 CH.sub.2 1 N N CH CH C CH CH N CH N absent H 357 S 1 N N CH CH C

CH CH N CH N H 358 CH.sub.2 1 CH N CH CH C CH CH CH CH CH F H 359 S 1 CH N CH CH C CH CH CH CH CH F H 360 CH.sub.2 1 CH N CH CH C N CH CH CH CH F H 361 S 1 CH N CH CH C N CH CH CH CH F H 362 CH.sub.2 1 CH N CH CH C CH N CH CH CH F H 363 S 1 CH N CH CH C CH N CH CH CH F H 364 CH.sub.2 1 CH N CH CH C CH N CH N CH F absent 365 S 1 CH N CH CH C CH N CH N CH F 366 CH.sub.2 1 CH N CH CH C N CH CH N CH F absent 367 S 1 CH N CH CH C N CH CH N CH F 368 CH.sub.2 1 CH N CH CH C CH CH N CH N absent H 369 S 1 CH N CH CH C CH CH N CH N H 370 CH.sub.2 1 N CH N CH C CH CH CH CH CH F H 371 S 1 N CH N CH C CH CH CH CH CH F H 372 CH.sub.2 1 N CH N CH C N CH CH CH CH F H 373 S 1 N CH N CH C N CH CH CH CH F H 374 CH.sub.2 1 N CH N CH C CH N CH CH CH F H 375 S 1 N CH N CH C CH N CH CH CH F H 376 CH.sub.2 1 CH N CH N C CH CH CH CH CH F H 377 S 1 CH N CH N C CH CH CH CH CH F H 378 CH.sub.2 1 CH CH N N C CH CH CH CH CH F H 379 S 1 CH CH N N C CH CH CH CH CH F H 380 CH.sub.2 1 CH CH CH N C CH CH CH CH CH F H 381 S 1 CH CH CH N C CH CH CH CH CH F H 382 CH.sub.2 1 CH CH CH N C CH N CH CH CH F H 383 S 1 CH CH CH N C CH N CH CH CH F H 384 CH.sub.2 1 CH CH CH CH C CH CH CH CH CH OMe OMe 385 S 1 CH CH CH CH C CH CH CH CH CH OMe OMe 386 CH.sub.2 1 CH CH CH CH C N CH CH CH CH OMe OMe 387 S 1 CH CH CH CH C N CH CH CH CH OMe OMe 388 CH.sub.2 1 CH CH CH CH C CH N CH CH CH OMe OMe 389 S 1 CH CH CH CH C CH N CH CH CH OMe OMe 390 CH.sub.2 1 CH CH CH CH C N CH CH CH N OMe OMe 391 S 1 CH CH CH CH C N CH CH CH N OMe OMe 392 CH.sub.2 1 CH CH CH CH C N N CH CH CH OMe OMe 393 S 1 CH CH CH CH C N N CH CH CH OMe OMe 394 CH.sub.2 1 CH CH CH CH C CH N CH N CH OMe absent 395 S 1 CH CH CH CH C CH N CH N CH OMe 396 CH.sub.2 1 CH CH CH CH C CH CH N CH N absent OMe 397 S 1 CH CH CH CH C CH CH N CH N OMe 398 CH.sub.2 1 CH CH CH CH C CH CH N CH CH absent OMe 399 S 1 CH CH CH CH C CH CH N CH CH OMe 400 CH.sub.2 1 N CH CH CH C CH CH CH CH CH OMe OMe 401 S 1 N CH CH CH C CH CH CH CH CH OMe OMe 402 CH.sub.2 1 N CH CH CH C N CH CH CH CH OMe OMe 403 S 1 N CH CH CH C N CH CH CH CH OMe OMe 404 CH.sub.2 1 N CH CH CH C CH N CH CH CH OMe OMe 405 S 1 N CH CH CH C CH N CH CH CH OMe OMe 406 CH.sub.2 1 N CH CH CH C N CH CH CH N OMe OMe 407 S 1 N CH CH CH C N CH CH CH N OMe OMe 408 CH.sub.2 1 N CH CH CH C CH CH N CH N absent OMe 409 S 1 N CH CH CH C CH CH N CH N OMe 410 CH.sub.2 1 N CH CH CH C N CH CH CH CH OMe OMe 411 S 1 N CH CH CH C N CH CH CH CH OMe OMe 412 CH.sub.2 1 N N CH CH C CH CH N CH N absent OMe 413 S 1 N N CH CH C CH CH N CH N OMe 414 CH.sub.2 1 N N CH CH C CH CH CH CH CH OMe OMe 415 S 1 N N CH CH C CH CH CH CH CH OMe OMe 416 CH.sub.2 1 CH N CH CH C CH CH CH CH CH OMe OMe 417 S 1 CH N CH CH C CH CH CH CH CH OMe OMe 418 CH.sub.2 1 CH N CH CH C N CH CH CH CH OMe OMe 419 S 1 CH N CH CH C N CH CH CH CH OMe OMe 420 CH.sub.2 1 CH N CH CH C CH N CH CH CH OMe OMe 421 S 1 CH N CH CH C CH N CH CH CH OMe OMe 422 CH.sub.2 1 CH N CH CH C CH N CH N CH OMe absent 423 S 1 CH N CH CH C CH N CH N CH OMe 424 CH.sub.2 1 CH N CH CH C N CH CH N CH OMe OMe 425 S 1 CH N CH CH C N CH CH N CH OMe OMe 426 CH.sub.2 1 CH N CH CH C CH CH N CH N absent OMe 427 S 1 CH N CH CH C CH CH N CH N OMe 428 CH.sub.2 1 CH N CH CH C CH CH N CH CH OMe absent 429 S 1 CH N CH CH C CH CH N CH CH OMe 430 CH.sub.2 1 N CH N CH C CH CH CH CH CH OMe OMe 431 S 1 N CH N CH C CH CH CH CH CH OMe OMe 432 CH.sub.2 1 N CH N CH C N CH CH CH CH OMe OMe 433 S 1 N CH N CH C N CH CH CH CH OMe OMe 434 CH.sub.2 1 N CH N CH C CH N CH CH CH OMe OMe 435 S 1 N CH N CH C CH N CH CH CH OMe OMe 436 CH.sub.2 1 CH N CH N C CH CH CH CH CH OMe OMe 437 S 1 CH N CH N C CH CH CH CH CH OMe OMe 438 CH.sub.2 1 CH CH N N C CH CH CH CH CH OMe OMe 439 S 1 CH CH N N C CH CH CH CH CH OMe OMe 440 CH.sub.2 1 CH CH CH N C CH CH CH CH CH OMe OMe 441 S 1 CH CH CH N C CH CH CH CH CH OMe OMe 442 CH.sub.2 1 CH CH CH N C CH CH N CH CH absent OMe 443 S 1 CH CH CH N C CH CH

N CH CH OMe
(7) In a further embodiment, the present invention provides compounds of formula (Iva) and (IVb), wherein X.sub.1, o, Z, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 444 to 795:
(8) ##STR00050##
(9) In both, formulae (IVa) and (IVb), o is 0.
(10) TABLE-US-00005 Comp p Z Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 444 0 CH CH CH CH CH C CH CH CH CH CH H H 445 0 N CH CH CH CH C CH CH CH CH CH H H 446 0 CH CH CH CH CH C N CH CH CH CH H H 447 0 N CH CH CH CH C N CH CH CH CH H H 448 0 CH CH CH CH CH C CH N CH CH CH H H 449 0 N CH CH CH CH C CH N CH CH CH H H 450 0 CH CH CH CH CH C N CH CH CH N H H 451 0 N CH CH CH CH C N CH CH CH N H H 452 0 CH CH CH CH CH C N N CH CH CH H H 453 0 N CH CH CH CH C N N CH CH CH H H 454 0 CH CH CH CH CH C CH N CH N CH H absent 455 0 N CH CH CH CH C CH N CH N CH H 456 0 CH CH CH CH CH C CH CH N CH N absent H 457 0 N CH CH CH CH C CH CH N CH N H 458 0 CH CH CH CH CH C CH CH N CH CH absent H 459 0 N CH CH CH CH C CH CH N CH CH H 460 0 CH N CH CH CH C CH CH CH CH CH H H 461 0 N N CH CH CH C CH CH CH CH CH H H 462 0 CH N CH CH CH C N CH CH CH CH H H 463 0 N N CH CH CH C N CH CH CH CH H H 464 0 CH N CH CH CH C CH N CH CH CH H H 465 0 N N CH CH CH C CH N CH CH CH H H 466 0 CH N CH CH CH C N CH CH CH N H H 467 0 N N CH CH CH C N CH CH CH N H H 468 0 CH N CH CH CH C CH CH N CH N absent H 469 0 N N CH CH CH C CH CH N CH N H 470 0 CH N CH CH CH C N CH CH CH CH H H 471 0 N N CH CH CH C N CH CH CH CH H H 472 0 CH N N CH CH C CH CH N CH N absent H 473 0 N N N CH CH C CH CH N CH N H 474 0 CH N N CH CH C CH CH CH CH CH H H 475 0 N N N CH CH C CH CH CH CH CH H H 476 0 CH CH N CH CH C CH CH CH CH CH H H 477 0 N CH N CH CH C CH CH CH CH CH H H 478 0 CH CH N CH CH C N CH CH CH CH H H 479 0 N CH N CH CH C N CH CH CH CH H H 480 0 CH CH N CH CH C CH N CH CH CH H H 481 0 N CH N CH CH C CH N CH CH CH H H 482 0 CH CH N CH CH C CH N CH N CH H absent 483 0 N CH N CH CH C CH N CH N CH H 484 0 CH CH N CH CH C N CH CH N CH H H 485 0 N CH N CH CH C N CH CH N CH H H 486 0 CH CH N CH CH C CH CH N CH N absent H 487 0 N CH N CH CH C CH CH N CH N H 488 0 CH CH N CH CH C CH CH N CH CH absent H 489 0 N CH N CH CH C CH CH N CH CH H 490 0 CH N CH N CH C CH CH CH CH CH H H 491 0 N N CH N CH C CH CH CH CH CH H H 492 0 CH N CH N CH C N CH CH CH CH H H 493 0 N N CH N CH C N CH CH CH CH H H 494 0 CH N CH N CH C CH N CH CH CH H H 495 0 N N CH N CH C CH N CH CH CH H H 496 0 CH CH N CH N C CH CH CH CH CH H H 497 0 N CH N CH N C CH CH CH CH CH H H 498 0 CH CH CH N N C CH CH CH CH CH H H 499 0 N CH CH N N C CH CH CH CH CH H H 500 0 CH CH CH CH N C CH CH CH CH CH H H 501 0 N CH CH CH N C CH CH CH CH CH H H 502 0 CH CH CH CH N C CH CH N CH CH absent H 503 0 N CH CH CH N C CH CH N CH CH H 504 0 CH CH CH CH CH C CH CH CH CH CH F H 505 0 N CH CH CH CH C CH CH CH CH CH F H 506 0 CH CH CH CH CH C N CH CH CH CH F H 507 0 N CH CH CH CH C N CH CH CH CH F H 508 0 CH CH CH CH CH C CH N CH CH CH F H 509 0 N CH CH CH CH C CH N CH CH CH F H 510 0 CH CH CH CH CH C N CH CH CH N F H 511 0 N CH CH CH CH C N CH CH CH N F H 512 0 CH CH CH CH CH C N N CH CH CH F H 513 0 N CH CH CH CH C N N CH CH CH F H 514 0 CH CH CH CH CH C CH N CH N CH F absent 515 0 N CH CH CH CH C CH N CH N CH F 516 0 CH CH CH CH CH C CH CH N CH N absent 517 0 N CH CH CH CH C CH CH N CH N 518 0 CH CH CH CH CH C CH CH N CH CH absent H 519 0 N CH CH CH CH C CH CH N CH CH H 520 0 CH N CH CH CH C CH CH CH CH CH F H 521 0 N N CH CH CH C CH CH CH CH CH F H 522 0 CH N CH CH CH C N CH CH CH CH F H 523 0 N N CH CH CH C N CH CH CH CH F H 524 0 CH N CH CH CH C CH N CH CH CH F H 525 0 N N CH CH CH C CH N CH CH CH F H 526 0 CH N CH CH CH C N CH CH CH N F H 527 0 N N CH CH CH C N CH

CH CH N F H 528 0 CH N CH CH CH C CH CH N CH N absent H 529 0 N N CH CH CH C CH CH N CH N H 530 0 CH N N CH CH C CH CH CH CH CH F H 531 0 N N N CH CH C CH CH CH CH CH F H 532 0 CH N N CH CH C CH CH N CH N absent H 533 0 N N N CH CH C CH CH N CH N H 534 0 CH CH N CH CH C CH CH CH CH CH F H 535 0 N CH N CH CH C CH CH CH CH CH F H 536 0 CH CH N CH CH C N CH CH CH CH F H 537 0 N CH N CH CH C N CH CH CH CH F H 538 0 CH CH N CH CH C CH N CH CH CH F H 539 0 N CH N CH CH C CH N CH CH CH F H 540 0 CH CH N CH CH C CH N CH N CH H absent 541 0 N CH N CH CH C CH N CH N CH F 542 0 CH CH N CH CH C N CH CH N CH F absent 543 0 N CH N CH CH C N CH CH N CH F 544 0 CH CH N CH CH C CH CH N CH N absent H 545 0 N CH N CH CH C CH CH N CH N H 546 0 CH N CH N CH C CH CH CH CH CH F H 547 0 N N CH N CH C CH CH CH CH CH F H 548 0 CH N CH N CH C N CH CH CH CH F H 549 0 N N CH N CH C N CH CH CH CH F H 550 0 CH N CH N CH C CH N CH CH CH F H 551 0 N N CH N CH C CH N CH CH CH F H 552 0 CH CH N CH N C CH CH CH CH CH F H 553 0 N CH N CH N C CH CH CH CH CH F H 554 0 CH CH CH N N C CH CH CH CH CH F H 555 0 N CH CH N N C CH CH CH CH CH F H 556 0 CH CH CH CH N C CH CH CH CH CH F H 557 0 N CH CH CH N C CH CH CH CH CH F H 558 0 CH CH CH CH N C CH N CH CH CH F H 559 0 N CH CH CH N C CH N CH CH CH F H 560 0 CH CH CH CH CH C CH CH CH CH CH OMe OMe 561 0 N CH CH CH CH C CH CH CH CH CH OMe OMe 562 0 CH CH CH CH CH C N CH CH CH CH OMe OMe 563 0 N CH CH CH CH C N CH CH CH CH OMe OMe 564 0 CH CH CH CH CH C CH N CH CH CH OMe OMe 565 0 N CH CH CH CH C CH N CH CH CH OMe OMe 566 0 CH CH CH CH CH C N CH CH CH N OMe OMe 567 0 N CH CH CH CH C N CH CH CH N OMe OMe 568 0 CH CH CH CH CH C N N CH CH CH OMe OMe 569 0 N CH CH CH CH C N N CH CH CH OMe OMe 570 0 CH CH CH CH CH C CH N CH N CH OMe absent 571 0 N CH CH CH CH C CH N CH N CH OMe 572 0 CH CH CH CH CH C CH CH N CH N absent OMe 573 0 N CH CH CH CH C CH CH N CH N OMe 574 0 CH CH CH CH CH C CH CH N CH CH absent OMe 575 0 N CH CH CH CH C CH CH N CH CH OMe 576 0 CH N CH CH CH C CH CH CH CH CH OMe OMe 577 0 N N CH CH CH C CH CH CH CH CH OMe OMe 578 0 CH N CH CH CH C N CH CH CH CH OMe OMe 579 0 N N CH CH CH C N CH CH CH CH OMe OMe 580 0 CH N CH CH CH C CH N CH CH CH OMe OMe 581 0 N N CH CH CH C CH N CH CH CH OMe OMe 582 0 CH N CH CH CH C N CH CH CH N OMe OMe 583 0 N N CH CH CH C N CH CH CH N OMe OMe 584 0 CH N CH CH CH C CH CH N CH N absent OMe 585 0 N N CH CH CH C CH CH N CH N OMe 586 0 CH N CH CH CH C N CH CH CH CH OMe OMe 587 0 N N CH CH CH C N CH CH CH CH OMe OMe 588 0 CH N N CH CH C CH CH N CH N absent OMe 589 0 N N N CH CH C CH CH N CH N OMe 590 0 CH N N CH CH C CH CH CH CH CH OMe OMe 591 0 N N N CH CH C CH CH CH CH CH OMe OMe 592 0 CH CH N CH CH C CH CH CH CH CH OMe OMe 593 0 N CH N CH CH C CH CH CH CH CH OMe OMe 594 0 CH CH N CH CH C N CH CH CH CH OMe OMe 595 0 N CH N CH CH C N CH CH CH CH OMe OMe 596 0 CH CH N CH CH C CH N CH CH CH OMe OMe 597 0 N CH N CH CH C CH N CH CH CH OMe OMe 598 0 CH CH N CH CH C CH N CH N CH OMe absent 599 0 N CH N CH CH C CH N CH N CH OMe 600 0 CH CH N CH CH C N CH CH N CH OMe OMe 601 0 N CH N CH CH C N CH CH N CH OMe OMe 602 0 CH CH N CH CH C CH CH N CH N absent OMe 603 0 N CH N CH CH C CH CH N CH N OMe 604 0 CH CH N CH CH C CH CH N CH CH absent OMe 605 0 N CH N CH CH C CH CH N CH CH OMe 606 0 CH N CH N CH C CH CH CH CH CH OMe OMe 607 0 N N CH N CH C CH CH CH CH CH OMe OMe 608 0 CH N CH N CH C N CH CH CH CH OMe OMe 609 0 N N CH N CH C N CH CH CH CH OMe OMe 610 0 CH N CH N CH C CH N CH CH CH OMe OMe 611 0 N N CH N CH C CH N CH CH CH OMe OMe 612 0 CH CH N CH N C CH CH CH CH CH OMe OMe 613 0 N CH N CH N C CH CH CH CH CH OMe OMe 614 0 CH CH CH N N C CH CH CH CH CH OMe OMe 615 0 N CH CH N N C CH CH CH CH CH OMe OMe 616 0 CH CH CH CH N C CH CH CH CH CH OMe OMe 617 0 N CH CH CH N C CH CH CH CH CH OMe OMe 618 0 CH CH CH CH N C CH CH N CH CH absent OMe 619 0 N CH CH

CH N C CH CH N CH CH OMe 620 1 CH CH CH CH CH C CH CH CH CH CH H H 621 1 N CH CH CH CH C CH CH CH CH CH H H 622 1 CH CH CH CH CH C N CH CH CH CH H H 623 1 N CH CH CH CH C N CH CH CH CH H H 624 1 CH CH CH CH CH C CH N CH CH CH H H 625 1 N CH CH CH CH C CH N CH CH CH H H 626 1 CH CH CH CH CH C N CH CH CH N H H 627 1 N CH CH CH CH C N CH CH CH N H H 628 1 CH CH CH CH CH C N N CH CH CH H H 629 1 N CH CH CH CH C N N CH CH CH H H 630 1 CH CH CH CH CH C CH N CH N CH H absent 631 1 N CH CH CH CH C CH N CH N CH H 632 1 CH CH CH CH CH C CH CH N CH N absent H 633 1 N CH CH CH CH C CH CH N CH N H 634 1 CH CH CH CH CH C CH CH N CH CH absent H 635 1 N CH CH CH CH C CH CH N CH CH H 636 1 CH N CH CH CH C CH CH CH CH CH H H 637 1 N N CH CH CH C CH CH CH CH CH H H 638 1 CH N CH CH CH C N CH CH CH CH H H 639 1 N N CH CH CH C N CH CH CH CH H H 640 1 CH N CH CH CH C CH N CH CH CH H H 641 1 N N CH CH CH C CH N CH CH CH H H 642 1 CH N CH CH CH C N CH CH CH N H H 643 1 N N CH CH CH C N CH CH CH N H H 644 1 CH N CH CH CH C CH CH N CH N absent H 645 1 N N CH CH CH C CH CH N CH N H 646 1 CH N CH CH CH C N CH CH CH CH H H 647 1 N N CH CH CH C N CH CH CH CH H H 648 1 CH N N CH CH C CH CH N CH N absent H 649 1 N N N CH CH C CH CH N CH N H 650 1 CH N N CH CH C CH CH CH CH CH H H 651 1 N N N CH CH C CH CH CH CH CH H H 652 1 CH CH N CH CH C CH CH CH CH CH H H 653 1 N CH N CH CH C CH CH CH CH CH H H 654 1 CH CH N CH CH C N CH CH CH CH H H 655 1 N CH N CH CH C N CH CH CH CH H H 656 1 CH CH N CH CH C CH N CH CH CH H H 657 1 N CH N CH CH C CH N CH CH CH H H 658 1 CH CH N CH CH C CH N CH N CH H absent 659 1 N CH N CH CH C CH N CH N CH H 660 1 CH CH N CH CH C N CH CH N CH H H 661 1 N CH N CH CH C N CH CH N CH H H 662 1 CH CH N CH CH C CH CH N CH N absent H 663 1 N CH N CH CH C CH CH N CH N H 664 1 CH CH N CH CH C CH CH N CH CH absent H 665 1 N CH N CH CH C CH CH N CH CH H 666 1 CH N CH N CH C CH CH CH CH CH H H 667 1 N N CH N CH C CH CH CH CH CH H H 668 1 CH N CH N CH C N CH CH CH CH H H 669 1 N N CH N CH C N CH CH CH CH H H 670 1 CH N CH N CH C CH N CH CH CH H H 671 1 N N CH N CH C CH N CH CH CH H H 672 1 CH CH N CH N C CH CH CH CH CH H H 673 1 N CH N CH N C CH CH CH CH CH H H 674 1 CH CH CH N N C CH CH CH CH CH H H 675 1 N CH CH N N C CH CH CH CH CH H H 676 1 CH CH CH CH N C CH CH CH CH CH H H 677 1 N CH CH CH N C CH CH CH CH CH H H 678 1 CH CH CH CH N C CH CH N CH CH absent H 679 1 N CH CH CH N C CH CH N CH CH H 680 1 CH CH CH CH CH C CH CH CH CH CH F H 681 1 N CH CH CH CH C CH CH CH CH CH F H 682 1 CH CH CH CH CH C N CH CH CH CH F H 683 1 N CH CH CH CH C N CH CH CH CH F H 684 1 CH CH CH CH CH C CH N CH CH CH F H 685 1 N CH CH CH CH C CH N CH CH CH F H 686 1 CH CH CH CH CH CH C N CH CH CH N F H 687 1 N CH CH CH CH C N CH CH CH N F H 688 1 CH CH CH CH CH CH C N N CH CH CH F H 689 1 N CH CH CH CH C N N CH CH CH F H 690 1 CH CH CH CH CH CH C CH N CH N CH F absent 691 1 N CH CH CH CH C CH N CH N CH F 692 1 CH CH CH CH CH C CH CH N CH N absent 693 1 N CH CH CH CH C CH CH N CH N 694 1 CH CH CH CH CH CH C CH CH N CH CH absent H 695 1 N CH CH CH CH C CH CH N CH CH H 696 1 CH N CH CH CH C CH CH CH CH CH F H 697 1 N N CH CH CH C CH CH CH CH CH CH F H 698 1 CH N CH CH CH C N CH CH CH CH F H 699 1 N N CH CH CH C N CH CH CH CH F H 700 1 CH N CH CH CH C CH N CH CH CH F H 701 1 N N CH CH CH C CH N CH CH CH F H 702 1 CH N CH CH CH C N CH CH CH N F H 703 1 N N CH CH CH C N CH CH CH N F H 704 1 CH N CH CH CH C CH CH N CH N absent H 705 1 N N CH CH CH C CH CH N CH N H 706 1 CH N N CH CH C CH CH CH CH CH F H 707 1 N N N CH CH C CH CH CH CH CH F H 708 1 CH N N CH CH C CH CH N CH N absent H 709 1 N N N CH CH C CH CH N CH N H 710 1 CH CH N CH CH C CH CH CH CH CH F H 711 1 N CH N CH CH C CH CH CH CH CH F H 712 1 CH CH N CH CH C N CH CH CH CH F H 713 1 N CH N CH CH C N CH CH CH CH F H 714 1 CH CH N CH CH C CH N CH CH CH F H 715 1 N CH N CH CH C CH N CH CH CH F H 716 1 CH CH N CH CH C CH N CH N CH F absent 717 1 N CH N CH CH

C CH N CH N CH F 718 1 CH CH N CH CH C N CH CH N CH F absent 719 1 N CH N CH CH C N CH CH N CH F 720 1 CH CH N CH CH C CH CH N N absent H 721 1 N CH N CH CH C CH CH N N H 722 1 CH N CH N CH C CH CH CH CH CH F H 723 1 N N CH N CH C CH CH CH CH CH F H 724 1 CH N CH N CH C N CH CH CH CH F H 725 1 N N CH N CH C N CH CH CH CH F H 726 1 CH N CH N CH C CH N CH CH CH F H 727 1 N N CH N CH C CH N CH CH CH F H 728 1 CH CH N CH N C CH CH CH CH CH F H 729 1 N CH N CH N C CH CH CH CH CH F H 730 1 CH CH CH N N C CH CH CH CH CH F H 731 1 N CH CH N N C CH CH CH CH CH F H 732 1 CH CH CH CH N C CH CH CH CH CH F H 733 1 N CH CH CH N C CH CH CH CH CH F H 734 1 CH CH CH CH N C CH N CH CH CH F H 735 1 N CH CH CH N C CH N CH CH CH F H 736 1 CH CH CH CH CH C CH CH CH CH CH OMe OMe 737 1 N CH CH CH CH C CH CH CH CH CH OMe OMe 738 1 CH CH CH CH CH C N CH CH CH CH OMe OMe 739 1 N CH CH CH CH C N CH CH CH CH OMe OMe 740 1 CH CH CH CH CH C CH N CH CH CH OMe OMe 741 1 N CH CH CH CH C CH N CH CH CH OMe OMe 742 1 CH CH CH CH CH C N CH CH CH N OMe OMe 743 1 N CH CH CH CH C N CH CH CH N OMe OMe 744 1 CH CH CH CH CH C N N CH CH CH OMe OMe 745 1 N CH CH CH CH C N N CH CH CH OMe OMe 746 1 CH CH CH CH CH C CH N CH N CH OMe absent 747 1 N CH CH CH CH C CH N CH N CH OMe 748 1 CH CH CH CH CH C CH CH N CH N absent OMe 749 1 N CH CH CH CH C CH CH N CH N OMe 750 1 CH CH CH CH CH C CH CH N CH CH absent OMe 751 1 N CH CH CH CH C CH CH N CH CH OMe 752 1 CH N CH CH CH C CH CH CH CH CH OMe OMe 753 1 N N CH CH CH C CH CH CH CH CH OMe OMe 754 1 CH N CH CH CH C N CH CH CH CH OMe OMe 755 1 N N CH CH CH C N CH CH CH CH OMe OMe 756 1 CH N CH CH CH C CH N CH CH CH OMe OMe 757 1 N N CH CH CH C CH N CH CH CH OMe OMe 758 1 CH N CH CH CH C N CH CH CH N OMe OMe 759 1 N N CH CH CH C N CH CH CH N OMe OMe 760 1 CH N CH CH CH C CH CH N CH N absent OMe 761 1 N N CH CH CH C CH CH N CH N OMe 762 1 CH N CH CH CH C N CH CH CH CH OMe OMe 763 1 N N CH CH CH C N CH CH CH CH OMe OMe 764 1 CH N N CH CH C CH CH N CH N absent OMe 765 1 N N N CH CH C CH CH N CH N OMe 766 1 CH N N CH CH C CH CH CH CH CH OMe OMe 767 1 N N N CH CH C CH CH CH CH CH OMe OMe 768 1 CH CH N CH CH C CH CH CH CH CH OMe OMe 769 1 N CH N CH CH C CH CH CH CH CH OMe OMe 770 1 CH CH N CH CH C N CH CH CH CH OMe OMe 771 1 N CH N CH CH C N CH CH CH CH OMe OMe 772 1 CH CH N CH CH C CH N CH CH CH OMe OMe 773 1 N CH N CH CH C CH N CH CH CH OMe OMe 774 1 CH CH N CH CH C CH N CH N CH OMe absent 775 1 N CH N CH CH C CH N CH N CH OMe 776 1 CH CH N CH CH C N CH CH N CH OMe OMe 777 1 N CH N CH CH C N CH CH N CH OMe OMe 778 1 CH CH N CH CH C CH CH N CH N absent OMe 779 1 N CH N CH CH C CH CH N CH N OMe 780 1 CH CH N CH CH C CH CH N CH CH absent OMe 781 1 N CH N CH CH C CH CH N CH CH OMe 782 1 CH N CH N CH C CH CH CH CH CH OMe OMe 783 1 N N CH N CH C CH CH CH CH CH OMe OMe 784 1 CH N CH N CH C N CH CH CH CH OMe OMe 785 1 N N CH N CH C N CH CH CH CH OMe OMe 786 1 CH N CH N CH C CH N CH CH CH OMe OMe 787 1 N N CH N CH C CH N CH CH CH OMe OMe 788 1 CH CH N CH N C CH CH CH CH CH OMe OMe 789 1 N CH N CH N C CH CH CH CH CH OMe OMe 790 1 CH CH CH N N C CH CH CH CH CH OMe OMe 791 1 N CH CH N N C CH CH CH CH CH OMe OMe 792 1 CH CH CH CH N C CH CH CH CH CH OMe OMe 793 1 N CH CH CH N C CH CH CH CH CH OMe OMe 794 1 CH CH CH CH N C CH CH N CH CH absent OMe 795 1 N CH CH CH N C CH CH N CH CH OMe

(11) In a further embodiment, the present invention provides compounds of formula (IVa) and (IVb), wherein X.sub.1, o, Z, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 1289 to 1296:

(12) ##STR00051##

(13) In both, formulae (IVa) and (Vb), o is 0.

(14) TABLE-US-00006 Comp p Z Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8

Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 1289 0 N CH CH CH CH C CH CH CH CH CH OMe H 1290 0 N N CH CH CH C CH CH CH CH CH OMe H 1291 0 N CH CH N CH C CH CH CH CH CH OMe H 1292 0 N CH CH N CH C CH CH CH CH CH OMe OMe 1293 0 N N CH CH N C CH CH CH CH CH F H 1294 0 N CH CH CH C CH CH CH CH CH CH O-Phenyl H 1295 0 N CH CH CH CH C CH CH CH CH CH propoxy H 1296 0 N CH CH CH CH C CH CH CH CH CH propan-2-yloxy H

(15) In a further embodiment, the present invention provides compounds of formula (Va) and (Vb), wherein o, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.8, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 796 to 971:

(16) ##STR00052##

(17) In both, formulae (Va) and (Vb), o is 0.

(18) TABLE-US-00007 Comp p Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 796 0 CH CH CH CH C CH CH CH CH CH H H 797 0 CH CH CH CH C N CH CH CH CH H H 798 0 CH CH CH CH C CH N CH CH CH H H 799 0 CH CH CH CH C N CH CH CH N H H 800 0 CH CH CH CH C N N CH CH CH H H 801 0 CH CH CH C CH N CH N CH H absent 802 0 CH CH CH CH C CH CH N CH N absent H 803 0 CH CH CH CH C CH CH N CH CH absent H 804 0 N CH CH CH C CH CH CH CH CH H H 805 0 N CH CH CH C N CH CH CH CH H H 806 0 N CH CH CH C CH N CH CH CH H H 807 0 N CH CH CH C N CH CH CH N H H 808 0 N CH CH CH C CH CH N CH N absent H 809 0 N CH CH CH C N CH CH CH CH H H 810 0 N N CH CH C CH CH N CH N absent H 811 0 N N CH CH C CH CH CH CH CH H H 812 0 CH N CH CH C CH CH CH CH CH H H 813 0 CH N CH CH C N CH CH CH CH H H 814 0 CH N CH CH C CH N CH CH CH H H 815 0 CH N CH CH C CH N CH N CH H absent 816 0 CH N CH CH C N CH CH N CH H H 817 0 CH N CH CH C CH CH N CH N absent H 818 0 CH N CH CH C CH CH N CH CH absent H 819 0 N CH N CH C CH CH CH CH CH H H 820 0 N CH N CH C N CH CH CH CH H H 821 0 N CH N CH C CH N CH CH CH H H 822 0 CH N CH N C CH CH CH CH CH H H 823 0 CH CH N N C CH CH CH CH CH H H 824 0 CH CH CH N C CH CH CH CH CH H H 825 0 CH CH CH N C CH CH N CH CH absent H 826 0 CH CH CH CH C CH CH CH CH CH F H 827 0 CH CH CH CH C N CH CH CH CH F H 828 0 CH CH CH CH C CH N CH CH CH F H 829 0 CH CH CH CH C N CH CH CH N F H 830 0 CH CH CH CH C N N CH CH CH F H 831 0 CH CH CH CH C CH N CH N CH F absent 832 0 CH CH CH CH C CH CH N CH N absent 833 0 CH CH CH CH C CH CH N CH CH absent H 834 0 N CH CH CH C CH CH CH CH CH F H 835 0 N CH CH CH C N CH CH CH CH F H 836 0 N CH CH CH C CH N CH CH CH F H 837 0 N CH CH CH C N CH CH CH N F H 838 0 N CH CH CH C CH CH N CH N absent H 839 0 N N CH CH C CH CH CH CH CH F H 840 0 N N CH CH C CH CH N CH N absent H 841 0 CH N CH CH C CH CH CH CH CH F H 842 0 CH N CH CH C N CH CH CH CH F H 843 0 CH N CH CH C CH N CH CH CH F H 844 0 CH N CH CH C CH N CH N CH F absent 845 0 CH N CH CH C N CH CH N CH F absent 846 0 CH N CH CH C CH CH N CH N absent H 847 0 N CH N CH C CH CH CH CH CH F H 848 0 N CH N CH C N CH CH CH CH F H 849 0 N CH N CH C CH N CH CH CH F H 850 0 CH N CH N C CH CH CH CH CH F H 851 0 CH CH N N C CH CH CH CH CH F H 852 0 CH CH CH N C CH CH CH CH CH F H 853 0 CH CH CH N C CH N CH CH CH F H 854 0 CH CH CH CH C CH CH CH CH CH OMe OMe 855 0 CH CH CH CH C N CH CH CH CH OMe OMe 856 0 CH CH CH CH C CH N CH CH CH OMe OMe 857 0 CH CH CH CH C N CH CH CH N OMe OMe 858 0 CH CH CH CH C N N CH CH CH OMe OMe 859 0 CH CH CH CH C CH N CH N CH OMe absent 860 0 CH CH CH CH C CH CH N CH N absent OMe 861 0 CH CH CH CH C CH CH N CH CH absent OMe 862 0 N CH CH CH C CH CH CH CH CH OMe OMe 863 0 N CH CH CH C N CH CH CH CH OMe OMe 864 0 N CH CH CH C CH N CH CH CH OMe OMe 865 0 N CH CH CH C N CH CH CH N OMe OMe 866 0 N CH CH CH C CH CH N CH N absent OMe 867 0 N CH CH CH C N CH CH CH CH OMe OMe 868 0 N N CH CH C CH CH N CH N absent OMe 869 0 N N CH CH C CH CH CH CH CH OMe OMe 870 0 CH N CH CH C CH CH CH CH CH OMe OMe 871 0 CH

N CH CH C N CH CH CH CH OMe OMe 872 0 CH N CH CH C CH N CH CH CH OMe OMe 873 0 CH N CH CH C CH N CH N CH OMe absent 874 0 CH N CH CH C N CH CH N CH OMe OMe 875 0 CH N CH CH C CH CH N CH N absent OMe 876 0 CH N CH CH C CH CH N CH CH absent OMe 877 0 N CH N CH C CH CH CH CH CH OMe OMe 878 0 N CH N CH C N CH CH CH CH OMe OMe 879 0 N CH N CH C CH N CH CH CH OMe OMe 880 0 CH N CH N C CH CH CH CH CH OMe OMe 881 0 CH CH N N C CH CH CH CH CH OMe OMe 882 0 CH CH CH N C CH CH CH CH CH OMe OMe 883 0 CH CH CH N C CH CH N CH CH absent OMe 884 1 CH CH CH CH C CH CH CH CH CH H H 885 1 CH CH CH CH C N CH CH CH CH H H 886 1 CH CH CH CH C CH N CH CH CH H H 887 1 CH CH CH CH C N CH CH CH N H H 888 1 CH CH CH CH C N N CH CH CH H H 889 1 CH CH CH CH C CH N CH N CH H absent 890 1 CH CH CH CH C CH CH N CH N absent H 891 1 CH CH CH CH C CH CH N CH CH absent H 892 1 N CH CH CH C CH CH CH CH CH H H 893 1 N CH CH CH C N CH CH CH CH H H 894 1 N CH CH CH C CH N CH CH CH H H 895 1 N CH CH CH C N CH CH CH N H H 896 1 N CH CH CH C CH CH N CH N absent H 897 1 N CH CH CH C N CH CH CH CH H H 898 1 N N CH CH C CH CH N CH N absent H 899 1 N N CH CH C CH CH CH CH CH H H 900 1 CH N CH CH C CH CH CH CH CH H H 901 1 CH N CH CH C N CH CH CH CH H H 902 1 CH N CH CH C CH N CH CH CH H H 903 1 CH N CH CH C CH N CH N CH H absent 904 1 CH N CH CH C N CH CH N CH H H 905 1 CH N CH CH C CH CH N CH N absent H 906 1 CH N CH CH C CH CH N CH CH absent H 907 1 N CH N CH C CH CH CH CH CH H H 908 1 N CH N CH C N CH CH CH CH H H 909 1 N CH N CH C CH N CH CH CH H H 910 1 CH N CH N C CH CH CH CH CH H H 911 1 CH CH N N C CH CH CH CH CH H H 912 1 CH CH CH N C CH CH CH CH CH H H 913 1 CH CH CH N C CH CH N CH CH absent H 914 1 CH CH CH CH C CH CH CH CH CH F H 915 1 CH CH CH CH C N CH CH CH CH F H 916 1 CH CH CH CH C CH N CH CH CH F H 917 1 CH CH CH CH C N CH CH CH N F H 918 1 CH CH CH CH C N N CH CH CH F H 919 1 CH CH CH CH C CH N CH N F absent 920 1 CH CH CH CH C CH CH N CH N absent 921 1 CH CH CH CH C CH CH N CH CH absent H 922 1 N CH CH CH C CH CH CH CH CH F H 923 1 N CH CH CH C N CH CH CH CH F H 924 1 N CH CH CH C CH N CH CH CH F H 925 1 N CH CH CH C N CH CH CH N F H 926 1 N CH CH CH C CH CH N CH N absent H 927 1 N N CH CH C CH CH CH CH CH F H 928 1 N N CH CH C CH CH N CH N absent H 929 1 CH N CH CH C CH CH CH CH CH F H 930 1 CH N CH CH C N CH CH CH CH F H 931 1 CH N CH CH C CH N CH CH CH F H 932 1 CH N CH CH C CH N CH N CH F absent 933 1 CH N CH CH C N CH CH N CH F absent 934 1 CH N CH CH C CH CH N CH N absent H 935 1 N CH N CH C CH CH CH CH CH F H 936 1 N CH N CH C N CH CH CH CH F H 937 1 N CH N CH C CH N CH CH CH F H 938 1 CH N CH N C CH CH CH CH CH F H 939 1 CH CH N N C CH CH CH CH CH F H 940 1 CH CH CH N C CH CH CH CH CH F H 941 1 CH CH CH N C CH N CH CH CH F H 942 1 CH CH CH CH C CH CH CH CH CH OMe OMe 943 1 CH CH CH CH C N CH CH CH CH OMe OMe 944 1 CH CH CH CH C CH N CH CH CH OMe OMe 945 1 CH CH CH CH C N CH CH CH N OMe OMe 946 1 CH CH CH CH C N N CH CH CH OMe OMe 947 1 CH CH CH CH C CH N CH N CH OMe absent 948 1 CH CH CH CH C CH CH N CH N absent OMe 949 1 CH CH CH CH C CH CH N CH CH absent OMe 950 1 N CH CH CH C CH CH CH CH CH OMe OMe 951 1 N CH CH CH C N CH CH CH CH OMe OMe 952 1 N CH CH CH C CH N CH CH CH OMe OMe 953 1 N CH CH CH C N CH CH CH N OMe OMe 954 1 N CH CH CH C CH CH N CH N absent OMe 955 1 N CH CH CH C N CH CH CH CH OMe OMe 956 1 N N CH CH C CH CH N CH N absent OMe 957 1 N N CH CH C CH CH CH CH CH OMe OMe 958 1 CH N CH CH C CH CH CH CH CH OMe OMe 959 1 CH N CH CH C N CH CH CH CH OMe OMe 960 1 CH N CH CH C CH N CH CH CH OMe OMe 961 1 CH N CH CH C CH N CH N CH OMe absent 962 1 CH N CH CH C N CH CH N CH OMe OMe 963 1 CH N CH CH C CH CH N CH N absent OMe 964 1 CH N CH CH C CH CH N CH CH absent OMe 965 1 N CH N CH C CH CH CH CH CH OMe OMe 966 1 N CH N CH C N CH CH CH CH OMe OMe 967 1 N CH N CH C CH N CH CH CH OMe OMe 968 1 CH N CH N C CH CH CH

CH CH OMe OMe 969 1 CH CH N N C CH CH CH CH CH OMe OMe 970 1 CH CH CH N C CH CH CH CH CH OMe OMe 971 1 CH CH CH N C CH CH N CH CH absent OMe
(19) In a further embodiment, the present invention provides compounds of formula (Va) and (Vb), wherein o, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 1297 to 1300:
(20) ##STR00053##
(21) In both, formulae (Va) and (Vb), o is 0.
(22) TABLE-US-00008 Comp p Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 1297 0 CH CH CH CH C CH CH CH CH CH OMe H 1298 0 CH CH CH N C CH CH CH CH CH OMe H 1299 0 CH CH CH CH C CH CH CH CH CH O-Phenyl H 1300 0 CH CH N CH C CH CH CH CH CH OMe OMe
(23) In a further embodiment, the present invention provides compounds of formula (VI), wherein X.sub.1, n, Z, R.sub.5, and R.sub.6 are as defined in examples 972 to 977:
(24) ##STR00054##
(25) TABLE-US-00009 Comp X.sub.1 Z n R.sub.5 R.sub.6 972 CH.sub.2 CH 1 F H 973 CH.sub.2 N 1 F H 974 S N 1 F H 975 CH.sub.2 CH 1 OMe OMe 976 CH.sub.2 N 1 OMe OMe 977 S N 1 OMe OMe
(26) In a further embodiment, the present invention provides compounds of formula (VII), wherein X.sub.1, n, Z, R.sub.2, R.sub.5, and R.sub.6 are as defined in examples 978 to 54:
(27) ##STR00055##
(28) TABLE-US-00010 Comp X.sub.1 Z n R.sub.2 R.sub.5 R.sub.6 978 CH.sub.2 CH 1 Me F H 979 CH.sub.2 N 1 Me F H 980 S N 1 Me F H 981 CH.sub.2 CH 1 Me OMe OMe 982 CH.sub.2 N 1 Me OMe OMe 983 S N 1 Me OMe OMe 984 CH.sub.2 CH 1 Cyclopropyl F H 985 CH.sub.2 N 1 Cyclopropyl F H 986 S N 1 Cyclopropyl F H 987 CH.sub.2 CH 1 Cyclopropyl OMe OMe 988 CH.sub.2 N 1 Cyclopropyl OMe OMe 989 S N 1 Cyclopropyl OMe OMe
(29) In a further embodiment, the present invention provides compounds of formula (VIII), wherein X.sub.1, n, R.sub.5, and R.sub.6 are as defined in examples 990 to 993:
(30) ##STR00056##
(31) TABLE-US-00011 Comp X.sub.1 n R5 R6 990 CH.sub.2 1 F H 991 S 1 F H 992 CH.sub.2 1 OMe OMe 993 S 1 OMe OMe
(32) In a further embodiment, the present invention provides compounds of formula (IX), wherein X.sub.1, n, R.sub.2, R.sub.5, and R.sub.6 are as defined in examples 994 to 1001:
(33) ##STR00057##
(34) TABLE-US-00012 Comp X.sub.1 n R.sub.2 R.sub.5 R.sub.6 994 CH.sub.2 1 Me F H 995 S 1 Me F H 996 CH.sub.2 1 Me OMe OMe 997 S 1 Me OMe OMe 998 CH.sub.2 1 Cyclopropyl F H 999 S 1 Cyclopropyl F H 1000 CH.sub.2 1 Cyclopropyl OMe OMe 1001 S 1 Cyclopropyl OMe OMe
(35) In a further embodiment, the present invention provides compounds of formula (X), wherein o, R.sub.5, and R.sub.6 are as defined in examples 1002 to 1005:
(36) ##STR00058##
(37) TABLE-US-00013 o is 0. Comp p R.sub.5 R.sub.6 1002 0 F H 1003 0 OMe OMe 1004 1 F H 1005 1 OMe OMe
(38) In a further embodiment, the present invention provides compounds of formula (XI), wherein o, R.sub.2, R.sub.5, and R.sub.6 are as defined in examples 1006 to 1013:
(39) ##STR00059##
(40) TABLE-US-00014 o is 0. Comp p R.sub.2 R.sub.5 R.sub.6 1006 0 Me F H 1007 0 Me OMe OMe 1008 0 Cyclopropyl F H 1009 0 Cyclopropyl OMe OMe 1010 1 Me F H 1011 1 Me OMe OMe 1012 1 Cyclopropyl F H 1013 1 Cyclopropyl OMe OMe
(41) In a further embodiment, the present invention provides compounds of formula (XIIa) and (XIIb), wherein Z, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9,

Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 1014 to 1189:

(42) ##STR00060##

(43) TABLE-US-00015 Comp Z Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 1014 CH CH CH CH CH C CH CH CH CH CH H H 1015 N CH CH CH CH C CH CH CH CH CH H H 1016 CH CH CH CH CH C N CH CH CH CH H H 1017 N CH CH CH CH C N CH CH CH CH H H 1018 CH CH CH CH CH C CH N CH CH CH H H 1019 N CH CH CH CH C CH N CH CH CH H H 1020 CH CH CH CH CH C N CH CH CH N H H 1021 N CH CH CH CH C N CH CH CH N H H 1022 CH CH CH CH CH C N N CH CH CH H H 1023 N CH CH CH CH C N N CH CH CH H H 1024 CH CH CH CH CH C CH N CH N CH H absent 1025 N CH CH CH CH C CH N CH N CH H 1026 CH CH CH CH CH C CH CH N CH N absent H 1027 N CH CH CH CH C CH CH N CH N H 1028 CH CH CH CH CH C CH CH N CH CH absent H 1029 N CH CH CH CH C CH CH N CH CH H 1030 CH N CH CH CH C CH CH CH CH CH H H 1031 N N CH CH CH C CH CH CH CH CH H H 1032 CH N CH CH CH C N CH CH CH CH H H 1033 N N CH CH CH C N CH CH CH CH H H 1034 CH N CH CH CH C CH N CH CH CH H H 1035 N N CH CH CH C CH N CH CH CH H H 1036 CH N CH CH CH C N CH CH CH N H H 1037 N N CH CH CH C N CH CH CH N H H 1038 CH N CH CH CH C CH CH N CH N absent H 1039 N N CH CH CH C CH CH N CH N H 1040 CH N CH CH CH C N CH CH CH CH H H 1041 N N CH CH CH C N CH CH CH CH H H 1042 CH N N CH CH C CH CH N CH N absent H 1043 N N N CH CH C CH CH N CH N H 1044 CH N N CH CH C CH CH CH CH CH H H 1045 N N N CH CH C CH CH CH CH CH H H 1046 CH CH N CH CH C CH CH CH CH CH H H 1047 N CH N CH CH C CH CH CH CH CH H H 1048 CH CH N CH CH C N CH CH CH CH H H 1049 N CH N CH CH C N CH CH CH CH H H 1050 CH CH N CH CH C CH N CH CH CH H H 1051 N CH N CH CH C CH N CH CH CH H H 1052 CH CH N CH CH C CH N CH N CH H absent 1053 N CH N CH CH C CH N CH N CH H 1054 CH CH N CH CH C N CH CH N CH H H 1055 N CH N CH CH C N CH CH N CH H H 1056 CH CH N CH CH C CH CH N CH N absent H 1057 N CH N CH CH C CH CH N CH N H 1058 CH CH N CH CH C CH CH N CH CH absent H 1059 N CH N CH CH C CH CH N CH CH H 1060 CH N CH N CH C CH CH CH CH CH H H 1061 N N CH N CH C CH CH CH CH CH H H 1062 CH N CH N CH C N CH CH CH CH H H 1063 N N CH N CH C N CH CH CH CH H H 1064 CH N CH N CH C CH N CH CH CH H H 1065 N N CH N CH C CH N CH CH CH H H 1066 CH CH N CH N C CH CH CH CH CH H H 1067 N CH N CH N C CH CH CH CH CH H H 1068 CH CH CH N N C CH CH CH CH CH H H 1069 N CH CH N N C CH CH CH CH CH H H 1070 CH CH CH CH N C CH CH CH CH CH H H 1071 N CH CH CH N C CH CH CH CH CH H H 1072 CH CH CH CH N C CH CH N CH CH absent H 1073 N CH CH CH N C CH CH N CH CH H 1074 CH CH CH CH CH C CH CH CH CH CH F H 1075 N CH CH CH CH C CH CH CH CH CH F H 1076 CH CH CH CH CH C N CH CH CH CH F H 1077 N CH CH CH CH C N CH CH CH CH F H 1078 CH CH CH CH CH C CH N CH CH CH F 1079 N CH CH CH CH C CH N CH CH CH F H 1080 CH CH CH CH CH C N CH CH CH N F H 1081 N CH CH CH CH C N CH CH CH N F H 1082 CH CH CH CH CH C N N CH CH CH F H 1083 N CH CH CH CH C N N CH CH CH F H 1084 CH CH CH CH CH C CH N CH N CH F absent 1085 N CH CH CH CH C CH N CH N CH F 1086 CH CH CH CH CH C CH CH N CH N absent 1087 N CH CH CH CH C CH CH N CH N 1088 CH CH CH CH CH C CH CH N CH CH absent H 1089 N CH CH CH CH C CH CH N CH CH H 1090 CH N CH CH CH C CH CH CH CH CH F H 1091 N N CH CH CH C CH CH CH CH CH F H 1092 CH N CH CH CH C N CH CH CH CH F H 1093 N N CH CH CH C N CH CH CH CH F H 1094 CH N CH CH CH C CH N CH CH CH F H 1095 N N CH CH CH C CH N CH CH CH F H 1096 CH N CH CH CH C N CH CH CH N F H 1097 N N CH CH CH C N CH CH CH N F H 1098 CH N CH CH CH C CH CH N CH N absent H 1099 N N CH CH CH C CH CH N CH N H 1100 CH N N CH CH C CH CH CH CH CH F H 1101 N N N CH CH C CH CH CH CH CH F H 1102 CH N N CH CH C CH CH N CH N absent H 1103 N N N CH CH C CH CH N CH N H 1104 CH CH N CH CH C CH CH CH CH CH F H 1105 N CH N CH CH C CH CH CH CH CH F H

1106 CH CH N CH CH C N CH CH CH CH F H 1107 N CH N CH CH C N CH CH CH CH F H 1108 CH CH N CH CH C CH N CH CH CH F H 1109 N CH N CH CH C CH N CH CH CH F H 1110 CH CH N CH CH C CH N CH N CH F absent 1111 N CH N CH CH C CH N CH N CH F 1112 CH CH N CH CH C N CH CH N CH F absent 1113 N CH N CH CH C N CH CH N CH F 1114 CH CH N CH CH C CH CH N CH N absent H 1115 N CH N CH CH C CH CH N CH N H 1116 CH N CH N CH C CH CH CH CH CH F H 1117 N N CH N CH C CH CH CH CH CH F H 1118 CH N CH N CH C N CH CH CH CH F H 1119 N N CH N CH C N CH CH CH CH F H 1120 CH N CH N CH C CH N CH CH CH F H 1121 N N CH N CH C CH N CH CH CH F H 1122 CH CH N CH N C CH CH CH CH CH F H 1123 N CH N CH N C CH CH CH CH CH F H 1124 CH CH CH N N C CH CH CH CH CH F H 1125 N CH CH N N C CH CH CH CH CH F H 1126 CH CH CH CH N C CH CH CH CH CH F H 1127 N CH CH CH N C CH CH CH CH CH F H 1128 CH CH CH CH N C CH N CH CH CH F H 1129 N CH CH CH N C CH N CH CH CH F H 1130 CH CH CH CH CH C CH CH CH CH CH OMe OMe 1131 N CH CH CH CH C CH CH CH CH CH OMe OMe 1132 CH CH CH CH CH C N CH CH CH CH OMe OMe 1133 N CH CH CH CH C N CH CH CH CH OMe OMe 1134 CH CH CH CH CH C CH N CH CH CH OMe OMe 1135 N CH CH CH CH C CH N CH CH CH OMe OMe 1136 CH CH CH CH CH C N CH CH CH N OMe OMe 1137 N CH CH CH CH C N CH CH CH N OMe OMe 1138 CH CH CH CH CH C N N CH CH CH OMe OMe 1139 N CH CH CH CH C N N CH CH CH OMe OMe 1140 CH CH CH CH CH C CH N CH N CH OMe absent 1141 N CH CH CH CH C CH N CH N CH OMe 1142 CH CH CH CH CH C CH CH N CH N absent OMe 1143 N CH CH CH CH C CH CH N CH N OMe 1144 CH CH CH CH CH C CH CH N CH CH absent OMe 1145 N CH CH CH CH C CH CH N CH CH OMe 1146 CH N CH CH CH C CH CH CH CH CH OMe OMe 1147 N N CH CH CH C CH CH CH CH CH OMe OMe 1148 CH N CH CH CH C N CH CH CH CH OMe OMe 1149 N N CH CH CH C N CH CH CH CH OMe OMe 1150 CH N CH CH CH C CH N CH CH CH OMe OMe 1151 N N CH CH CH C CH N CH CH CH OMe OMe 1152 CH N CH CH CH C N CH CH CH N OMe OMe 1153 N N CH CH CH C N CH CH CH N OMe OMe 1154 CH N CH CH CH C CH CH N CH N absent OMe 1155 N N CH CH CH C CH CH N CH N OMe 1156 CH N CH CH CH C N CH CH CH CH CH OMe OMe 1157 N N CH CH CH C N CH CH CH CH OMe OMe 1158 CH N N CH CH C CH CH N CH N absent OMe 1159 N N N CH CH C CH CH N CH N OMe 1160 CH N N CH CH C CH CH CH CH CH OMe OMe 1161 N N N CH CH C CH CH CH CH CH OMe OMe 1162 CH CH N CH CH C CH CH CH CH CH OMe OMe 1163 N CH N CH CH C CH CH CH CH CH OMe OMe 1164 CH CH N CH CH C N CH CH CH CH OMe OMe 1165 N CH N CH CH C N CH CH CH CH OMe OMe 1166 CH CH N CH CH C CH N CH CH CH OMe OMe 1167 N CH N CH CH C CH N CH CH CH OMe OMe 1168 CH CH N CH CH C CH N CH N CH OMe absent 1169 N CH N CH CH C CH N CH N CH OMe 1170 CH CH N CH CH C N CH CH N CH OMe OMe 1171 N CH N CH CH C N CH CH N CH OMe OMe 1172 CH CH N CH CH C CH CH N CH N absent OMe 1173 N CH N CH CH C CH CH N CH N OMe 1174 CH CH N CH CH C CH CH N CH CH absent OMe 1175 N CH N CH CH C CH CH N CH CH OMe 1176 CH N CH N CH C CH CH CH CH CH OMe OMe 1177 N N CH N CH C CH CH CH CH CH OMe OMe 1178 CH N CH N CH C N CH CH CH CH OMe OMe 1179 N N CH N CH C N CH CH CH CH OMe OMe 1180 CH N CH N CH C CH N CH CH CH OMe OMe 1181 N N CH N CH C CH N CH CH CH OMe OMe 1182 CH CH N CH N C CH CH CH CH CH OMe OMe 1183 N CH N CH N C CH CH CH CH CH OMe OMe 1184 CH CH CH N N C CH CH CH CH CH OMe OMe 1185 N CH CH N N C CH CH CH CH CH OMe OMe 1186 CH CH CH CH N C CH CH CH CH CH OMe OMe 1187 N CH CH CH N C CH CH CH CH CH OMe OMe 1188 CH CH CH CH N C CH CH N CH CH absent OMe 1189 N CH CH CH N C CH CH N CH CH OMe

(44) In a further embodiment, the present invention provides compounds of formula (XIII), wherein Z, R.sub.5, and R.sub.6 are as defined in examples 1190 to 1193:

(45) ##STR00061##

(46) TABLE-US-00016 Comp Z R.sub.5 R.sub.6 1190 CH F H 1191 N F H 1192 CH OMe OMe

1193 N OMe OMe
(47) In a further embodiment, the present invention provides compounds of formula (XIV), wherein R.sub.5, and R.sub.6 are as defined in examples 1194 to 1195:
(48) ##STR00062##
(49) TABLE-US-00017 Comp R.sub.5 R.sub.6 1194 F H 1195 OMe OMe
(50) In a further embodiment, the present invention provides compounds of formula (XVa) and (XVb), wherein Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 1196 to 1282:
(51) ##STR00063##
(52) TABLE-US-00018 Comp Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 1196 CH CH CH CH C CH CH CH CH CH H H 1197 CH CH CH CH C N CH CH CH CH H H 1198 CH CH CH CH C CH N CH CH CH H H 1199 CH CH CH CH C N CH CH CH N H H 1200 CH CH CH CH C N N CH CH CH H H 1201 CH CH CH CH C CH N CH N CH H absent 1202 CH CH CH CH C CH CH N CH N absent H 1203 CH CH CH CH C CH CH N CH CH absent H 1204 N CH CH CH C CH CH CH CH CH H H 1205 N CH CH CH C N CH CH CH CH H H 1206 N CH CH CH C CH N CH CH CH H H 1207 N CH CH CH C N CH CH CH N H H 1208 N CH CH CH C CH CH N CH N absent H 1209 N CH CH CH C N CH CH CH CH H H 1210 N N CH CH C CH CH N CH N absent H 1211 N N CH CH C CH CH CH CH CH H H 1212 CH N CH CH C CH CH CH CH CH H H 1213 CH N CH CH C N CH CH CH CH H H 1214 CH N CH CH C CH N CH CH CH H H 1215 CH N CH CH C CH N CH N CH H absent 1216 CH N CH CH C N CH CH N CH H H 1217 CH N CH CH C CH CH N CH N absent H 1218 CH N CH CH C CH CH N CH CH absent H 1219 N CH N CH C CH CH CH CH CH H H 1220 N CH N CH C N CH CH CH CH H H 1221 N CH N CH C CH N CH CH CH H H 1222 CH N CH N C CH CH CH CH CH H H 1223 CH CH N N C CH CH CH CH CH H H 1224 CH CH CH N C CH CH CH CH CH H H 1225 CH CH CH N C CH CH N CH CH absent H 1226 CH CH CH CH C CH CH CH CH CH F H 1227 CH CH CH CH C N CH CH CH CH F H 1228 CH CH CH CH C CH N CH CH CH F H 1229 CH CH CH CH C N CH CH CH N F H 1230 CH CH CH CH C N N CH CH CH F H 1231 CH CH CH CH C CH N CH N CH F absent 1232 CH CH CH CH C CH CH N CH N absent 1233 CH CH CH CH C CH CH N CH CH absent H 1234 N CH CH CH C CH CH CH CH CH F H 1235 N CH CH CH C N CH CH CH CH F H 1236 N CH CH CH C CH N CH CH CH F H 1237 N CH CH CH C N CH CH CH N F H 1238 N CH CH CH C CH CH N CH N absent H 1239 N N CH CH C CH CH CH CH CH F H 1240 N N CH CH C CH CH N CH N absent H 1241 CH N CH CH C CH CH CH CH CH F H 1242 CH N CH CH C N CH CH CH CH F H 1243 CH N CH CH C CH N CH CH CH F H 1244 CH N CH CH C CH N CH N CH F absent 1245 CH N CH CH C N CH CH N CH F absent 1246 CH N CH CH C CH CH N CH N absent H 1247 N CH N CH C CH CH CH CH CH F H 1248 N CH N CH C N CH CH CH CH F H 1249 N CH N CH C CH N CH CH CH F H 1250 CH N CH N C CH CH CH CH CH F H 1251 CH CH N N C CH CH CH CH CH F H 1252 CH CH CH N C CH CH CH CH CH F H 1253 CH CH CH N C CH N CH CH CH F H 1254 CH CH CH CH C CH CH CH CH CH OMe OMe 1255 CH CH CH CH C N CH CH CH CH OMe OMe 1256 CH CH CH CH C CH N CH CH CH OMe OMe 1257 CH CH CH CH C N CH CH CH N OMe OMe 1258 CH CH CH CH C N N CH CH CH OMe OMe 1259 CH CH CH CH C CH N CH N CH OMe absent 1260 CH CH CH CH C CH CH N CH N absent OMe 1261 CH CH CH CH C CH CH N CH CH absent OMe 1262 N CH CH CH C CH CH CH CH CH OMe OMe 1263 N CH CH CH C N CH CH CH CH OMe OMe 1264 N CH CH CH C CH N CH CH CH OMe OMe 1265 N CH CH CH C N CH CH CH N OMe OMe 1266 N CH CH CH C CH CH N CH N absent OMe 1267 N CH CH CH C N CH CH CH CH OMe OMe 1268 N N CH CH C CH CH N CH N absent OMe 1269 N N CH CH C CH CH CH CH CH OMe OMe 1270 CH N CH CH C CH CH CH CH CH OMe OMe 1271 CH N CH CH C N CH CH CH CH OMe OMe 1272 CH N CH CH C CH N CH CH CH OMe OMe 1273 CH N CH CH C CH N CH N CH OMe absent 1274 CH N CH CH C N CH CH N CH OMe OMe 1275 CH N CH CH C CH CH

N CH N absent OMe 1276 CH N CH CH C CH CH N CH CH absent OMe 1277 N CH N CH C CH CH CH CH CH OMe OMe 1278 N CH N CH C N CH CH CH CH OMe OMe 1279 N CH N CH C CH N CH CH CH OMe OMe 1280 CH N CH N C CH CH CH CH CH OMe OMe 1281 CH CH N N C CH CH CH CH CH OMe OMe 1282 CH CH CH N C CH CH CH CH CH OMe OMe

(53) In a further embodiment, the present invention provides compounds of formula (XVa) and (XVb), wherein Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Y.sub.7, Y.sub.8, Y.sub.9, Y.sub.10, R.sub.5, and R.sub.6 are as defined in examples 1310 to 1319:

(54) ##STR00064##

(55) TABLE-US-00019 Comp Y.sub.1 Y.sub.2 Y.sub.3 Y.sub.4 Y.sub.5 Y.sub.6 Y.sub.7 Y.sub.8 Y.sub.9 Y.sub.10 R.sub.5 R.sub.6 1301 CH CH CH CH C CH CH CH CH CH OMe H 1302 CH CH CH N C CH CH CH CH CH OMe H 1303 N CH CH CH C CH CH CH CH CH OMe H 1304 CH CH N CH C CH CH CH CH CH OMe H 1305 CH N CH CH C CH CH CH CH CH OMe H 1306 N CH N CH C CH CH CH CH CH OMe H 1307 N CH CH N C CH CH CH CH CH OMe H 1308 CH CH N CH C CH CH CH CH CH OMe OMe 1309 N CH CH N C CH CH CH CH CH OMe OMe 1310 N CH CH N C CH CH CH CH CH F H 1311 CH CH CH CH C CH CH CH CH CH O-phenyl H 1312 CH CH CH CH C CH CH CH CH CH O-cyclohexyl H 1313 CH CH CH CH C CH CH CH CH CH propyloxy H 1314 CH CH CH CH C CH CH CH CH CH propan-2-yloxy H 1315 CH CH CH CH subst. C CH CH CH CH CH OMe H with Me 1316 CH CH CH CH subst. C CH CH CH CH CH OMe OMe with Me 1317 CH CH CH CH subst. C CH CH CH CH CH Cl OMe with F 1318 CH CH CH CH subst. C CH CH CH CH CH OMe OMe with F 1319 CH CH CH CH subst. C CH CH CH CH CH F H with F

(56) In a further embodiment, the present invention provides compounds of formula (XVI), wherein R.sub.5, and R.sub.6 are as defined in examples 1283 to 1284:

(57) ##STR00065##

(58) TABLE-US-00020 Comp R5 R6 1283 F H 1284 OMe OMe

(59) In a further embodiment, the present invention provides compounds of formula (XVII), wherein R.sub.2, R.sub.5, and R.sub.6 are as defined in examples 1285 to 1288:

(60) ##STR00066##

(61) TABLE-US-00021 Comp R2 R5 R6 1285 Me F H 1286 Me OMe OMe 1287 Cyclopropy F H 1288 Cyclopropy OMe OMe

(62) In a further embodiment, the present invention provides compounds of formula (XVIII), wherein X.sub.1, n, R.sub.5, and R.sub.6 are as defined in examples 1320 to 1323:

(63) ##STR00067##

(64) TABLE-US-00022 Comp X.sub.1 n R5 R6 1320 CH.sub.2 1 F H 1321 S 1 F H 1322 CH.sub.2 1 OMe OMe 1323 S 1 OMe OMe

(65) In a preferred embodiment, the present invention provides compounds of formula (I), or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof, wherein said compound of formula (I) is selected from:

(66) TABLE-US-00023 Exam- Syn- hQC hQC ple thesis K.sub.i K.sub.i Com- Exam- Mol [μM] [μM] pound ple Compound Name Structure Formula Weight pH6 pH8 93 A2 5-[3-({4′-fluoro-[1,1′-biphenyl]- 2-yl}amino)propyl]-1,3,4- thiadiazol-2-amine  C.sub.17H.sub.17FN.sub.4S 328.40 2.6 1102 94 A3 5-{[2-({4′-fluoro-[1,1′-biphenyl]- 2-yl}amino)ethyl]sulfanyl}-1,3,4- thiadiazol-2-amine  C.sub.16H.sub.15FN.sub.4S.sub.2 346.44 2.97 11.51 178 A4 5-{[2-({3′,4′-dimethoxy-[1,1′-biphenyl]-2- yl}amino)ethyl]sulfanyl}-1,3,4- thiadiazol-2-amine 0  C.sub.18H.sub.20N.sub.4O.sub.2S.sub.2 388.50 1.10 0.97 328 B1 4′-fluoro-N-[3-(4-methyl-4H-1,2,4-triazol-3-yl)propyl]-[1,1′- biphenyl]-2-amine  C.sub.18H.sub.19FN.sub.4 310.36 1.97 2.86 384 B3 3′,4′-dimethoxy-N-[3-(4-methyl- 4H-1,2,4-triazol-3-yl)propyl]- [1,1′-biphenyl]-2-amine  C.sub.20H.sub.24N.sub.4O.sub.2 352.43 0.13 0.26 505 C2 5-[4-({4′-fluoro-[1,1-biphenyl]- 2-yl}amino)phenyl]-1,3,4- thiadiazol-2-amine

C.sub.20H.sub.15FN.sub.4S 362.42 1.52 1.81 561 C3 5-(4-{[2-(3,4-dimethoxyphenyl)phenyl]amino} phenyl)-1,3,4-thiadiazol-2- amine C.sub.22H.sub.20N.sub.4O.sub.2S 404.48 0.42 1.09 1289 C4 5-(4-{[2-(4-methoxyphenyl)phenyl]amino} phenyl)-1,3,4-thiadiazol-2-amine C.sub.21H.sub.18N.sub.4OS 374.46 1.87 1.48 1290 C5 N-[4-(5-amino-1,3,4-thiadiazol- 2-yl)phenyl]-3-(4- methoxyphenyl)pyridin-2-amine C.sub.20H.sub.17N.sub.5O.sub.S 375.44 4.17 4.70 1291 C6 N-[4-(5-amino-1,3,4-thiadiazol 2-yl)phenyl]-3-(4- methoxyphenyl)pyridin-4-amine C.sub.20H.sub.17N.sub.5OS 375.44 7.16 4.22 1292 C7 N-[4-(5-amino-1,3,4-thiadiazol- 2-yl)phenyl]-3-(3,4-dimethoxyphenyl)pyridin-4- amine C.sub.21H.sub.19N.sub.5O.sub.2S 405.47 54.69 7.46 521 C8 N-[4-(5-amino-1,3,4-thiadiazol- 2-yl)phenyl]-3-(4- fluorophenyl)pyridin-2-amine C.sub.19H.sub.14FN.sub.5S 363.41 2.69 4.27 1293 C9 N-[4-(5-amino-1,3,4-thiadiazol- 2-yl)phenyl]-3-(4- fluorophenyl)pyrazin-2-amine 0 C.sub.18H.sub.13FN.sub.6S 364.39 1.66 6.89 1294 C10 5-(4-{[2-(4-phenoxyphenyl)phenyl]amino} phenyl)-1,3,4-thiadiazol-2-amine C.sub.26H.sub.20N.sub.4OS 436.52 4.37 2.23 1295 C11 5-(4-{[2-(4-propoxyphenyl)phenyl]amino} phenyl)-1,3,4-thiadiazol-2-amine C.sub.23H.sub.22N.sub.4OS 402.51 2.15 2.36 1296 C12 5-[4-({2-[4-(propan-2-yloxy)phenyl]phenyl}amino)phe- nyl]-1,3,4-thiadiazol-2-amine C.sub.23H.sub.22N.sub.4OS 402.51 1.51 3.27 826 D1 4′-fluoro-N-[4-(4-methyl-4H- 1,2,4-triazol-3-yl)phenyl]-[1,1‘- biphenyl]-2-amine C.sub.21H.sub.17FN.sub.4 344.38 1.44 1.74 854 D2 3′,4′-dimethoxy-N-[4-(4-methyl- 4H-1,2,4-triazol-3-yl)phenyl]- [1,1′-biphenyl]-2-amine C.sub.23H.sub.22N.sub.4O.sub.2 386.45 0.44 1.48 1297 D3 N-[2-(4-methoxyphenyl)phenyl]-4-(4- methyl-4H-1,2,4-triazol-3- yl)aniline C.sub.22H.sub.20N.sub.4O 356.42 0.99 1.69 1298 D4 2-(4-methoxyphenyl)-N-[4-(4- methyl-4H-1,2,4-triazol-3- yl)phenyl]pyridin-3-amine C.sub.21H.sub.19N.sub.5O 357.40 1.70 3.37 852 D5 2-(4-fluorophenyl)-N-[4-(4- methyl-4H-1,2,4-triazol-3- yl)phenyl]pyridin-3-amine C.sub.20H.sub.16FN.sub.5 345.37 2.69 5.05 1299 D6 4-(4-methyl-4H-1,2,4-triazol-3- yl)-N-[2-(4- phenoxyphenyl)phenyl]aniline C.sub.27H.sub.22N.sub.4O 418.48 1.33 1.81 1300 D7 3-(3,4-dimethoxyphenyl)-N-[4- (4-methyl-4H-1,2,4-triazol-3- yl)phenyl]pyridin-4-amine 0 C.sub.22H.sub.21N.sub.5O.sub.2 387.43 Not deter- mined 10.07 973 E2 N-[3-(5-amino-1,3,4-thiadiazol- 2-yl)propyl]-4-fluorobenzene-1- sulfonamide C.sub.11H.sub.13FN.sub.4O.sub.2S.sub.2 316.37 18.08 9.38 974 E3 N-{2-[(5-amino-1,3,4-thiadiazol- 2-yl)sulfanyl]ethyl}-4- fluorobenzene-1-sulfonamide C.sub.10H.sub.11FN.sub.4O.sub.2S.sub.3 334.41 19.91 26.48 979 F2 5-(3-{[(4- fluorophenyl)(methyl)oxo-λω- sulfanylidene]amino}propyl)- 1,3,4-thiadiazol-2-amine C.sub.12H.sub.15FN.sub.4OS.sub.2 314.40 11.41 11.70 990 G1 4-fluoro-N-[3-(4-methyl-4H-1,2,4-triazol-3- yl)propyl]benzene-1- sulfonamide C.sub.12H.sub.15FN.sub.4O.sub.2S 298.33 — — 991 G2 4-fluoro-N-{2-[(4-methyl-4H- 1,2,4-triazol-3- yl)sulfanyl]ethyl}benzene-1- sulfonamide C.sub.11H.sub.13FN.sub.4O.sub.2S.sub.2 316.37 8.84 11.49 1332 G5 [(3,4-dimethoxyphenyl)sulfamoyl]({2- [(4-methyl-4H-1,2,4-triazol-3- yl)sulfanyl]ethyl})amine C.sub.13H.sub.19N.sub.5O.sub.4S.sub.2 373.45 13.63 11.76 1002 I1 N-[4-(2-amino-1,3-thiazol-5- yl)phenyl]-4-fluorobenzene-1- sulfonamide C.sub.15H.sub.12FN.sub.3O.sub.2S.sub.2 349.40 2.93 2.64 1003 I2 N-[4-(2-amino-1,3-thiazol-5-yl)phenyl]-3,4- dimethoxybenzene-1- sulfonamide C.sub.17H.sub.17N.sub.3O.sub.4S.sub.2 391.46 0.20 0.34 1075 L2 5-(1-{4′-fluoro-[1,1′-biphenyl]-2- yl}piperidin-4-yl)-1,3,4- thiadiazol-2-amine C.sub.19H.sub.19FN.sub.4S 354.44 0.09 0.248 1190 M1 5-[1-(4- fluorobenzenesulfonyl)piperidin-

4-yl]-1,3-thiazol-amine 00 C.sub.14H.sub.16FN.sub.3O.sub.2S.sub.2 341.42 1.32 1.70 1191 M2 5-[1-(4- fluorobenzenesulfonyl)piperidin- 4-yl]-1,3,4-thiadiazol-2-amine 01 C.sub.13H.sub.15FN.sub.4O.sub.2S.sub.2 342.41 1.18 1.60 1194 N1 1-(4-fluorobenzenesulfonyl)-4- (4-methyl-4H-1,2,4-triazol-3- yl)piperidine 02 C.sub.14H.sub.17FN.sub.4O.sub.2S 324.37 3.05 3.30 1226 O1 N-[(1H-1,3-benzodiazol-5-yl)methyl]-4′-fluoro-[1,1′- biphenyl]-2-amine 03 C.sub.20H.sub.16FN.sub.3 317.35 5.91 5.29 1254 O2 N-[(1H-1,3-benzodiazol-5- yl)methyl]-3′,4′-dimethoxy-[1,1′-biphenyl]-2-amine 04 C.sub.22H.sub.21N.sub.3O.sub.2 359.42 0.12 0.27 1301 O3 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(4- methoxyphenyl)amine 05 C.sub.21H.sub.19N.sub.3O 329.39 1.44 1.65 1302 O4 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(4-methoxyphenyl)pyridin-3-amine 06 C.sub.20H.sub.18N.sub.4O 330.38 9.52 2.96 1303 O5 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(4- methoxyphenyl)pyridin-2-amine 07 C.sub.20H.sub.18N.sub.4O 330.38 2.74 2.41 1304 O6 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(4- methoxyphenyl)pyridin-4-amine 08 C.sub.20H.sub.18N.sub.4O 330.38 15.05 10.85 1305 O7 N-(1H-1,3-benzodiazol-5- ylmethyl)-4-(4- methoxyphenyl)pyridin-3-amine 09 C.sub.20H.sub.18N.sub.4O 330.38 11.14 4.24 1306 O8 N-(1H-1,3-benzodiazol-5- ylmethyl)-5-(4-methoxyphenyl) pyrimidin-4-amine 0 C.sub.19H.sub.17N.sub.5O 331.37 Not deter- mined 18.31 1307 O9 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(4- methoxyphenyl)pyrazin-2- amine C.sub.19H.sub.17N.sub.5O 331.37 1.90 2.21 1308 O10 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(3,4- dimethoxyphenyl)pyridin-4- amine C.sub.21H.sub.20N.sub.4O.sub.2 360.40 1.63 0.88 1262 O11 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(3,4- dimethoxyphenyl)pyridin-2- amine C.sub.21H.sub.20N.sub.4O.sub.2 360.40 0.10 0.23 1309 O12 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(3,4- dimethoxyphenyl)pyrazin-2- amine C.sub.20H.sub.19N.sub.5O.sub.2 361.39 0.13 0.42 1252 O13 N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4- fluorophenyl)pyridin-3-amine C.sub.19H.sub.15FN.sub.4 318.34 145.42 21.96 1234 O14 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(4- fluorophenyl)pyridin-2-amine C.sub.19H.sub.15FN.sub.4 318.34 58.79 12.28 1310 O15 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-(4- fluorophenyl)pyrazin-2-amine C.sub.18H.sub.14FN.sub.5 319.33 10.52 11.74 1311 O16 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(4- phenoxyphenyl)aniline C.sub.26H.sub.21N.sub.3O 391.46 4.34 2.11 1312 O17 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-[4- (cyclohexyloxy)phenyl]aniline C.sub.26H.sub.27N.sub.3O 397.51 2.03 4.17 1313 O18 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(4-propoxyphenyl)aniline 0 C.sub.23H.sub.23N.sub.3O 357.44 3.59 2.64 1314 O19 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-[4-(propan-2- yloxy)phenyl]aniline C.sub.23H.sub.23N.sub.3O 357.44 1.53 3.39 1315 O20 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(4-methoxyphenyl)- 3-methylaniline C22H21N3O 343.42 2.38 1.64 1316 O21 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(3,4- dimethoxyphenyl)-3- methylaniline C23H23N3O2: 373.45 0.43 0.42 1317 O22 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(4-chlorophenyl)-3- fluoroaniline C20H15ClFN3 351.8 4.89 6.83 1318 O23 N-(1H-1,3-benzodiazol-5- ylmethyl)-2-(3,4- dimethoxyphenyl)-3- fluoroaniline C22H20FN3O2 377.41 0.055 0.10 1319 O24 N-(1H-1,3-benzodiazol-5- ylmethyl)-3-fluoro-2-(4-fluoropheny)aniline C20H15F2N3 335.35 5.81 9.41 1283 P1 N-[(1H-1,3-benzodiazol-5- yl)methyl]-4-fluorobenzene-1- sulfonamide C.sub.14H.sub.12FN.sub.3O.sub.2S 305.32 38.34 24.74 1285 Q1 [(1H-1,3-benzodiazol-5-yl)methyl][(4- fluorophenyl)(methyl)oxo-λω- sulfanylidene]amine C.sub.15H.sub.14FN.sub.3OS 303.35 8.05 5.18

SYNTHESIS OF THE EXAMPLES

(67) Synthesis Method A

(68) ##STR00129##

(69) 4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)butanenitrile 4′-fluoro-[1,1′-biphenyl]-2-amine (0.5 g, 2.7 mmol), sodium cyanoborohydride (0.25 g, 4.0 mmol) and 4-oxobutanenitrile (0.44 g, 5.3 mmol) were dissolved in dry MeOH (15 mL) and acetic acid was added (0.5 mL). Reaction was stirred over 2 h until full consumption of amine was observed via UPLC analysis. After this time reaction mixture was diluted with saturated sodium bicarbonate solution (40 mL) and extracted with ethyl acetate (3×20 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated and purified via column chromatography using ethyl acetate in hexanes 10-20% as eluent to give pure title compound (0.17 g, 12%).
(70) 5-[3-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)propyl]-1,3,4-thiadiazol-2-amine (A2) 4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)butanenitrile (0.16 g, 0.6 mmol) and tiosemicarbazide (0.06 g, 0.7 mmol) were dissolved in trifluoroacetic acid (1.3 mL). Reaction was monitored via UPLC analysis. After completion of the reaction, solvent was removed in vacuo and crude material was purified via column chromatography using MeOH in DCM 0-2% as eluent to give pure title compound (70 mg, 33%). LCMS-Method 10 (200 nm); RT=5.81 min, 95.2% purity, [M+1]=329.2, .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 7.46-7.36 (m, 2H), 7.32-7.23 (m, 2H), 7.20-7.11 (m, 1H), 7.05-6.89 (m, 3H), 6.76-6.55 (m, 2H), 4.61 (t, J=5.9 Hz, 1H), 3.10 (q, J=6.6 Hz, 2H), 2.82 (t, J=7.5 Hz, 2H), 1.85 (p, J=7.2 Hz, 2H).
(71) Synthesis Method B
(72) ##STR00130##
(73) Step 1
(74) ##STR00131##
(75) 2-substituted aniline (1.0 eq.), sodium cyanoborohydride (1.5 eq.) and t-butyldimethylsilyloxyacetaldehyde (2.0 eq.) were dissolved in dry MeOH (30.0 vol.) and acetic acid was added (1.0 vol.). Reaction was stirred over 1-2 h until full consumption of amine was observed via UPLC analysis. After this time reaction mixture was diluted with saturated sodium bicarbonate solution (40 mL) and extracted with ethyl acetate (3×20 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated, used in next step without further purification.
(76) Step 2
(77) ##STR00132##
(78) Product from step 1 (1.0 eq.) and tetrabutylammonium fluoride trihydrate (1.05 eq.) were dissolved in THF (40.0 vol.). Reaction was monitored via UPLC analysis. After completion the reaction, solvent was removed in vacuo and crude material was taken to step 3.
(79) 5-{[2-({4′-fluoro-[1,1′-b]phenyl]-2-yl}amino)ethyl]sulfanyl}-1,3,4-thiadiazol-2-amine (A3). To solution of 2-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)ethan-1-ol (0.58 g, 2.5 mmol), 2-amino-5-mercapto-thiadiazole (0.50 g, 3.8 mmol) and triphenylphosphine (1.18 g, 4.5 mmol) in anhydrous THF (16.0 mL) diethyleneazodicarboxylate (0.66 g, 3.8 mmol) was added dropwise. Reaction mixture was stirred overnight at room temperature. After this time solvents were removed in vacuo. Crude product was purified via column chromatography using 0-3% MeOH in DCM and additional repurified via preparative TLC method using MeOH in DCM as eluent. Final re-purification was performed via preparative HPLC method to give pure product (40 mg. 7%) LCMS-Method 7 (200 nm): RT=5.81 min, 98.7% purity, [M]=346.0, .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 7.48-7.31 (m, 1H), 7.27-7.10 (m, 2H), 7.01 (dd, J=7.4, 1.6 Hz, 1H), 6.84-6.52 (m, 1H), 3.47 (t, J=6.6 Hz, 1H), 3.26 (t, J=6.6 Hz, 1H).
(80) 5-{[2-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl}amino)ethyl]sulfanyl}-1,3,4-thiadiazol-2-amine (A4). To solution of 2-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl}amino)ethan-1-ol (0.9 g, 8.3 mmol), 2-amino-5-mercapto-thiadiazole (1.0 g, 7.5 mmol) and triphenylphosphine (2.17 g, 8.3 mmol) in anhydrous THF (10.0 mL) diethyleneazadicarboxylate (2.25 g, 9.8 mmol) was added dropwise in 5 mL of anhydrous tetrahydrofurane. Reaction mixture was stirred overnight at room temperature. After this time solvents were removed in vacuo. Crude product was purified via column

chromatography using 0-3% MeOH in DCM and re-purified via preparative HPLC method to give pure product (80 mg, 7%) LCMS-Method 7 (205 nm): RT=5.27 min, 98.1% purity, [M]=386.9. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 7.30 (s, 1H), 7.14 (td, J=7.8, 7.3, 1.7 Hz, 1H), 7.09-6.96 (m, 2H), 6.89 (dd, J=8.2, 2.0 Hz, 0H), 6.75-6.61 (m, 1H), 4.94 (t, J=6.0 Hz, 1H), 3.79 (d, J=1.8 Hz, 3H), 3.38 (d, J=6.5 Hz, 1H), 3.24 (t, J=6.4 Hz, 1H).
(81) Synthesis Method C
(82) ##STR00133##
(83) Step 1
(84) ##STR00134##
(85) To the solution of amine (4.27 mmol) in MeOH (25.0 mL) methyl 4-oxobutanoate (0.99 g, 8.54 mmol) and acetic acid (0.8 mL) was added. The reaction mixture was stirred for 1.5 hours at ambient temperature. After that time NaBH.sub.3CN (0.40 mg, 6.41 mmol) was added and the mixture was stirred for 1 h. Reaction was quenched with saturated solution of NaHCO.sub.3. The water layer was extracted with DCM (3×20 mL). Combined organic layers were dried over sodium sulfate, filtered, evaporated to provide the product.
(86) methyl 4-(4′-fluoro-[1,1′-biphenyl]-2-yl)amino)butanoate (0.875 g, 71%) 4′-fluoro-[1,1′-biphenyl]-2-amine was used. Crude (1.47 g) was purified via column chromatography using 100% DCM as eluent. UPLC (254 nm): RT=4.14 min, 76% purity, [M+H]=288.20.
(87) methyl 4-((3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl)amino)butanoate (1.00 g, 71%) 3′,4′-dimethoxy-[1,1′-biphenyl]-2-amine was used. Crude product was purified via column chromatography using 0-20% EA in hexane as eluent.
(88) Step 2
(89) ##STR00135##
(90) To the solution of corresponding starting material (3.04 mmol) in EtOH (30 mL) 50% hydrazine in H.sub.2O (5.0 eq) was added. Reaction mixture was stirred for 18 hour at 80° C. After that time the solvent was evaporated to give pure compound.
(91) 4-(4′-fluoro-[1,1′-biphenyl]-2-yl)amino)butanehydrazide (0.85 g, 96%). Methyl 4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)butanoate (0.875 g. 3.04 mmol) as starting material was used. UPLC (254 nm): RT=3.06 min, [M+H]=288.35.
(92) 4-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl}amino)butanehydrazide (0.97 g, 97%). Methyl 4-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl}amino)butanoate (1.0 g, 3.04 mmol) as starting material was used. UPLC (254 nm): RT=2.82 min, [M+H]=330.30.
(93) Step 3
(94) ##STR00136##
(95) To the solution of corresponding starting material (2.6 mmol) in MeOH (8 mL) N,N-dimethylformamide dimethylacetal (311 mg, 2.6 mmol) was added. Reaction mixture was stirred for 1 hour at 80° C. After that time solvent was evaporated to obtain desired product.
(96) N′-[(1E)-(dimethylamino)methylidene]-4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)butane-hydrazide (0.894 g, 100%). 4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)butanehydrazide (0.75 g, 2.61 mmol) was used as starting material. UPLC (254 nm): RT=3.40 min, [M+H]=343.15.
(97) 4-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl}amino)-N′-[(1E)-(dimethylamino)methylidene]-butanehydrazide (1.014 g, 100%). 4-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl}amino)butane-hydrazide (0.869 g, 2.64 mmol) was used as starting material. UPLC (254 nm): RT=3.40 min, [M+H]=385.30.
(98) Step 4
(99) ##STR00137##
(100) MeNH.sub.2 2M in THF (20 eq) was added to the solution of corresponding starting material in anhydrous THF (10.0 mL) under argon atmosphere. Reaction mixture was cooled to 0° C. and acetic acid (2 mL) was carefully added. Reaction mixture was stirred for 18 hours at 100° C. After that time reaction was cooled to room temperature and water (5 mL) was added. Layers were

separated and water layer was extracted three times with EA (3×20 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using 0-4% MeOH in DCM as eluent and then re-purified via preparative HPLC. Fraction containing the title compound in pure form was concentrated to give the product.
(101) 4′-fluoro-N-[3-(4-methyl-4H-1,2,4-triazol-3-yl)propyl]-[1,1′-biphenyl]-2-amine (B1) (101 mg, 11%) N′-[(1E)-(dimethylamino)methylidene]-4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)butane-hydrazide (1.00 g, 2.92 mmol) was used as starting material. LCMS-Method 2 (220 nm): RT=4.78 min, 98.89% purity. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.32 (s, 1H), 7.46-7.36 (m, 2H), 7.32-7.21 (m, 2H), 7.21-7.14 (m, 1H), 6.95 (d, J=1.7 Hz, 1H), 6.72-6.61 (m, 2H). 4.10 (q, J=5.3 Hz, 2H), 3.54 (s, 3H). 2.69 (d, J=7.5 Hz, 2H), 1.95-1.84 (m, 2H).
(102) 3′,4′-dimethoxy-N-[3-(4-methyl-4H-1,2,4-triazol-3-yl)propyl]-[1,1′-biphenyl]-2-amine (B3) (5 mg, 0.4%). 4-({3′,4′-dimethoxy-[1,1′-biphenyl]-2-yl}amino)-N′-[(1E)-(dimethylamino)-methylidene]-butanehydrazide (1.10 g, 2.86 mmol) was used as starting material. LCMS-Method 8 (210 nm): RT=12.12 min, 99.45% purity. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.32 (s, 1H), 7.09-6.84 (m, 4H), 6.66 (d, J=7.9 Hz, 2H), 4.11 (q, J=5.4 Hz, 2H), 3.79 (d, J=5.4 Hz, 3H), 3.53 (s, 3H), 3.40 (t, J=7.0 Hz, 2H), 3.18 (d, J=5.3 Hz, 3H), 1.89-1.96 (m, 2H).
(103) ##STR00138##
(104) Step 1
(105) ##STR00139##
(106) N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine (0.5 g, 2.0 mmol), triethylamine (0.54 mL, 4.0 mmol), were dissolved in DCM (5 mL) and acetyl chloride (0.17 g, 2.15 mmol) was added dropwise at 5° C., reaction was stirred at room temperature over 1h, after this time another portion of triethylamine and acetyl chloride was added at 5° C. and reaction mixture was stirred over additional 30 min. The mixture was diluted with DCM (15.0 mL) and washed with sat. solution of sodium bicarbonate (20 mL), water (20 mL). Title compound was obtained as 1:1 mixture of acetylated (UPLC (254 nm): RT=3.13 min[M+H]=297.9) and diacetylated amine (UPLC (254 nm): RT=3.58 min[M+H]=338.9). (0.40 g, 60%). Used in next step without purification.
(107) Step 2
(108) ##STR00140##
(109) N-(5-[4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)phenyl]-1,3,4-thiadiazol-2-yl)acetamide N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (0.2 g, 0.67 mmol), 4′-fluoro-[1,1′-biphenyl]-2-amine (0.12 g, 0.56 mmol), sodium tert-butanolate (0.15 mg, 1.56 mmol) and XantPhos (40 mg, 0.07 mmol) were suspended in 1,4-dioxane (6 ml), Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (35 mg, 0.035 mmol) was added. Reaction was stirred overnight at 100° C. After that time reaction mixture was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using MeOH in DCM 0-3% as aluent to give pure product (0.24 g, 88%). UPLC (254 nm): RT=3.78 min. 85% purity, [M+H]=404.8.
(110) ##STR00141##
(111) 5-[4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)phenyl]-1,3,4-thiadiazol-2-amine (C.sub.2) To solution of N-{5-[4-({4′-fluoro-[1,1′-biphenyl]-2-yl}amino)phenyl]-1,3,4-thiadiazol-2-yl}acetamide (0.17 g, 0.42 mmol) in methanol (2.5 mL) concentrated hydrochloric acid (2.5 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with DCM (6×15 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative HPLC method to give pure product (40 mg, 25%) LCMS-Method 6 (200 nm): RT=20.57 min, 91.6% purity, [M+H]=363.14, LCMS (340 nm): RT=20.57 min, 99.2% purity, [M+H]=363.14, 1H NMR (300 MHz, DMSO-d6) δ 7.82 (s, 1H), 7.59-7.33 (m, 7H), 7.27-7.04 (m, 5H), 6.89-6.54 (m, 2H).

(112) ##STR00142##
(113) N-{5-(4-{[2-(3,4-dimethoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-yl}acetamide N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (100 mg, 0.34 mmol), 2-(3,4-dimethoxyphenyl)aniline (60 mg, 0.28 mmol), sodium tert-butanolate (75 mg, 1.56 mmol) and XantPhos (40 mg, 0.035 mmol) were suspended in 1,4-dioxane (3 ml), Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (17 mg, 0.017 mmol) was added. Reaction was stirred overnight at 100° C. After that time reaction mixture was cooled to room temperature, Filtered through celite, evaporated and purified via column chromatography using MeOH in DCM 0-3% as aluent to give pure product (0.2 g, 80%). UPLC (254 nm): RT=3.64 min, 85% purity, [M+H]=447.15.
(114) ##STR00143##
(115) 5-(4-([2-(3,4-dimethoxyphenyl)phenyl]amino)phenyl)-1,3,4-thiadiazol-2-amine (C3). To solution of N-{5-(4-{[2-(3,4-dimethoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-yl}acetamide (0.20 g, 0.42 mmol) in methanol (3.0 mL) concentrated hydrochloric acid (3.0 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with DCM (6×15 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative HPLC method to give pure product (44 mg, 25%) LCMS (LCMS-Method 10, 200 nm), RT=5.22 min, 96.1% purity, [M+H]=405.11, 1H NMR (300 MHz, DMSO-d6) δ 7.87 (s, 1H), 7.55-7.31 (m, 6H), 7.37-7.13 (m, 5H), 6.81-6.64 (m, 2H), 3.53 (s, 3H), 3.50 (s, J=7.0 Hz, 3H).
(116) ##STR00144##
(117) N-[5-(4-{[2-(4-methoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (128 mg, 0.43 mmol), 2-(4-methoxyphenyl)aniline (102 mg, 0.51 mmol), cesium carbonate (279 mg, 0.86 mmol) and XantPhos (50 mg, 0.09 mmol) were suspended in 1,4-dioxane (3.8 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (35 mg. 0.04 mmol) was added. Reaction was stirred at 100° C. for 96 hours. After that time reaction mixture was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.98:2 as a eluent to give product as a yellow solid (62.5 mg, 35.01%). UPLC (254 nm): RT=7.14 min, 80.9% purity, [M+H]=417.10.
(118) ##STR00145##
(119) 5-(4-{[2-(4-methoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-amine C4. To solution of N-[5-(4-{[2-(4-methoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide (63 mg, 0.15 mmol) in methanol (1.0 mL) concentrated hydrochloric acid (1.0 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL), methanol was evaporated and extraction with ethyl acetate (2×10 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with Hex/EtOAc/MeOH 70:25:5 to give desired product as a yellow solid (19.6 mg, 35%). LCMS (LCMS-Method 11, 200 nm): RT=2.75 min, 98.9% purity, [M+H]=375.21. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 7.74 (s, 1H), 7.50-7.43 (m, 2H), 7.40-7.28 (m, 5H), 7.23-7.14 (m, 3H), 6.98-6.91 (m, 2H), 6.84-6.78 (m, 2H), 3.75 (s, 3H).
(120) ##STR00146##
(121) N-[5-(4-([3-(4-methoxyphenyl)pyridin-2-yl)]amino)phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (87 mg, 0.29 mmol), 3-(4-methoxyphenyl)pyridin-2-amine (70 mg, 0.35 mmol), cesium carbonate (190 mg, 0.58 mmol) and XantPhos (34 mg, 0.06 mmol) were suspended in 1,4-dioxane (2.6 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (24 mg, 0.03 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture

was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.95:5 as a eluent to give product as a pale-yellow solid (114 mg, 93.6%). UPLC (254 nm): RT=5.35 min. 65% purity, [M+H]=418.70.
(122) ##STR00147##
(123) N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-methoxyphenyl)pyridin-2-amine (C5). To solution of N-[5-(4-{[3-(4-methoxyphenyl)pyridin-2-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide (114 mg, 0.27 mmol) in methanol (1.7 mL) concentrated hydrochloric acid (1.7 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL), methanol was evaporated and extraction with ethyl acetate (2×15 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with DCM/MeOH 9:1 to give desired product as a yellowish solid (16.4 mg, 16%). LCMS-Method 5 (200 nm): RT=1.75 min, 99.3% purity, [M+H]=376.19. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.20 (dd, J=4.9, 1.9 Hz, 1H), 7.96 (s, 1H), 7.67-7.56 (m, 4H), 7.53 (dd, J=7.4, 1.9 Hz, 1H), 7.47-7.40 (m, 2H), 7.25 (s, 2H), 7.10-7.04 (m, 2H), 6.98 (dd, J=7.4, 4.9 Hz, 1H), 3.82 (s, 3H).
(124) ##STR00148##
(125) N-[5-(4-{[3-(4-methoxyphenyl)pyridin-4-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (100 mg, 0.34 mmol), 3-(4-methoxyphenyl)pyridin-4-amine (81 mg, 0.40 mmol), cesium carbonate (219 mg, 0.67 mmol) and XantPhos (39 mg, 0.07 mmol) were suspended in 1,4-dioxane (3 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.95:5 as a eluent to give product as a yellow solid (75 mg, 53.6%). UPLC (310 nm): RT=3.96 min, 93% purity, [M+H]=418.95.
(126) ##STR00149##
(127) N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-methoxyphenyl)pyridin-4-amine (C6). To solution of N-[5-(4-{[3-(4-methoxyphenyl)pyridin-4-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide (75 mg, 0.18 mmol) in methanol (1.12 mL) concentrated hydrochloric acid (1.12 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL), methanol was evaporated and extraction with ethyl acetate (2×15 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with DCM/MeOH 9:1. Re-purification was performed via preparative TLC eluted with DCM/MeOH 9:1 to give desired product as a whitish solid (32.0 mg, 47%). LCMS-Method 3 (200 nm): RT=3.01 min, 99.8% purity, [M+H]=376.18. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.26-8.20 (m, 2H). 8.00 (s, 1H), 7.66-7.61 (m, 2H), 7.45-7.40 (m, 2H), 7.32-7.18 (m, 5H), 7.07-7.02 (m, 2H), 3.80 (s, 3H).
(128) ##STR00150##
(129) N-[5-(4-{[3-(3,4-dimethoxyphenyl)pyridin-4-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (100 mg, 0.34 mmol), 3-(3,4-dimethoxyphenyl)pyridin-4-amine (93 mg, 0.40 mmol), cesium carbonate (219 mg, 0.67 mmol) and XantPhos (39 mg, 0.07 mmol) were suspended in 1,4-dioxane (3 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.95:5 as a eluent to give product as a pale-yellow solid (49 mg, 32.7%). UPLC (310 nm): RT=4.72 min, 100% purity, [M+H]=448.15.
(130) ##STR00151##
(131) N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(3,4-dimethoxyphenyl)pyridin-4-amine (C7). To solution of N-[5-(4-{[3-(3,4-dimethoxyphenyl)pyridin-4-yl]amino}phenyl)-1,3,4-thiadiazol-2-

yl]acetamide (49 mg, 0.11 mmol) in methanol (0.75 mL) concentrated hydrochloric acid (0.75 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (10 mL), methanol was evaporated and extraction with ethyl acetate (2×10 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as a light yellow solid (11 mg, 24.8%). LCMS-Method 3 (200 nm): RT=2.90 min, 99.6% purity, [M+H]=406.17. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.28-8.22 (m, 2H), 8.01 (s, 1H), 7.67-7.60 (m, 2H), 7.33-7.17 (m, 5H), 7.09-6.99 (m, 3H), 3.77 (d, J=12.1 Hz, 6H).
(132) ##STR00152##
(133) N-[5-(4-{[3-(4-fluorophenyl)pyridin-2-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (100 mg, 0.34 mmol), 3-(4-fluorophenyl)pyridin-2-amine (52 mg, 0.28 mmol), cesium carbonate (219 mg, 0.67 mmol) and XantPhos (39 mg, 0.07 mmol) were suspended in 1,4-dioxane (3 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.99:1 as a eluent to give product as a yellowish solid (75 mg, 55.6%). UPLC (254 nm): RT=5.92 min, 96.8% purity, [M+H]=406.95.
(134) ##STR00153##
(135) N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-fluorophenyl)pyridin-2-amine (C.sub.8). To solution of N-[5-(4-{[3-(4-fluorophenyl)pyridin-2-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide (75 mg, 0.18 mmol) in methanol (1.2 mL) concentrated hydrochloric acid (1.2 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL), methanol was evaporated and extraction with ethyl acetate (2×15 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with DCM/MeOH 95:5. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as a yellowish solid (4.3 mg, 6.4%). LCMS-Method 2 (200 nm): RT=4.69 min, 98.9% purity, [M+H]=364.18. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.22 (dd, J=5.0, 1.9 Hz, 1H), 7.68-7.61 (m, 2H), 7.60-7.47 (m, 5H), 7.30-7.20 (m, 2H), 7.02 (dd, J=7.4, 5.0 Hz, 1H).
(136) ##STR00154##
(137) N-[5-(4-{[3-(4-fluorophenyl)pyrazin-2-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (100 mg, 0.34 mmol), 3-(4-fluorophenyl)pyrazin-2-amine (76 mg, 0.40 mmol), cesium carbonate (219 mg, 0.67 mmol) and XantPhos (39 mg, 0.07 mmol) were suspended in 1,4-dioxane (3 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture was cooled to room temperature. Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3 as a eluent to give product as a yellowish solid (68 mg, 49.8%). UPLC (254 nm): RT=5.88 min, 95.5% purity, [M+H]=407.05.
(138) ##STR00155##
(139) N-[4-(5-amino-1,3,4-thiadiazol-2-yl)phenyl]-3-(4-fluorophenyl)pyrazin-2-amine (C9). To solution of N-[5-(4-{[3-(4-fluorophenyl)pyrazin-2-yl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide (68 mg, 0.17 mmol) in methanol (1 mL) concentrated hydrochloric acid (1 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL), methanol was evaporated and extraction with ethyl acetate (2×15 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with DCM/MeOH 9:1. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired

product as a yellow solid (20.2 mg, 33.2%). LCMS-Method 4 (328 nm): RT=2.44 min, 97.0% purity, [M+H]=365.15. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.70 (s, 1H), 8.19 (s, 2H), 7.86-7.79 (m, 2H), 7.64 (s, 4H), 7.46-7.27 (m, 4H).
(140) ##STR00156##
(141) N-[5-(4-{[2-(4-phenoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (100 mg, 0.34 mmol), 2-(4-phenoxyphenyl)aniline (105 mg, 0.40 mmol), cesium carbonate (219 mg, 0.67 mmol) and XantPhos (39 mg, 0.07 mmol) were suspended in 1,4-dioxane (3 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.98:2 as a eluent to give product as a yellow solid (115 mg, 71.7%). UPLC (254 nm): RT=7.96 min, 88.6% purity, [M+H]=479.15.
(142) ##STR00157##
(143) 5-(4-{[2-(4-phenoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-amine (C10). To solution of N-[5-(4-{[2-(4-phenoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide (95 mg, 0.20 mmol) in methanol (1.4 mL) concentrated hydrochloric acid (1.4 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (20 mL), methanol was evaporated and extraction with ethyl acetate (2×15 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with DCM/MeOH 8:2. Re-purification was performed via preparative TLC eluted with Hex/EtOAc/MeOH 70:25:5 to give desired product as a yellowish solid (17.2 mg, 19.9%). LCMS-Method 11 (200 nm): RT=3.57 min, 97.5% purity, [M+H]=437.16. .sup.1H NMR (300 MHz. Methanol-d.sub.4) δ 7.52-7.43 (m, 2H), 7.41-7.15 (m, 8H), 7.10-7.01 (m, 1H), 6.97-6.84 (m, 4H), 6.82-6.72 (m, 2H).
(144) ##STR00158##
(145) N-[5-(4-([2-(4-propoxyphenyl)phenyl]amino)phenyl)-1,3,4-thiadiazol-2-yl]acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (120 mg, 0.40 mmol), 2-(4-propoxyphenyl)aniline (110 mg, 0.48 mmol), cesium carbonate (262 mg, 0.80 mmol) and XantPhos (47 mg, 0.08 mmol) were suspended in 1,4-dioxane (3.6 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (33 mg, 0.04 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture was cooled to room temperature, Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3 as a eluent to give product as a yellowish solid (55.7 mg, 31.1%). UPLC (254 nm): RT=8.07 min, 86.8% purity, [M+H]=445.30.
(146) ##STR00159##
(147) 5-(4-([2-(4-propoxyphenyl)phenyl]amino)phenyl)-1,3,4-thiadiazol-2-amine (C11). To solution of N-[5-(4-{[2-(4-propoxyphenyl)phenyl]amino}phenyl)-1,3,4-thiadiazol-2-yl]acetamide (56 mg, 0.13 mmol) in methanol (0.84 mL) concentrated hydrochloric acid (0.84 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (10 mL), methanol was evaporated and extraction with ethyl acetate (2×10 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with Hex/EtOAc/MeOH 70:25:5. Re-purification was performed via maceration with diethyl ether to give desired product as a light brown solid (11 mg, 22%). LCMS-Method 4 (200 nm): RT=3.67 min, 98.9% purity, [M+H]=403.19. .sup.1H NMR (300 MHz. Methanol-d.sub.4) δ 7.56-7.47 (m, 2H), 7.41-7.27 (m, 5H), 7.17 (td, J=7.3, 1.5 Hz, 1H), 6.96-6.81 (m, 4H), 3.94 (t, J=6.5 Hz, 2H), 1.79 dtd, J=13.8, 7.4, 6.4 Hz, 2H), 1.04 (t, J=7.4 Hz, 3H).
(148) ##STR00160##
(149) N-(5-[4-(2-[4-(propan-2-yloxy)phenyl]phenyl)amino)phenyl]-1,3,4-thiadiazol-2-

yl)acetamide. N-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide (100 mg, 0.34 mmol), 2-[4-(propan-2-yloxy)phenyl]aniline (91 mg, 0.40 mmol), cesium carbonate (219 mg, 0.67 mmol) and XantPhos (39 mg, 0.07 mmol) were suspended in 1,4-dioxane (3 mL). Reaction mixture was degassed with argon flow over 20 min and tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol) was added. Reaction was stirred at 100° C. for 72 hours. After that time reaction mixture was cooled to room temperature. Filtered thru celite, evaporated and purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3 as a eluent to give product as a yellowish solid (87.4 mg, 58.6%). UPLC (254 nm): RT=7.59 min, 87.6% purity, [M+H]=445.15.
(150) ##STR00161##
(151) 5-[4-({2-[4-{propan-2-yloxy)phenyl]phenyl}amino)phenyl]-1,3,4-thiadiazol-2-amine (C12). To solution of N-{5-[4-((2-[4-(propan-2-yloxy)phenyl]phenyl}amino)phenyl]-1,3,4-thiadiazol-2-yl}acetamide (87 mg, 0.20 mmol) in methanol (1.3 mL) concentrated hydrochloric acid (1.3 mL) was added dropwise. Reaction mixture was refluxed overnight. After this time reaction was diluted with saturated sodium bicarbonate solution (15 mL), methanol was evaporated and extraction with ethyl acetate (2×15 mL) was made. Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via preparative TLC eluted with Hex/EtOAc/MeOH 70:25:5. Re-purification was performed via maceration with methanol, to give desired product as a yellow solid (7 mg, 8.8%). LCMS-Method 4 (200 nm): RT=3.54 min, 97.4% purity, [M+H]=403.20. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 7.55-7.47 (m, 2H), 7.41-7.27 (m, 5H), 7.18 (td, J=7.3, 1.5 Hz, 1H), 6.94-6.81 (m, 4H), 4.59 (dq, J=12.1, 6.1 Hz, 1H), 1.30 (d, J=6.0 Hz, 6H).
(152) Synthesis Method E
(153) ##STR00162##
(154) To a solution of 4-(chlorophenyl)-4-methyl-4-H-1,2,4-triazole (100 mg, 0.52 mmol) and corresponding base (1.20 mmol, 2.3 eq) in 1,4-dioxane (3.0 mL) amine (1.0 eq) was added. Reaction mixture was degassed for 30 minutes. Then xantphos (30 mg, 0.05 mmol) and corresponding catalyst were added and the mixture was stirred at 100° C. for 5 days. The reaction mixture was filtrated throw cellite, the filtrate was concentrated and purified via column chromatography using 0-10% MeOH in DCM as eluent. Fractions containing the title compound were combined and concentrated. Product was re-purified via P-TLC using 4% MeOH in DCM as an eluent.
(155) 4′-fluoro-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]-[1,1′-biphenyl]-2-amine (D1) (34 mg, 19%). 4′-fluoro-[1,1′-biphenyl]-2-amine (97 mg, 0.52 mmol), t-BuONa (115 mg, 1.2 mmol), chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) (26 mg 0.05 mmol), tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.05 mmol) were used. LCMS-Method 2 (200 nm): RT=5.54 min, 97.6% purity, [M+H]=345.15. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.46 (s, 1H), 7.82 (s, 1H), 7.45-7.49 (m, 4H), 7.34-7.40 (m, 3H), 7.17-7.25 (m, 3H), 6.88 (d, J=9.0 Hz, 2H), 3.69 (s, 3H).
(156) 3′,4′-dimethoxy-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]-[1,1′-biphenyl]-2-amine (D2) (45 mg, 28%). 3′,4′-dimethoxy-[1,1′-biphenyl]-4-amine (120 mg, 0.52 mmol), Cs.sub.2CO.sub.3 (396 mg, 1.2 mmol), chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) (26 mg 0.05 mmol) were used. LCMS-Method 2 (200 nm) RT=4.8 min, 98.7% purity, [M+H]=387.14. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.46 (s, 1H), 7.74 (s, 1H), 7.47 (d, J=9 Hz, 2H), 7.31-7.42 (m, 3H), 7.19-7.25 (m, 1H), 6.99 (d, 2H, J=6 Hz), 6.88 (d, 2H, J=9 Hz), 3.76 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H).
(157) ##STR00163##
(158) N-[2-(4-methoxyphenyl)phenyl]-4-(4-methyl-4H-1,2,4-triazol-3-yl)aniline (D3). To a solution of 4-(chlorophenyl)-4-methyl-4-H-1,2,4-triazole (73 mg, 0.38 mmol) and Cs.sub.2CO.sub.3 (285 mg, 0.87 mmol) in 1,4-dioxane (2.25 mL) 2-(4-methoxyphenyl)aniline (75 mg, 0.38 mmol) was added. Reaction mixture was degassed for 30 minutes. Then xantphos (22 mg,

0.04 mmol) and chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) (19 mg 0.02 mmol) were added and the mixture was stirred at 100° C. overnight. The reaction mixture was filtrated through cellite, washed with MeOH. Filtrate was concentrated and purified via column chromatography using 0-10% MeOH in DCM as eluent. Fractions containing the title compound were combined and concentrated. Product was re-purified via P-TLC using 4% MeOH in DCM as an eluent to give desired product as an orange solid (13 mg, 10%). LCMS-Method 2 (200 nm): RT=5.38 min, 94.03% purity, [M+H]=357.21. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.48 (s, 1H), 7.45 (d, J=8.8 Hz, 2H), 7.39 (s, 1H), 7.37-7.28 (m, 4H), 7.29-7.13 (m, 1H), 6.94 (dd, J=8.8, 3.3 Hz, 4H), 3.80 (s, 3H), 3.78 (s, 3H).
(159) ##STR00164##
(160) 2-(4-methoxyphenyl)-N-[4(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]pyridin-3-amine (D4). To a solution of 4-(chlorophenyl)-4-methyl-4-H-1,2,4-triazole (68 mg, 0.35 mmol) and Cs.sub.2CO.sub.3 (264 mg, 0.81 mmol) in 1,4-dioxane (2.10 mL) 2-(4-methoxyphenyl)pyridin-3-amine (70 mg, 0.35 mmol) was added. Reaction mixture was degassed for 30 minutes. Then xantphos (20 mg, 0.03 mmol) and chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) (18 mg 0.02 mmol) were added and the mixture was stirred at 100° C. overnight. The reaction mixture was filtrated through cellite, washed with MeOH. Filtrate was concentrated and purified via column chromatography using 0-10% MeOH in DCM as eluent. Fractions containing the title compound were combined and concentrated. Product was re-purified via P-TLC using 4% MeOH in DCM as an eluent to give desired product as white solid (35 mg, 28%). LCMS-Method 1 (200 nm): RT=5.58 min, 96.3% purity, [M+H]=358.22. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.67 (s, 1H), 8.43 (d, J=5.9 Hz, 1H), 8.24 (s, 1H), 7.84 (d, J=8.8 Hz, 1H), 7.71 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.3 Hz, 2H), 7.39 (dd, J=8.1, 4.7 Hz, 3H), 6.98 (t, J=9.1 Hz, 4H), 3.78 (s. 3H), 3.74 (s, 3H).
(161) ##STR00165##
(162) 2-(4-fluorophenyl)-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]pyridin-3-amine (D5). To a solution of 4-(chlorophenyl)-4-methyl-4-H-1,2,4-triazole (77 mg, 0.40 mmol) and Cs.sub.2CO.sub.3 (301 mg, 0.92 mmol) in 1,4-dioxane (2.25 mL) 2-(4-fluorophenyl)pyridin-3-amine (75 mg, 0.40 mmol) was added. Reaction mixture was degassed for 30 minutes. Then xantphos (23 mg, 0.04 mmol) and chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) (20 mg 0.02 mmol) were added and the mixture was stirred at 100° C. overnight. The reaction mixture was filtrated through cellite, washed with MeOH. Filtrate was concentrated and purified via column chromatography using 0-10% MeOH in DCM as eluent. Fractions containing the title compound were combined and concentrated. Product was re-purified via P-TLC using 4% MeOH in DCM as an eluent to give desired product as light orange solid (5 mg, 4%). LCMS-Method 1 (205 nm): RT=5.82 min, 99.46% purity, [M+H]=346.22. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.50 (s, 1H), 8.37 (dd, J=4.7, 1.5 Hz, 1H), 7.89 (d, J=7.2 Hz, 1H), 7.70 (dd, J=9.1, 5.6 Hz, 2H), 7.51 (d, J=8.8 Hz, 2H), 7.42 (dd, J=8.2, 4.7 Hz, 1H), 7.16 (t, J=8.7 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 3.78 (s, 3H).
(163) ##STR00166##
(164) 4-(4-methyl-4H-1,2,4-triazol-3-yl)-N-[2-(4-phenoxyphenyl)phenyl]aniline (D6). To a solution of 4-(chlorophenyl)-4-methyl-4-H-1,2,4-triazole (74 mg, 0.38 mmol) and Cs.sub.2CO.sub.3 (289 mg, 0.89 mmol) in 1,4-dioxane (3.00 mL) 2-(4-phenoxyphenyl)aniline (100 mg, 0.38 mmol) was added. Reaction mixture was degassed for 30 minutes. Then xantphos (22 mg, 0.04 mmol) and chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) (20 mg 0.02 mmol) were added and the mixture was stirred at 100° C. overnight. The reaction mixture was filtrated through celite, washed with MeOH. Filtrate was concentrated and purified via column chromatography using 0-5% MeOH in DCM as eluent. Fractions containing the title compound were combined and concentrated. Product was re-purified via P-TLC using 4% MeOH in DCM as an eluent to give desired product as white solid (25 mg, 16%). LCMS-Method 5 (200 nm):

RT=2.25 min, 99.51% purity. [M+H]=419.20. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.47 (s, 1H), 7.74-7.14 (m, 11H), 7.09 (t, J=7.9 Hz, 1H), 7.09-6.77 (m, 6H), 3.75 (s, 3H).
(165) ##STR00167##
(166) 3-(3,4-dimethoxyphenyl)-N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]pyridin-4-amine (D7). To a solution of 4-(chlorophenyl)-4-methyl-4-H-1,2,4-triazole (59 mg, 0.30 mmol) and Cs.sub.2CO.sub.3 (230 mg, 0.71 mmol) in 1,4-dioxane (2.10 mL) 3-(3,4-dimethoxyphenyl)pyridin-4-amine (70 mg, 0.30 mmol) was added. Reaction mixture was degassed for 30 minutes. Then xantphos (18 mg, 0.03 mmol) and chloroform adduct of tris(dibenzylideneacetone)dipalladium(0) (16 mg 0.02 mmol) were added and the mixture was stirred at 100° C. overnight. The reaction mixture was filtrated through celite, washed with MeOH. Filtrate was concentrated and purified via column chromatography using 0-10% MeOH in DCM as eluent. Fractions containing the title compound were combined and concentrated. Product was re-purified via P-TLC using 4% MeOH in DCM as an eluent to give desired product as white solid (20 mg, 16%). LCMS-Method 3 (305 nm): RT=2.69 min, 98.21% purity, [M+H]=388.24. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.55 (s, 1H), 8.26-8.19 (m, 2H), 7.72-7.58 (m, 2H). 7.43-7.25 (m, 3H), 7.09 (d, J=4.2 Hz, 3H). 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s. 3H).
(167) Synthesis Method F
(168) ##STR00168##
(169) 5-(3-bromopropyl)-1,3,4-thiadiazol-2-amine. Phosphoryl chloride (7.37 mL, 79.0 mmol) was added to aminothiourea (2.185 g, 24.0 mmol) and 4-bromobutanoic acid. The mixture was stirred at 85° C. overnight, cooled and poured into ice. Solution of saturated sodium biscarbonate was added the solution and the water layer was extracted three times with EA (3×80 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using 0-10% DCM in MeOH as eluent. Fractions containing the title compound were combined and concentrated (3.301 g, 62%). UPLC (254 nm): RT=1.91 min, 68% purity, [M−H]=223.7.
(170) ##STR00169##
(171) N-[5-(3-bromopropyl)-1,3,4-thiadiazol-2-yl]acetamide. To the solution of 5-(3-bromopropyl)-1,3,4-thiadiazol-2-amine (3.3 g, 14.8 mmol) in anhydrous DCM (35 mL), under argon atmosphere, trietylamine (4.14 mL, 29.7 mmol) and acetylchloride (1.16 mL, 16.3 mmol) were added. Reaction mixture was stirred for 6 hours at ambient temperature. After that time 1M HCl was added (50 mL) and the water layer was extracted three times with DCM (3×80 mL). Combined organic layers were dried over sodium sulfate, filtered, evaporated to provide the pure product (3.144 g, 80%). UPLC (254 nm): RT=2.43 min. 89% purity, [M+H]=265.65.
(172) ##STR00170##
(173) N-[5-(3-azidopropyl)-1,3,4-thiadiazol-2-yl]acetamide. To the solution of N-[5-(3-bromopropyl)-1,3,4-thiadiazol-2-yl]acetamide (1.0 g, 3.8 mmol) in anhydrous DMF (20.0 mL), under argon atmosphere, sodium azide (0.37 g, 5.7 mmol) was added. Reaction mixture was stirred for 2 hours. After that time water (10 mL) was added and the water layer was extracted with DCM (3×80 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated to provide the pure product (0.6 g, 71%). UPLC (254 nm): RT=2.29 min, 98% purity, [M+H]=227.0.
(174) ##STR00171##
(175) N-[5-(3-aminopropyl)-1,3,4-thiadiazol-2-yl]acetamide. Solution of methyl N-[5-(3-azidopropyl)-1,3,4-thiadiazol-2-yl]acetamide (0.6 g, 2.7 mmol) in anhydrous tetrahydrofuran (7 mL was dropped to the suspension of LAH pellets (0.1 g, 2.8 mmol) in anhydrous THF (5 mL) under argon atmosphere. Reaction mixture was stirred 1h at ambient temperature. After that time LAH (0.1 g. 2.8 mmol) was added. The stirring was continued for 2 hours. After that time 0.2 mL of water was added, followed by addition of 0.4 mL of 20% NaOH and 0.6 mL of water. The suspension was filtered throw cellite and washed with DCM/MeOH 9:1. Evaporation of solvents gave titled compound (0.22 g, 41%). UPLC (254 nm): RT=1.17 min, 57% purity, [M−H]=201.2.

(176) ##STR00172##
(177) N-{5-[3-(4-fluorobenzenesulfonamido)propyl]-1,3,4-thiadiazol-2-yl}acetamide. To the solution of 3,4-dichlorobenzenosulfonyl chloride (165 mg, 0.85 mmol) in the mixture of solvents DCM (1.0 mL) and pyridine (1.0 mL) N-[5-(3-aminopropyl)-1,3,4-thiadiazol-2-yl]acetamide (170 mg, 0.85 mmol) was added. The reaction mixture was stirred for 18 hours at ambient temperature. After that time solvents were evaporated and to the residues 1M HCl was added and the water layer was extracted with DCM (3×20 mL). Combined organic layers were dried over sodium sulfate, filtered, evaporated to provide the product (0.02 g, 7%). UPLC (254 nm): RT=2.56 min, 98% purity, [M+H]=358.85.
(178) ##STR00173##
(179) N-[3-(5-amino-1,3,4-thiadiazol-2-yl)propyl]-4-fluorobenzene-1-sulfonamide (E2). N-{5-[3-(4-fluorobenzenesulfonamido)propyl]-1,3,4-thiadiazol-2-yl}acetamide (20 mg, 0.06 mmol) was dissolved in the solution of HCl (2 mL) and MeOH (2 mL). The reaction mixture was stirred for 18 hours at 80° C. After that time solution of sodium biscarbonate was added and the water layer was extracted with DCM (3×10 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated. Purification of crude product via P-TLC using 4% methanol in dichloromethane as an eluent gave desired product (3 mg, 17%). LCMS-Method 1 (200 nm): RT=2.56 min, 96.0% purity. [M+H]=317.15. .sup.1H NMR (300 MHz, MeOH-d.sub.4) δ 7.87-7.94 (m, 2H), 7.29-7.39 (m, 2H), 2.86-2.97 (m, 4H), 1.82-1.91 (m, 2H).
(180) Synthesis Method G
(181) ##STR00174##
(182) N-(2-chloroethyl)-4-fluorobenzene-1-sulfonamide 2-chloroethylamine hydrochloride (0.25 g, 2.2 mmol), 4-fluorobenzenesulfonyl chloride (0.42 g, 2.2 mmol), were dissolved in DCM (2.5 mL) and pyridine (2.5 mL). Reaction was stirred at room temperature overnight. The mixture was diluted with DCM (15.0 mL) and washed with 1M solution of hydrochloric acid (20 mL). Organic layer was dried over sodium sulfate, filtered and evaporated. Title compound was obtained as yellow oil (0.5 g, 86% yield). .sup.1H NMR (300 MHz, CDCl.sub.3) δ 7.82-7.95 (m, 2H), 7.25-7.33 (m, 2H), 4.92 (t, 1H), 3.54-3.64 (t, 2H), 3.32-3.44 (dt, 2H).
(183) ##STR00175##
(184) N-{2-[(5-amino-1,3,4-thiadiazol-2-yl)sulfanyl]ethyl}-4-fluorobenzene-1-sulfonamide (E3) N-(2-chloroethyl)-4-fluorobenzene-1-sulfonamide (0.18 g, 0.75 mmol), 2-Amino-5-mercapto-1,3,4-thiadiazole (0.10 g, 0.75 mmol), potassium carbonate (0.31 g, 2.25 mmol) were dissolved in acetonitrile (2.0 mL) and stirred at 80° C. overnight. After that time reaction mixture was cooled to room temperature, filtered thru celite, evaporated and purified via column chromatography using MeOH in DCM 0-5% as aluent to give pure product (120 mg, 48%) LCMS-Method 2 (200 nm): RT=4.24 min, 99.71% purity, [M+H]=334.97, .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 7.92 (br s, 1H), 7.80-7.90 (m, 2H), 7.37-7.47 (m, 2H), 7.30 (br s. 2H), 3.07 (m, 4H).
(185) ##STR00176##
(186) 4-fluoro-N-{2-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]ethyl}benzene-1-sulfonamide (G2) N-(2-chloroethyl)-4-fluorobenzene-1-sulfonamide (0.21 g, 0.87 mmol), 3-mercapto-4-methyl-4H-1,2,4-triazole (0.10 g, 0.87 mmol), potassium carbonate (0.36 g, 2.61 mmol) were dissolved in acetonitrile (2.0 mL) and stirred at 80° C. overnight. After that time reaction mixture was cooled to room temperature, filtered thru celite, evaporated and purified via column chromatography using MeOH in DCM 0-5% as eluent to give pure product (200 mg, 73%) LCMS-Method 2 (200 nm): RT=3.79 min, 97.39% purity, [M+H]=317.05, 1H NMR (300 MHz, DMSO-d6) δ 8.53 (s, 1H), 7.97 (s, 1H), 7.88-7.77 (m, 2H). 7.49-7.35 (m, 2H), 3.53 (s, 3H), 3.21-2.99 (m, 4H).
(187) Synthesis Method H
(188) ##STR00177##
(189) N-[5-(3-bromopropyl)-1,3,4-thiadiazol-2-yl]acetamide was synthesized according to the procedure described for E2.

(190) ##STR00178##
(191) N-[5-(3-{[(4-fluorophenyl)(methyl)oxo-λ.sup.6-sulfanylidene]amino}propyl)-1,3,4-thiadiazol-2-yl]acetamide. To the solution of (4-fluorophenyl)(imino)methyl-λ.sub.6-sulfanone (0.1 g, 0.58 mmol) in anhydrous DMSO (4 mL), under argon atmosphere, KOH (0.065 g, 1.15 mmol) was added. The suspension was stirred for 1.5 hours at ambient temperature. After that time solution of N-[5-(3-bromopropyl)-1,3,4-thiadiazol-2-yl]acetamide (0.229 g, 0.87 mmol) in anhydrous DMSO (4 mL) was slowly (1.5 hours) dropped. The reaction was quenched with water (5 mL) immediately after the dropping was completed. The water layer was extracted with DCM (10 mL) and after that extracted 5 times with mixture of chloroform/isopropyl alcohol 3:1 (5×20 mL). Combined organic layers were dried over sodium sulfate, filtered, evaporated to provide the pure product (0.06 g, 29%). UPLC (254 nm): RT=2.2 min, 61% purity, [M+H]=357.2
(192) ##STR00179##
(193) 5-(3-{[(4-fluorophenyl)(methyl)oxo-λ.sup.6-sulfanylidene]amino}propyl)-1,3,4-thiadiazol-2-amine (F2). N-[5-(3-{[(4-fluorophenyl)(methyl)oxo-λ.sup.6-sulfanylidene]amino}propyl)-1,3,4-thiadiazol-2-yl]acetamide (20 mg, 0.06 mmol) was dissolved in the solution of HCl (2 mL) and MeOH (2 mL). The reaction mixture was stirred for 3 hours at 80° C. After that time solution of sodium biscarbonate was added and the water layer was extracted with DCM (3×10 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated. Purification of crude product via P-TLC using 4% methanol in dichloromethane as an eluent gave desired product (5 mg, 9%). LCMS (245 nm): RT=5.91 min, 98.88% purity. [M+H]=315.17 .sup.1H NMR (300 MHz. CDCl.sub.3) δ 7.98-7.87 (m, 2H), 7.22-7.26 (m, 2H), 5.21 (s, 2H), 3.11 (s, 2H), 2.89-3.09 (m, 2H), 1.97-2.00 (m, 2H).
(194) Synthesis Method I
(195) ##STR00180##
(196) Methyl-4-(4-fluorobenzenesulfonamido)butanoate. To the solution of 3,4-dichlorobenzenosulfonyl chloride (633 mg, 3.25 mmol) in DCM (3.0 mL) trietylamine (1.3 mL, 9.76 mmol) and methyl-4-aminobutanoate hydrochloride (500 mg, 3.25 mmol) was added. The reaction mixture was stirred for 18 hours at ambient temperature. After that time 1M HCl (5 mL) was added and the water layer was extracted with DCM (3×5 mL). Combined organic layers were dried over sodium sulfate, filtered, evaporated to provide the product (0.605 g, 68%). UPLC (254 nm): RT=2.89 min, [M+H]=275.85.
(197) ##STR00181##
(198) 4-Fluoro-N-[3-(hydrazinecarbonyl)propyl]benzene-1-sulfonamide. To the solution of methyl-4-(4-fluorobenzenesulfonamido)butanoate (605 mg, 2.09 mmol) in EtOH (10 mL) 50% hydrazine in H.sub.2O (0.65 mL, 10.4 mmol) was added. Reaction mixture was stirred for 1 hour at 80° C. After that time the reaction mixture was cooled, water (20 mL) was added and water layer was extracted three times with EA (3×10 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated to provide the pure product (180 mg, 31%). UPLC (254 nm): RT=1.88 min, 65% purity, [M+H]=276.2.
(199) ##STR00182##
(200) N-(3-(N′-[(1-dimethylamino)methylidene]hydrazinecarbonyl)propyl)-4-fluorobenzene-1-sulfonamide. To the solution of 4-fluoro-N-[3-(hydrazinecarbonyl)propyl]benzene-1-sulfonamide (180 mg, 0.65 mmol) in MeOH (2 mL) N,N-dimethylformamide dimethylacetal (78 mg, 0.65 mmol) was added. Reaction mixture was stirred for 1 hour at 80° C. After that time solvent was evaporated to obtain desired product. (216 mg, 100%). UPLC (254 nm): RT=1.78 min. 60% purity, [M+H]=331.3.
(201) ##STR00183##
(202) 4-fluoro-N-[3-(4-methyl-4H-1,2,4-triazol-3-yl)propyl]benzene-1-sulfonamide (G1). MeNH.sub.2 2M in THF (32 mL, 3.3 mmol) was added to the solution of N-(3-{N′-[(1-dimethylamino)methylidene]hydrazinecarbonyl}propyl)-4-fluorobenzene-1-sulfonamide (216 mg,

0.63 mmol) in anhydrous THF (5.0 mL) under argon atmosphere. Reaction mixture was cooled to 0° C. and acetic acid (2 mL) was carefully added. Reaction mixture was stirred for 1 hour at 100° C. After that time reaction was cooled to room temperature and water (5 mL) was added and water layer was extracted three times with EA (3×20 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using 0-4% MeOH in DCM as eluent. Obtained 40 mg of product was re-purified via P-TLC using 4% MeOH in DCM as an eluent and then re-purified via preparative HPLC. Fraction containing the title compound in pure form was concentrated (3 mg, 2%). LCMS-Method 1 (200 nm): RT=6.17 min, 99.5% purity, [M+H]=299.2. .sup.1H NMR (300 MHz, CDCl.sub.3) δ 8.09 (s, 1H). 7.84-7.90 (m, 2H), 7.15-7.23 (m, 2H), 5.62 (t. J=5.6 Hz, 1H), 3.64 (s. 3H), 3.12 (q, J=3.1 Hz, 2H), 2.85 (t, J=6.6 Hz, 2H) 2.06-2.15 (m, 2H).

(203) Synthesis Method K

(204) ##STR00184##

(205) N-(2-chloroethyl)sulfamoyl chloride 2-chloroethylamine hydrochloride (0.50 g, 4.3 mmol), sulfuryl chloride (3.49 g, 2.10 mL. 25.8 mmol), were dissolved in acetonitrile (5.0 mL) Reaction was stirred at 80° C. overnight. The mixture was concentrated and used directly into next step. Title compound was obtained as yellow oil (0.5 g, 86% yield). .sup.1H NMR (300 MHz, d.sub.6-DMSO) δ 11.0 (bs, 1H), 3.83 (t, 2H), 3.36 (t, 2H)

(206) ##STR00185##

(207) (2-chloroethyl)[(3,4-dimethoxyphenyl)sulfamoyl]amine N-(2-chloroethyl)sulfamoyl chloride (0.14 g, 0.78 mmol) and 3,4-dimetoxyaniline (0.12 g, 0.78 mmol) were dissolved in DCM (1.2 mL) and pyridine (1.2 mL). Reaction was stirred at room temperature overnight. After that time reaction mixture was cooled to room temperature. The mixture was diluted with DCM (15.0 mL) and washed with 1M solution of hydrochloric acid (20 mL). Organic layer was dried over sodium sulfate, filtered and evaporated. Title compound was obtained as yellow oil (0.23 g. 100% yield). Compound was used in the next step without further purification. UPLC (280 nm): RT=3.14 min, 11% purity. [M+H]=294.95

(208) ##STR00186##

(209) [(3,4-dimethoxyphenyl)sulfamoyl]((2-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]ethyl))amine (G5) (2-chloroethyl)[(3,4-dimethoxyphenyl)sulfamoyl]amine (0.085 g, 0.74 mmol), 3-mercapto-4-methyl-4H-1,2,4-triazole (0.22 g, 0.74 mmol), potassium carbonate (0.31 g, 2.21 mmol) were dissolved in acetonitrile (1.7 mL) and stirred at 80° C. for 3 hours. After that time reaction mixture was cooled to room temperature, filtered thru celite, evaporated and purified via column chromatography using MeOH in DCM 0-5% as eluent to give pure product (8 mg, 3%) LCMS-Method 2 (200 nm): RT=3.08 min, 99.1% purity, [M+H]=374.03, 1H NMR (400 MHz, DMSO-d6) δ 7.57 (s, 1H), 6.96-6.75 (m, 2H), 6.72-6.63 (m, 1H), 3.71 (d, J=2.7 Hz, 6H), 3.51 (s, 3H), 3.23-3.08 (m, 4H).

(210) Synthesis Method L

(211) ##STR00187##

(212) [4-(4-fluorobenzenesulfonamido)phenyl]boronic acid 4-aminophenylboronic acid (1.5 g, 8.7 mmol), and 4-fluorophenylsulfonyl chloride (1.53 g, 7.9 mmol) were dissolved in pyridine (43 mL). The mixture was stirred at 5000 overnight, cooled to room temperature and solvent was removed in vacuo. Crude product was used in next step without any further purification (5.4 g, 200%). UPLC (254 nm): RT=2.88 min, 50% purity, [M-2H]=293.5.

(213) ##STR00188##

(214) [4-(3,4-dimethoxybenzenesulfonamdo)phenyl]boronic acid 4-aminophenylboronic acid (2.35 g, 11.6 mmol), and 3,4-dimethoxyphenylsulfonyl chloride (1.53 g, 7.9 mmol) were dissolved in pyridine (80 mL). The mixture was stirred at 50° C. overnight, cooled to room temperature and solvent was removed in vacuo. Crude product was used in next step without any further purification (8.1 g, 200%). UPLC (254 nm): RT=2.77 min, 50% purity, [M-2H]=335.6.

(215) ##STR00189##
(216) N-[4-(2-amino-1,3-thiazol-5-yl)phenyl]-4-fluorobenzene-1-sulfonamide (11). Solution of [4-(4-fluorobenzenesulfonamido)phenyl]boronic acid (2.75 g, 9.2 mmol), 2-amino-5-bromo-thiazole hydrobromide (2.00 g, 7.7 mmol) and potassium carbonate (3.21 g, 23.1 mmol) in 1,4-dioxane (40.0 mL) and water (4.0 mL) was degassed with argon flow over 20 min and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.84 g, 1.2 mmol) was added as one portion. Reaction mixture was stirred overnight at 130° C. After this time reaction was filtered thru celite, which was washed with DCM, water (40 mL) was added, layers were separated and water layer was extracted three with DCM (3×25 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using Methanol in DCM (0-3%) as eluent, and fraction containing product was additional re-purified via preparative HPLC method to give the pure product as red solid (48 mg, 2%). LCMS-Method 1 (254 nm): RT=6.73 min, 99.6% purity, [M+H]=349.7. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 10.36 (s, 1H), 7.84-7.76 (m, 2H), 7.45-7.36 (m, 2H), 7.28 (dd, J=6.6, 2.0 Hz, 3H), 7.14-6.97 (m, 4H).
(217) ##STR00190##
(218) N-[4-(2-amino-1,3-thiazol-5-yl)phenyl]-3,4-dimethoxybenzene-1-sulfonamide (12). Solution [4-(3,4-dimethoxybenzenesulfonamido)phenyl]boronic acid (1.64 g, 5.5 mmol), 2-amino-5-bromo-thiazole hydrobromide (1.20 g, 4.6 mmol) and potassium carbonate (3.21 g, 23.1 mmol) in 1,4-dioxane (40.0 mL) and water (4.0 mL) was degassed with argon flow over 20 min and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.51 g, 0.7 mmol) was added as one portion. Reaction mixture was stirred overnight at 130° C. After this time reaction was filtered thru celite, which was washed with DCM, water (40 mL) was added, layers were separated and water layer was extracted three with DCM (3×25 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using Methanol in DCM (0-3%) as eluent, and fraction containing product was additional re-purified via preparative HPLC method to give the pure product as orange solid (45 mg, 3%). LCMS-Method 2 (200 nm): RT=2.99 min, 99.9% purity, [M+H]=392.0. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.16 (s, 1H), 7.34-7.22 (m, 5H), 7.13-6.95 (m, 5H), 3.79 (s, 3H), 3.76 (s, 3H).
(219) Synthesis Method M
(220) ##STR00191##
(221) 2-bromo-4′-fluoro-1,1′-biphenyl Solution of 1,2-dibromobenzene (8.26 g, 35.0 mmol), 4-flurophenylboronic acid (2.5 g, 17.9 mmol) and sodium carbonate (3.79 g, 35.0 mmol) in ethanol (35.0 mL), toluene (35.0 mL) and water (35.0 mL) was degassed with argon flow over 20 min and tetrakis (triphenylphosphine) palladium (0) (1.00 g, 0.9 mmol) was added as one portion. Reaction mixture was stirred overnight at 100° C. After this time reaction was filtered thru celite, layers were separated and water layer was extracted twice with ethyl acetate (2×15 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using hexanes as eluent to give the title product (5.50 g, 122%). UPLC (254 nm): RT=4.33 min, 91% purity, [M+H]=not observed.
(222) ##STR00192##
(223) 1-{4′-fluoro-[1,1′-biphenyl]-2-yl} piperidine-4-carbonitrile Solution of 2-bromo-4′-fluoro-1,1′-biphenyl (0.3 g, 1.2 mmol), piperidine-4-carbonitrile (0.2 g, 1.8 mmol), XantPhos (0.14 g, 0.24 mmol) and cesium carbonate (0.78 g, 2.4 mmol) in anhydrous 1,4-dioxane (3.0 mL), was degassed with argon flow over 20 min and tris (dibenzylideneacetone) dipalladium (0) (0.11 g, 0.12 mmol) was added as one portion. Reaction mixture was stirred overnight at 100° C. After this time reaction was filtered thru celite, washed with ethyl acetate and evaporated. Crude product was purified via column chromatography using ethyl acetate in hexanes (0-4%) as eluent to give the title product (0.18 g, 54%). UPLC (254 nm): RT=4.25 min, 90% purity, [M+H]=281.4.

(224) ##STR00193##
(225) 5-(1-{4′-fluoro-[1,1′-biphenyl]-2-yl}piperidin-4-yl)-1,3,4-thiadiazol-2-amine (L2) Solution of 1-{4′-fluoro-[1,1′-biphenyl]-2-yl}piperidine-4-carbonitrile (0.18 g, 0.7 mmol) and thiosemicarbazide (0.09 g, 1.05 mmol) trifluoroacetic acid (1.5 mL) was stirred at 65° C. over 2 hours. After this time reaction was cooled to room temperature diluted with saturated sodium bicarbonate solution (15 mL) and extracted with DCM (3×15 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was triturated with ethyl acetate (1 mL) filtered off and dried under vacuum to give pure product (100 mg, 45%) LCMS (LCMS method: LCMS-002-20-80-95-12-05-25 (Gemini-BCM)-UV, 200 nm): RT=4.97 min, 96.7% purity, [M+H]=355.2. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 7.70-7.58 (m, 2H), 7.38-7.17 (m, 4H), 7.16-6.89 (m, 4H), 3.05 (d, J=11.8 Hz, 2H), 2.87 (ddd, J=11.5, 7.6, 3.9 Hz, 1H), 2.62 (t, J=11.3 Hz, 2H), 1.86 (d, J=12.7 Hz, 2H), 1.54 (qd, J=12.0, 3.8 Hz, 2H).
(226) Synthesis Method N
(227) ##STR00194##
(228) tert-Butyl-4-(2-amino-1,3-thiazol-5-yl)piperidine-1-carboxylate was synthesized in two steps according to the literature (overall yield: 60%).
(229) ##STR00195##
(230) tert-Butyl-4-(2-acetamido-1,3-thiazol-5-yl)piperidine-1-carboxylate. To the solution of tert-butyl-4-(2-amino-1,3-thiazol-5-yl)piperidine-1-carboxylate (3.75 g, 13.23 mmol) in anhydrous DCM (35 mL), under argon atmosphere, trietylamine (3.69 mL, 26.4 mmol) and acetylchloride (1.00 mL, 14.6 mmol) were added. Reaction mixture was stirred for 48 hours at ambient temperature. After that time water was added (50 mL) and the water layer was extracted five times with DCM (5×80 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated to provide the pure product (4.175 g, 97%). UPLC (254 nm): RT=4.27 min. [M+H]=326.25.
(231) ##STR00196##
(232) N-[5-(piperidin-4-yl)-1,3-thiazol-2-yl]acetamide. To the solution of tert-butyl 4-(2-acetamido-1,3-thiazol-5-yl)piperdino-1-carboxylate (4.175 g, 12.83 mmol) in THF (90.0 mL), 4M HCl in dioxane (10 mL) was added. Reaction mixture was stirred for 18 hours. After that time reaction mixture was filtered, the precipitation was washed with EA (2×40 mL) and dried under reduced pressure to give pure product (2.752 g, 82%). UPLC (254 nm): RT=2.1 min, [M+H]=226.25.
(233) ##STR00197##
(234) N-{5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3-thiazol-2-yl}acetamide. To a solution of 3,4-dichlorobenzenosulfonyl chloride (182 mg, 0.94 mmol) in the mixture of solvents DCM (3.0 mL) and pyridine (3.0 mL) N-[5-(piperidin-4-yl)-1,3-thiazol-2-yl]acetamide (211 mg, 0.94 mmol) was added. The reaction mixture was stirred for 48 hours at ambient temperature. After that time solvents were evaporated and crude was taken to the next step.
(235) ##STR00198##
(236) 5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3-thiazol-2-amine (M1). N-{5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3-thiazol-2-yl}acetamide (300 mg, 0.78 mmol) was dissolved in the solution of HCl (12 mL) and MeOH (12 mL). The reaction mixture was stirred for 18 hours at 80° C. After that time solution of saturated sodium biscarbonate was added and the water layer was extracted with DCM (3×10 mL). Combined organic layers were dried over sodium sulfate, filtered, evaporated and purified via column chromatography using 0-10% MeOH in DCM as eluent. Fractions containing the title compound were combined and concentrated. Product was re-purified via P-TLC using 4% MeOH in DCM as an eluent (16 mg, 6%). LCMS-Method 1 (220 nm): RT=6.37 min, 95.99% purity, [M+H]=342.07. .sup.1H NMR (300 MHz, CD.sub.3OD) δ 7.85-7.90 (m, 2H), 7.35-7.41 (m, 2H), 6.7 (s, 1H), 3.82 (d, J=12.0 Hz, 2H), 2.61-2.73 (m, 1H), 2.40-2.49 (m, 2H), 1.98-2.04 (m, 2H), 1.60-1.75 (m, 2H).

(237) ##STR00199##
(238) 1-(4-fluorobenzenesulfonyl)piperidine-4-carbonitrile. To a solution of piperidine-4-carbonitrile (500 mg, 4.54 mmol) in the mixture of solvents DCM (5.0 mL) and pyridine 4-fluorobenzenesulfonyl chloride (880 mg, 4.54 mmol) was added. The reaction mixture was stirred for 16 hours at ambient temperature. Reaction mixture was diluted with 1M HCl (50 ml) and DCM (50 ml) and layers were separated. Organic layer was washed twice with 1M HCl (2×50 ml) and concentrated to give desired product as beige solid. .sup.1H NMR (400 MHz, Chloroform-d) δ 7.98-7.66 (m, 2H), 7.36-7.12 (m, 2H), 3.29-3.06 (m, 4H), 2.91-2.71 (m, 1H), 2.17-1.89 (m, 4H).
(239) ##STR00200##
(240) 5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3,4-thiadiazol-2-amine (M2). 1-(4-fluorobenzenesulfonyl)piperidine-4-carbonitrile (500 mg, 1.86 mmol) and thisemicarbazide (190 mg, 2.05 mmol) were dissolved in TFA (4.0 mL) and the reaction mixture was stirred for 2 hours at 60° C. After that time solvent was concentrated and residue was suspended in DCM:MeOH (4.0 ml, 95:5; vol:vol) solution and precipitate was filtered to afford desired compound as white solid (610 mg, 96.0%). LCMS-Method 2 (method: LCMS Method 2 (Gemini BCM)-UV, 200 nm): RT=4.29 min, 97.59% purity, [M+H]=343.13. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.20-7.71 (m, 2H), 7.51 (t, J=8.8 Hz, 2H), 3.66 (dt, J=12.2, 3.7 Hz, 2H), 2.95 (ddd, J=11.3, 7.5, 3.8 Hz, 1H), 2.43 (dd. J=11.8, 2.6 Hz, 2H), 2.10-1.91 (m, 2H), 1.76-1.43 (m, 2H).
(241) Synthesis Method O
(242) ##STR00201##
(243) tert-butyl 4-(N′-[(1E)-(dimethylamino)methylidene]hydrazinecarbonyl)piperidine-1-carboxylate. To the solution tert-butyl 4-(hydrazinecarbonyl)piperdino-1-carboxylate (500 mg, 2.05 mmol) in DMF (5 mL) N,N-dimethylforamide dimethylacetal (245 mg, 2.05 mmol) was added. Reaction mixture was stirred for 18 hour at 100° C. After that time solvent was evaporated to obtain desired product (601 mg, 98%).
(244) ##STR00202##
(245) tert-butyl 4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate. MeNH.sub.2 2M in THF (15 mL, 40.2 mmol) was added to the solution of tert-butyl 4-{N′-[(1E)-(dimethylamino)methylidene]hydrazinecarbonyl}piperidine-1-carboxylate (600 mg, 2.01 mmol) in anhydrous THF (6.0 mL) under argon atmosphere. Reaction mixture was cooled to 0° C. and acetic acid (2 mL) was carefully added. Reaction mixture was stirred for 18 hour at 100° C. After that time reaction was cooled to room temperature and water (20 mL) was added and water layer was extracted three times with EA (3×50 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated to give crude compound (511 mg, 95%).
(246) ##STR00203##
(247) 4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine. To the solution of tert-butyl 4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (511 mg, 1.71 mmol) in THF (5.0 mL), 4M HCl in dioxane (6.0 mL) was added. Reaction mixture was stirred for 18 hours. After that time reaction mixture was filtered, the precipitate was washed with EA (2×40 mL) and dried under reduced pressure to give product (347 mg, 100%).
(248) ##STR00204##
(249) 1-(4-fluorobenzenesulfonyl)-4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine (N1). To a solution of 4-fluorobenzenosulfonyl chloride (117 mg, 0.60 mmol) in pyridine (1.0 mL) 4-(4-methyl-4H-1,2,4-triazol-3-yl)piperadine (100 mg, 0.60 mmol) was added. The reaction mixture was stirred for 18 hours at ambient temperature. After that time solvent was evaporated and 1 M HCl (5 mL) was added and the water layer was extracted with DCM (3×10 mL). Combined organic layers were dried over sodium sulfate, filtered and evaporated. Product was purified via P-TLC using 5% MeOH in DCM as an eluent (6 mg, 3%). LCMS-Method 2 (220 nm): RT=3.63 min, 96.34% purity, [M+H]=325.11 .sup.1H NMR (300 MHz, CDCl.sub.3) δ 8.05 (s, 1H), 7.77-7.90 (m, 2H), 7.20-7.28 (m, 2H), 7.78-7.83 (m, 1H), 3.62 (s, 3H), 2.60-2.86 (m, 4H), 2.02-2.15 (m, 4H).

(250) Synthesis Method P
(251) ##STR00205##
(252) tert-butyl 5-methyl-1H-1,3-benzodiazole-1-carboxylate 5-methyl-1H-1,3-benzodiazole (0.5 g, 7.6 mmol), Boc anhydride (2.44 g, 11.4 mmol), DMAP (92 mg, 0.76 mmol) and triethylamine (2.11 mL, 15 mmol) were dissolved in acetonitrile (10 mL). The mixture was stirred at 80° C. overnight, cooled and solvent was removed in vacuo. Crude product was purified via column chromatography using DCM as eluent. Fractions containing the title compound were combined and concentrated (0.80 g, 46%). UPLC (254 nm): RT=3.75 min, 93.2% purity, [M+H]=233.2.
(253) ##STR00206##
(254) tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate, tert-butyl 5-methyl-1H-1,3-benzodiazole-1-carboxylate (0.8 g, 3.44 mmol), N-bromosuccimide (0.64 g, 3.62 mmol), dibenzoyl peroxide (22 mg, 0.1 mmol) were suspended in tetrachloromethane (16 ml), Reaction mixture was stirred overnight at 90° C. After that time reaction mixture was cooled to 0° C., precipitate was filtered off and filtrate was concentrated in vacuo to give desired product as pale yellow oil. (0.95 g, 89%). UPLC (254 nm): RT=3.75 min, 80% purity, [M+H]=312.75.
(255) ##STR00207##
(256) 4′-fluoro-[1,1′-biphenyl]-2-amine. Solution of 2-bromoaniline (1.5 g, 8.7 mmol), 4-flurophenylboronic acid (1.46 g, 10.5 mmol) and potassium carbonate (4.16 g, 30.1 mmol) in 1,4-dioxane (15.0 mL) and water (15.0 mL) was degassed with argon flow over 20 min and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.43 g, 0.5 mmol) was added as one portion. Reaction mixture was stirred overnight at 100° C. After this time reaction was filtered thru celite, layers were separated and water layer was extracted twice with ethyl acetate (2×15 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using 10% ethyl acetate in hexanes as eluent to give the pure product (1.65 g, 100%). UPLC (254 nm): RT=3.31 min, 99% purity, [M+H]=187.9.
(257) ##STR00208##
(258) N-[(1H-1,3-benzodiazol-5-yl)methyl]-4′-fluoro-[1,1′-biphenyl]-2-amine (01). To the solution of 4′-fluoro-[1,1′-biphenyl]-2-amine (100 mg, 0.53 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (244 mg, 0.59 mmol) in DMF (1.0 mL) sodium carbonate (170 mg, 1.6 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was diluted with ethyl acetate (15.0 mL) and washed with semi-saturated brine (3×20 mL). Organic layer were dried over sodium sulfate, filtered, evaporated to provide the crude product, which was purified via column chromatography using MeOH in DCM 0-2% as an eluent to give desired product as off white solid (48 mg, 22%) LCMS-Method 2 (200 nm): RT=4.13 min, 97.2% purity. [M+H]=318.25. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.15 (s, 1H), 7.62-7.43 (m, 3H), 7.32 (t, J=8.9 Hz, 2H), 7.18 (d, J=8.2 Hz, 1H), 7.05 (ddd, J=8.5, 7.4, 1.6 Hz, 1H), 6.97 (dd, J=7.5, 1.6 Hz, 1H), 6.70-6.44 (m, 2H), 5.32 (s, 1H), 4.40 (d, J=5.9 Hz, 2H).
(259) ##STR00209##
(260) 3′,4′-dimethoxy-[1,1′-biphenyl]-2-amine. Solution of 2-bromoaniline (3.0 g, 17.4 mmol), 3,4-dimethoxyphenylboronic acid (3.81 g, 20.9 mmol) and potassium carbonate (8.32 g, 30.1 mmol) in 1,4-dioxane (30.0 mL) and water (30.0 mL) was degassed with argon flow over 20 min and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.85 g, 1.1 mmol) was added as one portion. Reaction mixture was stirred overnight at 100° C. After this time reaction was filtered thru celite, layers were separated and water layer was extracted twice with ethyl acetate (2×15 mL), organic layers were combined, dried over sodium sulfate, filtered and evaporated. Crude product was purified via column chromatography using ethyl acetate in hexanes 2-10% as eluent to give the pure product (3.2 g, 80%). UPLC (254 nm): RT=3.25 min, 90% purity, [M+H]=229.9.
(261) ##STR00210##

(262) N-[(1H-1,3-benzodiazol-5-yl)methyl]-3′,4′-dimethoxy-[1,1′-biphenyl]-2-amine(O2). To the solution of 3′,4′-dimethoxy-[1,1′-biphenyl]-2-amine (200 mg, 0.87 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (0.398 g, 0.96 mmol) in DMF (1.0 mL) sodium carbonate (277 mg, 2.62 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was diluted with ethyl acetate (15.0 mL) and washed with semi-saturated brine (3×20 mL). Organic layer were dried over sodium sulfate, filtered, evaporated to provide the crude product, which was purified via column chromatography using MeOH in DCM 0-2% as an eluent to give desired product as off white solid (70 mg, 17%) LCMS-Method 2 (205 nm): RT=3.66 min. 96.5% purity, [M+H]=360.1. .sup.1H NMR (300 MHz. DMSO-d.sub.6) δ 8.16 (s, 1H), 7.52 (d, J=8.3 Hz, 2H), 7.20 (dd, J=8.3, 1.6 Hz, 1H), 7.12-6.87 (m, 5H), 6.61 (ddd, J=8.3, 5.9, 1.2 Hz, 2H), 5.26 (t, J=5.9 Hz, 1H), 4.40 (d, J=5.9 Hz, 2H).
(263) ##STR00211##
(264) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)aniline (03). To the solution of 2-(4-methoxyphenyl)aniline (90 mg, 0.45 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (156 mg, 0.50 mmol) in DMF (1.0 mL) sodium carbonate (144 mg, 1.36 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 100:0.fwdarw.98:2. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as off white solid (35 mg, 23%). LCMS-Method 2 (230 nm): RT=3.90 min, 96.6% purity, [M+H]=330.24. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.13 (s, 1H), 7.56 (d, J=5.5 Hz, 2H), 7.36 (d, J=8.8 Hz, 2H), 7.25 (dd, J=8.4, 1.2 Hz, 1H), 7.15-6.93 (m, 4H), 6.75-6.63 (m, 2H), 4.45 (s, 2H), 3.84 (s, 3H).
(265) ##STR00212##
(266) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)pyridin-3-amine (04). To the solution of 2-(4-methoxyphenyl)pyridin-3-amine (90 mg, 0.45 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (155 mg, 0.50 mmol) in DMF (1.0 mL) sodium carbonate (143 mg, 1.36 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 100:0:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.1 to give desired product as off white solid (10 mg, 7%). LCMS-Method 1 (205 nm): RT=4.66 min, 97.8% purity, [M+H]=331.27. .sup.1H NMR (300 MHz. Methanol-d.sub.4) δ 8.14 (s, 1H), 7.81 (d, J=5.7 Hz, 1H), 7.58 (t, J=3.9 Hz, 4H), 7.27 (d, J=9.6 Hz, 1H), 7.20-6.97 (m, 4H), 4.49 (s, 2H), 3.86 (s, 3H).
(267) ##STR00213##
(268) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyridin-2-amine (05). To the solution of 3-(4-methoxyphenyl)pyridin-2-amine (100 mg, 0.50 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (202 mg, 0.65 mmol) in DMF (1.0 mL) sodium carbonate (159 mg, 1.50 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1 to give desired product as white solid (4 mg, 2.5%). LCMS-Method 3 (200 nm): RT=2.66 min, 96.3% purity, [M+H]=331.11. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.12 (s, 1H), 7.97 (dd, J=5.2, 1.8 Hz, 1H). 7.62-7.51 (m, 2H). 7.35 (t, J=8.7 Hz, 3H), 7.25 (d, J=9.7 Hz, 1H). 7.03 (d, J=8.8 Hz, 2H), 6.69 (dd, J=7.2, 5.2 Hz, 1H), 4.69 (s, 2H), 3.83 (s, 3H).
(269) ##STR00214##
(270) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyridin-4-amine (06). To the

solution of 3-(4-methoxyphenyl)pyridin-4-amine (100 mg, 0.50 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (172 mg, 0.55 mmol) in DMF (1.0 mL) sodium carbonate (159 mg, 1.50 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1 to give desired product as white solid (12 mg, 7%). LCMS-Method 3 (245 nm): RT=2.36 min, 97.4% purity, [M+H]=331.25. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.28 (s, 1H), 8.26-8.18 (m, 2H), 7.77-7.67 (m, 2H), 7.42-7.32 (m, 3H), 7.11 (d, J=6.7 Hz, 2H), 6.98 (d, J=7.1 Hz, 1H), 5.52 (s, 2H), 3.87 (s, 3H).

(271) ##STR00215##

(272) N-(1H-1,3-benzodiazol-5-ylmethyl)-4-(4-methoxyphenyl)pyridin-3-amine 07. To the solution of 4-(4-methoxyphenyl)pyridin-3-amine (100 mg, 0.50 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (172 mg, 0.55 mmol) in DMF (1.0 mL) sodium carbonate (159 mg, 1.50 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative HPLC to give desired product as white solid (5 mg, 4%). LCMS (LCMS-Method 3, 245 nm): RT=2.43 min, 73.7% purity, [M+H]=331.25. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.36 (s, 1H), 8.30 (s, 1H), 8.23 (d, J=6.0 Hz, 1H), 7.91 (s, 1H), 7.73 (d, J=8.3 Hz, 1H), 7.67-7.51 (m, 4H), 7.44 (d, J=8.3 Hz, 1H), 7.12 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.4 Hz, 1H), 5.77 (s, 2H), 3.88 (s, 3H).

(273) ##STR00216##

(274) N-(1H-1,3-benzodiazol-5-ylmethyl)-5-(4-methoxyphenyl)pyrimidin-4-amine (08). To the solution of 5-(4-methoxyphenyl)pyrimidin-4-amine (50 mg, 0.25 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (86 mg, 0.28 mmol) in DMF (0.5 mL) sodium carbonate (79 mg, 0.75 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via preparative HPLC to give desired product as yellowish solid (1.96 mg, 1.8%). LCMS-Method 12 (200 nm): RT=4.5 min, 100.0% purity, [M+H]=332.20. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.86 (d, J=1.9 Hz, 1H), 8.30 (s, 1H), 8.22 (d, J=1.9 Hz, 1H), 7.80 (s. 1H), 7.72 (d, J=8.3 Hz, 1H), 7.44-7.35 (m, 3H), 7.14-7.06 (m, 2H), 5.51 (s, 2H), 3.87 (s, 3H).

(275) ##STR00217##

(276) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-methoxyphenyl)pyrazin-2-amine (09). To the solution of 3-(4-methoxyphenyl)pyrazin-2-amine (140 mg, 0.70 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (240 mg, 0.77 mmol) in DMF (1.0 mL) sodium carbonate (221 mg, 2.09 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1 to give desired product as off white solid (5 mg, 2%). LCMS-Method 3 (270 nm): RT=3.04 min, 87.4% purity, [M+H]=332.24. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.13 (s, 1H), 7.96 (d, J=2.9 Hz, 1H), 7.76 (d, J=2.9 Hz, 1H), 7.58 (dd, J=12.8, 8.6 Hz, 4H), 7.29 (dd, J=8.3, 1.4 Hz, 1H), 7.09 (d, J=8.8 Hz, 2H), 4.73 (s, 2H), 3.86 (s, 3H).

(277) ##STR00218##

(278) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-4-amine (010). To the

solution of 3-(3,4-dimethoxyphenyl)pyridin-4-amine (100 mg, 0.43 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (214 mg, 0.69 mmol) in DMF (1.0 mL) sodium carbonate (137 mg, 1.30 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 95:5.fwdarw.9:1. Fractions containing product were collected and evaporated. Residue was suspended in MeOH and filtered to give desired product as white solid (11 mg, 7%). LCMS-Method 9 (200 nm): RT=2.8 min, 95.2% purity, [M+H]=361.16. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.28 (d, J=2.2 Hz, 2H), 8.21 (dd, J=7.2, 1.9 Hz, 1H), 7.75 (s, 2H), 7.37 (dd, J=8.4, 1.5 Hz, 1H), 7.13 (d, J=8.2 Hz, 1H), 7.07-6.94 (m, 3H), 5.52 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H).

(279) ##STR00219##

(280) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyridin-2-amine (011). To the solution of 3-(3,4-dimethoxyphenyl)pyridin-2-amine (100 mg, 0.43 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (150 mg, 0.48 mmol) in DMF (1.0 mL) sodium carbonate (138 mg, 1.30 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1 to give desired product as off white solid (11 mg, 7%). LCMS-Method 1 (200 nm): RT=4.98 min, 93.2% purity, [M+H]=361.25. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.13 (s, 1H), 7.98 (dd, J=5.2, 1.8 Hz, 1H), 7.55 (d, J=8.7 Hz, 2H), 7.37 (dd, J=7.2, 1.8 Hz, 1H), 7.27 (dd, J=8.3, 1.4 Hz, 1H), 7.09-6.91 (m, 3H), 6.69 (dd, J=7.2, 5.2 Hz, 1H), 4.70 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H).

(281) ##STR00220##

(282) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(3,4-dimethoxyphenyl)pyrazin-2-amine (012). To the solution of 3-(3,4-dimethoxyphenyl)pyrazin-2-amine (100 mg, 0.43 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (175 mg, 0.56 mmol) in DMF (1.0 mL) sodium carbonate (137 mg, 1.30 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1 to give desired product as off white solid (8 mg, 5%). LCMS-Method 3 (200 nm): RT=2.97 min, 87.7% purity, [M+H]=362.21. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.14 (s, 1H), 7.98 (d, J=2.8 Hz, 1H), 7.77 (d, J=2.8 Hz, 1H), 7.65-7.44 (m, 2H), 7.37-7.20 (m, 3H), 7.09 (d, J=8.2 Hz, 1H), 4.73 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H).

(283) ##STR00221##

(284) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-fluorophenyl)pyridin-3-amine (013). To the solution of 2-(4-fluorophenyl)pyridin-3-amine (110 mg, 0.58 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (202 mg, 0.65 mmol) in DMF (1.0 mL) sodium carbonate (186 mg, 1.75 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1 to give desired product as off white solid (8 mg, 4%). LCMS-Method 1 (200 nm): RT=3.04 min, 96.1% purity, [M+H]=319.23. .sup.1H NMR (300 MHz, .sup.1H NMR (300 MHz,) δ 8.20 (s, 1H), 7.84 (d, J=4.5 Hz, 1H), 7.77-7.51 (m, 4H), 7.30 (t, J=8.6 Hz, 3H), 7.23-7.01 (m, 2H), 4.53 (s, 2H).

(285) ##STR00222##

(286) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-fluorophenyl)pyridin-2-amine (014). To the solution of 3-(4-fluorophenyl)pyridin-2-amine (70 mg, 0.37 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (128 mg, 0.41 mmol) in DMF (0.7 mL) sodium carbonate (118 mg, 1.12 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via preparative HPLC. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.1 to give desired product as a white solid (7.7 mg, 4.95%). LCMS-Method 1 (200 nm): RT=5.04 min, 97.1% purity, [M+H]=319.23. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.09 (s, 1H), 8.00 (dd, J=5.2, 1.8 Hz, 1H), 7.58-7.41 (m, 4H), 7.34 (dd. J=7.2, 1.8 Hz, 1H), 7.25-7.14 (m, 3H), 6.70 (dd, J=7.2, 5.2 Hz, 1H), 4.69 (s, 2H).
(287) ##STR00223##
(288) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-(4-fluorophenyl)pyrazin-2-amine (015). To the solution of 3-(4-fluorophenyl)pyrazin-2-amine (100 mg, 0.53 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (214 mg, 0.69 mmol) in DMF (1.0 mL) sodium carbonate (137 mg, 1.30 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.fwdarw.9:1:0.1 to give desired product as off white solid (3 mg, 2%). LCMS-Method 1 (202 nm): RT=3.08 min, 95.4% purity, [M+H]=320.22. .sup.1H NMR (300 MHz. Methanol-d.sub.4) δ 8.13 (s, 1H). 8.00 (d, J=2.8 Hz, 1H), 7.79 (d, J=2.8 Hz, 1H), 7.70 (dd, J=8.8, 5.4 Hz, 2H), 7.62-7.51 (m, 2H), 7.33-7.23 (m, 3H). 4.73 (s, 2H).
(289) ##STR00224##
(290) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-phenoxyphenyl)aniline (016). To the solution of 2-(4-phenoxyphenyl)aniline (100 mg, 0.38 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (132 mg, 0.42 mmol) in DMF (1.0 mL) sodium carbonate (122 mg, 1.15 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.96:4. Re-purification was performed via preparative TLC eluted with DCM/MeOH/NH.sub.3 95:5:0.1 to give desired product as a white solid (25 mg, 16.7%). LCMS-Method 2 (205 nm): RT=4.99 min, 99.6% purity, [M+H]=392.26. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.13 (s, 1H), 7.57 (d, J=8.1 Hz, 2H), 7.47-7.33 (m, 4H), 7.27 (dd, J=8.5, 1.5 Hz, 1H), 7.17-7.02 (m, 7H), 6.71 (ddd, J=7.8, 6.2, 1.2 Hz, 2H), 4.48 (s, 2H).
(291) ##STR00225##
(292) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(cyclohexyloxy)phenyl]aniline (017). To the solution of 2-[4-(cyclohexyloxy)phenyl]aniline (100 mg, 0.37 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (129 mg, 0.42 mmol) in DMF (1.0 mL) sodium carbonate (119 mg, 1.12 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via preparative TLC eluted with DCM/MeOH 95:5. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as a white solid (4.9 mg, 3.3%). LCMS-Method 2 (200 nm): RT=5.17 min, 100% purity, [M+H]=398.26. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.12 (s, 1H), 7.55 (d, J=7.9 Hz, 2H), 7.37-7.21 (m, 3H), 7.11-6.96 (m, 4H), 6.68 (ddd, J=8.6, 5.5, 1.3 Hz, 2H), 4.44 (s, 2H), 4.34 (tt, J=8.4, 3.6 Hz, 1H), 2.06-1.75 (m, 4H), 1.66-1.28 (m, 6H).

(293) ##STR00226##
(294) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-propoxyphenyl)aniline (018). To the solution of 2-(4-propoxyphenyl)aniline (100 mg, 0.44 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (152 mg, 0.49 mmol) in DMF (1.0 mL) sodium carbonate (140 mg, 1.32 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.98:2. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as a white solid (34.4 mg, 21.9%). LCMS-Method 2 (200 nm): RT=4.58 min, 100% purity, [M+H]=358.25. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ 8.09 (s, 1H), 7.53 (d, J=7.8 Hz, 2H), 7.36-7.25 (m, 2H), 7.20 (dd, J=8.4, 1.5 Hz, 1H), 7.10-6.89 (m, 4H), 6.66 (t, J=7.3 Hz, 2H), 4.37 (s, 2H), 3.90 (t, J=6.5 Hz, 2H), 1.77 (dtd, J=13.8, 7.4, 6.4 Hz, 2H), 1.02 (t, J=7.4 Hz, 3H).
(295) ##STR00227##
(296) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-[4-(propan-2-yloxy)phenyl]aniline (019). To the solution of 2-[4-(propan-2-yloxy)phenyl]aniline (100 mg, 0.44 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (152 mg, 0.49 mmol) in DMF (1.0 mL) sodium carbonate (140 mg, 1.32 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.99:1. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as a white solid (24.3 mg, 15.5%). LCMS-Method 4 (200 nm): RT=2.42 min, 97.3% purity, [M+H]=358.26. .sup.1H NMR (300 MHz, Methanol-d.sub.4) δ8.10 (s, 1H), 7.54 (d, J=7.9 Hz, 2H), 7.37-7.26 (m, 2H), 7.21 (dd, J=8.4, 1.5 Hz, 1H), 7.10-6.91 (m, 4H), 6.66 (t, J=7.3 Hz, 2H), 4.57 (hept, J=12.0, 6.0 Hz, 1H), 4.39 (s, 2H), 1.31 (d, J=6.0 Hz, 6H).
(297) ##STR00228##
(298) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-methoxyphenyl)-3-methylaniline (020). To the solution of 2-(4-methoxyphenyl)-3-methylaniline (100 mg, 0.47 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (162 mg, 0.52 mmol) in DMF (1.0 mL) sodium carbonate (149 mg, 1.41 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3. Re-purification was performed via preparative TLC eluted with DCM/MeOH 9:1 to give desired product as a white solid (40.7 mg, 25.3%). LCMS (LCMS-Method 4, 205 nm): RT=2.14 min, 98.9% purity, [M+H]=344.27. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 12.33 (d, J=11.8 Hz, 1H), 8.14 (s, 1H), 7.57-7.36 (m, 2H), 7.18-7.05 (m, 5H), 6.93 (t, J=7.8 Hz, 1H), 6.54-6.38 (m, 2H), 4.44 (d, J=17.8 Hz, 1H), 4.34 (d, J=5.1 Hz, 2H), 3.81 (s, 3H), 1.88 (s, 3H).
(299) ##STR00229##
(300) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-methylaniline (021). To the solution of 2-(3,4-dimethoxyphenyl)-3-methylaniline (100 mg, 0.41 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (142 mg, 0.46 mmol) in DMF (1.0 mL) sodium carbonate (131 mg, 1.23 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as a white solid (47.5 mg, 31%). LCMS (LCMS-Method 4, 205 nm): RT=1.99 min, 97.3% purity, [M+H]=374.27. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 12.33 (s, 1H), 8.14 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 7.10 (t,

J=7.8 Hz, 2H), 6.93 (t, J=7.8 Hz, 1H), 6.79-6.71 (m, 2H), 6.47 (dd, J=15.8, 7.8 Hz, 2H), 4.55 (s, 1H), 4.34 (d, J=6.0 Hz, 2H), 3.79 (d, J=9.0 Hz, 6H), 1.92 (s, 3H).
(301) ##STR00230##
(302) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(4-chlorophenyl)-3-fluoroaniline(O22). To the solution of 2-(4-chlorophenyl)-3-fluoroaniline (100 mg, 0.45 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (156 mg, 0.50 mmol) in DMF (1.0 mL) sodium carbonate (143 mg, 1.35 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3. Re-purification was performed via preparative TLC eluted with DCM/MeOH 95:5 to give desired product as a white solid (40.6 mg, 25.6%). LCMS (LCMS-Method 4, 200 nm): RT=2.29 min, 94.2% purity, [M+H]=344.27. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 12.33 (d, J=17.3 Hz, 1H), 8.15 (d, J=4.1 Hz, 1H), 7.58 (dd, J=8.8, 7.0 Hz, 3H), 7.50-7.36 (m, 3H), 7.20-7.10 (m, 1H). 7.05 (td, J=8.3, 6.8 Hz, 1H), 6.46-6.34 (m, 2H), 5.48 (dt, J=16.2, 6.0 Hz, 1H), 4.38 (t, J=6.0 Hz, 2H).
(303) ##STR00231##
(304) N-(1H-1,3-benzodiazol-5-ylmethyl)-2-(3,4-dimethoxyphenyl)-3-fluoroaniline (023). To the solution of 2-(3,4-dimethoxyphenyl)-3-fluoroaniline (100 mg, 0.40 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (140 mg, 0.45 mmol) in DMF (1.0 mL) sodium carbonate (129 mg, 1.21 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3. Re-purification was performed via preparative TLC eluted with DCM/MeOH 9:1 to give desired product as a white solid (29.3 mg, 19.2%). LCMS (LCMS-Method 4, 200 nm): RT=1.92 min, 90.1% purity, [M+H]=378.23. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 12.38 (s, 1H), 8.16 (s, 1H), 7.50 (s, 2H), 7.21-6.98 (m, 3H), 6.93-6.85 (m, 2H), 6.45-6.37 (m, 2H), 5.27 (s, 1H), 4.39 (d, J=6.0 Hz, 2H), 3.80 (d, J=7.1 Hz, 6H).
(305) ##STR00232##
(306) N-(1H-1,3-benzodiazol-5-ylmethyl)-3-fluoro-2-(4-fluorophenyl)aniline (024). To the solution of 3-fluoro-2-(4-fluorophenyl)aniline (100 mg, 0.49 mmol) and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (168 mg, 0.54 mmol) in DMF (1.0 mL) sodium carbonate (155 mg, 1.46 mmol) was added. The reaction mixture was stirred overnight at 80° C. After that time reaction mixture was cooled down to RT and filtered through celite. Celite pad was washed with MeOH. Filtrate was evaporated to provide the crude product, which was purified via column chromatography using DCM/MeOH 1:0.fwdarw.97:3. Re-purification was performed via preparative TLC eluted with DCM/MeOH 9:1 to give desired product as a white solid (29.3 mg, 19.2%). LCMS (LCMS-Method 4, 205 nm): RT=2.12 min, 96.6% purity, [M+H]=336.23. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 12.32 (s, 1H), 8.15 (s, 1H), 7.55 (s, 1H), 7.45-7.32 (m, 5H), 7.15 (s, 1H), 7.10-6.99 (m, 1H), 6.46-6.36 (m, 2H), 5.37 (s, 1H), 4.39 (d, J=6.0 Hz, 2H).
(307) Synthesis Method Q
(308) ##STR00233##
(309) N-[(1H-1,3-benzodiazol-5-yl)methyl]-4-fluorobenzene-1-sulfonamide (P1) (1H-1,3-benzodiazol-5-yl)methanamine dihydrochloride (0.25 g, 1.15 mmol) was dissolved in pyridine (7 mL) and stirred at room temperature over 30 min. Then 4-fluorophenylsulfonyl chloride (0.21 g, 1.08 mmol), was added and reaction mixture was heated to 70° C. and stirred overnight. The mixture was quenched with 10 mL of 20% aqueous solution of sodium hydroxide and stirred at 70° C. for another night. Layers were separated and Pyridine was evaporated in vacuo. Crude product was purified via column chromatography using MeOH in DCM (0-3%) as eluent. Fractions containing the title compound were combined and concentrated (55 mg, 19%). LCMS-Method 1 (200 nm): RT=5.81 min, 93.2% purity, [M+ACN]=347.27. .sup.1H NMR (300 MHz, DMSO-

d.sub.6) δ 8.17 (s, 1H), 8.04-7.66 (m, 2H), 7.56-7.31 (m, 4H), 7.05 (d, J=8.4 Hz, 1H), 4.10 (s, 2H).
(310) Synthesis Method R
(311) ##STR00234##
(312) [(1H-1,3-benzodiazol-5-yl)methyl][(4-fluorophenyl)methyl)oxo-λ.sup.6-sulfanylidene]amine (Q1) (4-fluorophenyl)(imino)methyl-λ.sup.6-sulfanone (250 mg, 1.5 mmol) and potassium hydroxide (234 mg, 2.18 mmol) in DMSO (13.0 mL) were stirred at 50° C. over 1h. After this time reaction was cooled to room temperature and tert-butyl 5-(bromomethyl)-1H-1,3-benzodiazole-1-carboxylate (650 mg, 2.10 mmol) was added. Reaction was stirred overnight, and after this time water (50 mL) was added and extracted with DCM (5×30 mL). Combined organic layers were dried over sodium sulfate, filtered, evaporated to provide the solution of crude product in DMSO, which was purified preparative HPLC method to give title compound as colorless oil. (26 mg, 5%) LCMS-Method 1 (200 nm): RT=5.72 min, 96.3% purity, [M+H]=304.15. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.14 (s, 1H). 8.03-7.91 (m, 2H). 7.54 (s, 1H), 7.51-7.42 (m, 3H), 7.12 (dd, J=8.3, 1.6 Hz, 1H), 4.15 (d, J=14.4 Hz, 1H), 3.98 (d, J=14.5 Hz, 1H), 3.25 (s, 3H).
(313) Analytical Methods
(314) NMR
(315) The .sup.1H NMR-Spectra (300 MHz) were recorded at a BRUKER FOURIER 300. The solvent was DMSO-De, unless otherwise specified. Chemical shifts are expressed as parts per million (ppm) downfiled from tetramethylsilan. Splitting patterns have been designated as follows: s (singulet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet) and br (broad signal).
(316) HPLC-MS
(317) LCMS-Method 1
(318) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(319) Column: Gemini-NX 3μ C18 (4.6×50 mm), 110A, column no. OOB-4453-EO, internal column no. 002
(320) Reagents:—Formic acid ≥98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker μQ-water for LCMS
(321) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 0.5 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 μl Analysis time: 14 min Elution: gradient
(322) TABLE-US-00024 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 95 5 0.5 2.0 95 5 0.5 9.5 20 80 0.5 10.5 20 80 0.5 12.0 95 5 0.5 14.0 95 5 0.5 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH
(323) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec
LCMS-Method 2
(324) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(325) Column: Gemini-NX 3μ C18 (4.6×50 mm), 110A, column no. OOB-4453-EO, internal column no. 002
(326) Reagents:—Formic acid ≥98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker μQ-water for LCMS
(327) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 0.5 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 μl Analysis time: 12 min Elution: gradient
(328) TABLE-US-00025 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 80 20 0.5 6.7 20 80 0.5 7.5 20 80 0.5 7.8 5 95 0.5 9.5 5 95 0.5 10.0 80 20 0.5 12.0 80 20 0.5 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH
(329) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000

amu/sec
LCMS-Method 3
(330) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(331) Column: Kinetex® 2.6 µm XB-C18 (4.6×50 mm), 110A, column no. OOB-4496-EO, internal column no. 019
(332) Reagents:—Formic acid a 98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS
(333) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 1.0 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 7 min Elution: gradient
(334) TABLE-US-00026 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 95 5 1.0 1.0 95 5 1.0 4.75 20 80 1.0 5.25 20 80 1.0 6.0 95 5 1.0 7.0 95 5 1.0 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH
(335) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec
LCMS-Method 4
(336) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(337) Column: Kinetex® 2.6 µm XB-C18 (4.6×50 mm), 110A, column no. OOB-4496-EO, internal column no. 019
(338) Reagents:—Formic acid ≥98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS
(339) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 1.0 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 6 min Elution: gradient
(340) TABLE-US-00027 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 80 20 1.0 3.35 20 80 1.0 3.75 20 80 1.0 3.9 5 95 1.0 4.75 5 95 1.0 5.0 80 20 1.0 6.0 80 20 1.0 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH
(341) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec
LCMS-Method 5
(342) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(343) Column: Kinetex® 2.6 µm XB-C18 (4.6×50 mm), 110A, column no. OOB-4496-EO, internal column no. 019
(344) Reagents:—Formic acid ≥98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade. Baker µQ-water for LCMS
(345) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 1.0 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 7 min Elution: gradient
(346) TABLE-US-00028 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 80 20 1.0 2.0 20 80 1.0 2.35 20 80 1.0 2.45 5 95 1.0 4.25 5 95 1.0 5.0 80 20 1.0 7.0 80 20 1.0 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH
(347) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec
HPLC-Method 6
(348) Apparatus: HPLC—MERCK CHROMASTER with gradient pump and DAD detector
(349) Column: XBridge C18 3.5µ (4.6×150 mm), column no. 186003034, internal column no. 009
(350) Reagents:

(351) Methanol for HPLC Ultra Gradient HPLC Grade. Baker Boric acid ≥99.5%, Sigma-Aldrich Sodium hydroxide analytical grade, Eurochem BGD purified water for HPLC
HPLC Conditions: Wavelength: 210.0 nm±4.0 nm Flow: 0.5 mL/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 5 µL Analysis time: 30 min Elution: gradient
(352) TABLE-US-00029 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [mL/min] 0.0 50 50 0.5 22.0 5 95 0.5 25.0 5 95 0.5 27.0 50 50 0.5 30.0 50 50 0.5
Mobile phase A: Borate buffer c=5 mM, pH=9.6 Preparation: 0.618 g of boric acid placed in 2 L volumetric flask were dissolved in 1.5 L purified water. pH value was adjusted to 9.6 using 1M solution of NaOH (6 mL). Finally, solution was diluted to the mark using purified water.
Mobile phase B: 1 L MeOH with the analogous amount of 1M NaOH as in phase A (3 mL).
(353) Solution for syringe washing: acetonitrile
(354) LCMS-Method 7
(355) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(356) Column: Gemini-NX 3µ C18 (4.6×50 mm), 110A, column no. OOB-4453-EO, internal column no. 002
(357) Reagents:—Formic acid a 98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS
(358) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 0.5 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 12 min Elution: gradient
(359) TABLE-US-00030 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 60 40 0.5 6.7 20 80 0.5 7.5 20 80 0.5 7.8 5 95 0.5 9.5 5 95 0.5 10.0 60 40 0.5 12.0 60 40 0.5 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH
(360) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec
LCMS-Method 8
(361) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(362) Column: Gemini-NX 3µ C18 (4.6×50 mm), 110A, column no. OOB-4453-EO, internal column no. 002
(363) Reagents:—Formic acid ≥98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS
(364) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 0.5 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 28 min Elution: gradient
(365) TABLE-US-00031 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 95 5 0.5 4.0 95 5 0.5 19.0 20 80 0.5 21.0 20 80 0.5 24.0 95 5 0.5 28.0 95 5 0.5 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH
(366) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec
LCMS-Method 9
(367) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus
(368) Column: Kinetex XB-C18 2.6 µm (4.6×50 mm), 100A, column no. OOB-4496-EO, internal column no. 019
(369) Reagents:—Formic acid ≥98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS
(370) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 1.0 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 7 min Elution: gradient

(371) TABLE-US-00032 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 100 0 1.0 1.0 95 5 1.0 4.0 80 20 1.0 4.75 20 80 1.0 5.25 20 80 1.0 6.0 95 5 1.0 7.0 100 0 1.0 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH

(372) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec

LCMS-Method 10

(373) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus

(374) Column: Gemini-NX 3µ C18 (4.6×50 mm), 110A, column no. OOB-4453-EO, internal column no. 002

(375) Reagents:—Formic acid a 98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS

(376) HPLC conditions:—Wavelength range: (190-340) nm t 4 nm Flow: 0.5 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 12 min Elution: gradient

(377) TABLE-US-00033 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 70 30 0.5 6.7 20 80 0.5 7.5 20 80 0.5 7.8 5 95 0.5 9.5 5 95 0.5 10.0 70 30 0.5 12.0 70 30 0.5 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH

(378) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec

LCMS-Method 11

(379) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus

(380) Column: Kinetex® 2.6 µm XB-C18 (4.6×50 mm), 110A, column no. OOB-4496-EO, internal column no. 019

(381) Reagents:—Formic acid a 98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS

(382) HPLC conditions:—Wavelength range: (190-340) nm t 4 nm Flow: 1.0 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 6 min Elution: gradient

(383) TABLE-US-00034 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 30 70 1.0 3.35 20 80 1.0 3.75 20 80 1.0 3.9 5 95 1.0 4.75 5 95 1.0 5.0 30 70 1.0 6.0 30 70 1.0 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH

(384) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000 amu/sec

LCMS-Method 12

(385) Apparatus: Dionex UHPLC Ultimate 3000 with DAD detector/Thermo Scientific MSQ Plus

(386) Column: Gemini-NX 3µ C18 (4.6×50 mm), 110A, column no. OOB-4453-EO, internal column no. 002

(387) Reagents:—Formic acid ≥98%, Sigma-Aldrich Acetonitrile for HPLC UV/gradient grade, Baker µQ-water for LCMS

(388) HPLC conditions:—Wavelength range: (190-340) nm±4 nm Flow: 0.5 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 2.0 µl Analysis time: 14 min Elution: gradient

(389) TABLE-US-00035 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.0 100 0 0.5 2.0 95 5 0.5 8.0 80 20 0.5 9.5 20 80 0.5 10.5 20 80 0.5 12.0 95 5 0.5 14.0 100 0 0.5 Mobile phase A: 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 20% MeOH

(390) MS conditions:—Mass range: 100-1000 m/z Ionization: alternate Scan speed: 12 000

amu/sec
UPLC-MS
(391) Apparatus: Shimadzu LCMS-2020 Single Quadrupole Liquid Chromatograph Mass Spectrometer
(392) Column: Acquity UPLC 1.8 μm C18 (2.1×50 mm), 100 Å, column no. 186003532, internal column no. Pur CC—MS001
(393) Reagents:
(394) Formic acid≥98%, Sigma-Aldrich, Acetonitrile for HPLC UV/gradient grade, Baker, purified water for HPLC.
UPLC Conditions: Wavelength: 254 nm and 280 nm Flow: 0.5 ml/min Column temperature: 25° C. Autosampler temperature: 20° C. Injection volume: 3 μl Analysis time: 6.0 min Elution: gradient
(395) TABLE-US-00036 Time [min] Mobile phase A [%] Mobile phase B [%] Flow [ml/min] 0.01 95 5 0.5 4.00 5 95 0.5 5.00 5 95 0.5 5.20 95 5 0.5 6.00 95 5 0.5 Mobile phase A 0.1% v/v water solution of formic acid Mobile phase B: 0.1% v/v acetonitrile solution of formic acid Solution for syringe washing: 100% acetonitrile
MS Conditions: Mass range: 50-1000 m/z Ionization: alternate Scan speed: 7500 u/sec
Activity Screening
Glutaminyl Cyclase, Assay Determination of IC50 Values and Calculation of KI Values
(396) 10 mM compound stock solutions were prepared in DMSO. For IC50 determination compound stocks were serially diluted (1:3) in DMSO.
(397) All measurements were performed with an EnSpire Perkin Elmer multimode reader using glutaminyl-7-amino-4-methylcoumarin (H-Gin-AMC) as substrate and recombinant pyroglutamyl aminopeptidase (pGAP) as auxiliary enzyme. Reactions were carried out at ambient temperature in black 96-well half area microplates. Each sample consisted of 1 μl test compound solution or solvent (DMSO) and 49 μl QC appropriately diluted in assay buffer (50 mM Tris/HCl, pH 8.0 or 50 mM MES buffer, pH=6.0). After a 10 min preincubation at ambient temperature the enzyme reaction was started by adding 50 μl of Gln-AMC-substrate/pGAP mixture in assay buffer. Final substrate concentrations were 50 and 200 μM for measurement at pH 8.0 or 6.0, respectively. Release of flourogenic AMC were recorded at excitation/emission wavelengths of 380/460 nm. Initial velocity of the enzyme reaction was calculated by linear regression of the first 10 data points using the Enspire Manager software. Final evaluation and calculation of IC50s were performed using GraphPad Prism software. IC.sub.50 values were calculated from normalized data (QC activity without inhibitor=100%) by nonlinear regression according to a 4-parameter logistic equation.
(398) Ki-values were calculated according to the following formula: Ki=IC50/(1+[S]/Km), where:
(399) [S] reflects to the concentration of substrate in the assay (200 μM for pH 6.0, 50 μM for pH 8.0) and Km is the respective Michaelis-Menten constant (390 μM at pH 6.0, 62 μM at pH 8.0).
(400) MALDI-TOF Mass Spectrometry
(401) Matrix-assisted laser desorption/ionization mass spectrometry was carried out using the Hewlett-Packard G2025 LD-TOF System with a linear time of flight analyzer. The instrument was equipped with a 337 nm nitrogen laser, a potential acceleration source (5 kV) and a 1.0 m flight tube. Detector operation was in the positive-ion mode and signals are recorded and filtered using LeCroy 9350M digital storage oscilloscope linked to a personal computer. Samples (5 μl) were mixed with equal volumes of the matrix solution. For matrix solution DHAP/DAHC was used, prepared by solving 30 mg 2′,6′-dihydroxyacetophenone (Aldrich) and 44 mg diammonium hydrogen citrate (Fluka) in 1 ml acetonitrile/0.1% TFA in water (1/1, v/v). A small volume (≈1 μl) of the matrix-analyte-mixture was transferred to a probe tip and immediately evaporated in a vacuum chamber (Hewlett-Packard G2024A sample prep accessory) to ensure rapid and homogeneous sample crystallization.
(402) For long-term testing of Glu.sup.1-cyclization. Aβ-derived peptides were incubated in 100 μl

0.1 M sodium acetate buffer, pH 5.2 or 0.1 M Bis-Tris buffer, pH 6.5 at 30° C. Peptides were applied in 0.5 mM [Aβ(3-11)a] or 0.15 mM [Aβ(3-21)a] concentrations, and 0.2 U QC is added all 24 hours. In case of Aβ(3-21)a, the assays contained 1% DMSO. At different times, samples are removed from the assay tube, peptides extracted using ZipTips (Millipore) according to the manufacturer's recommendations, mixed with matrix solution (1:1 v/v) and subsequently the mass spectra recorded. Negative controls either contain no QC or heat deactivated enzyme. For the inhibitor studies the sample composition was the same as described above, with exception of the inhibitory compound added (5 mM or 2 mM of a test compound of the invention).
(403) Compounds and combinations of the invention may have the advantage that they are, for example, more potent, more selective, have fewer side-effects, have better formulation and stability properties, have better pharmacokinetic properties, be more bioavailable, be able to cross blood brain barrier and are more effective in the brain of mammals, are more compatible or effective in combination with other drugs or be more readily synthesized than other compounds of the prior art.
(404) Throughout the specification and the claims which follow, unless the context requires otherwise, the word ‘comprise’, and variations such as ‘comprises’ and ‘comprising’, will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.
(405) All patents and patent applications mentioned throughout the specification of the present invention are herein incorporated in their entirety by reference.
(406) The invention embraces all combinations of preferred and more preferred groups and embodiments of groups recited above.

Claims

1. A compound of formula (XIIa): ##STR00235## wherein Z is selected from CH and N; Y.sub.1 to Y.sub.4 and Y.sub.6, Y.sub.7 and Y.sub.10 are CH; Y.sub.5 is C; Y.sub.8 and Y.sub.9 are C; R.sub.5 is selected from halogen, alkyl and O-alkyl; R.sub.6 is selected from hydrogen, alkyl and O-alkyl.
2. A compound of formula (XIII): ##STR00236## wherein Z is selected from CH and N; R.sub.5 is selected from halogen, alkyl and O-alkyl; and R.sub.6 is selected from hydrogen, alkyl and O-alkyl.
3. The compound according to claim 2, which is a compound selected from: 5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3-thiazol-2-amine; 5-[1-(4-fluorobenzenesulfonyl)piperidin-4-yl]-1,3,4-thiadiazol-2-amine; or a pharmaceutically acceptable salt or solvate thereof, including all tautomers and stereoisomers.
4. A pharmaceutical composition comprising a compound according to claim 2 optionally in combination with one or more therapeutically acceptable diluents or carriers.
5. The pharmaceutical composition of claim 4, which comprises additionally at least one compound, selected from the group consisting of neuroprotectants, antiparkinsonian drugs, amyloid protein deposition inhibitors, beta amyloid synthesis inhibitors, antidepressants, anxiolytic drugs, antipsychotic drugs and anti-multiple sclerosis drugs.
6. The pharmaceutical composition of claim 4, which comprises additionally at least one compound, selected from the group consisting of PEP-inhibitors, LiCl, inhibitors of inhibitors of DP IV or DP IV-like enzymes, acetylcholinesterase (ACE) inhibitors, PIMT enhancers, inhibitors of beta secretases, inhibitors of gamma secretases, inhibitors of neutral endopeptidase, inhibitors of Phosphodiesterase-4 (PDE-4), TNFalpha inhibitors, muscarinic M1 receptor antagonists, NMDA receptor antagonists, sigma-1 receptor inhibitors, histamine H3 antagonists, immunomodulatory agents, immunosuppressive agents or an agent selected from the group consisting of antegren (natalizumab), Neurelan (fampridine-SR), campath (alemtuzumab), IR 208, NBI 5788/MSP 771 (tiplimotide), paclitaxel, Anergix.MS (AG 284), SH636, Differin (CD 271, adapalene), BAY 361677 (interleukin-4), matrix-metalloproteinase-inhibitors, interferon-tau (trophoblastin) and

SAIK-MS.
7. 5-{[2-({3′,4′-dimethoxy-[1,1′-bipheny]-2-yl}amino)ethyl]sulfanyl}-1,3,4-thiadiazol-2-amine.