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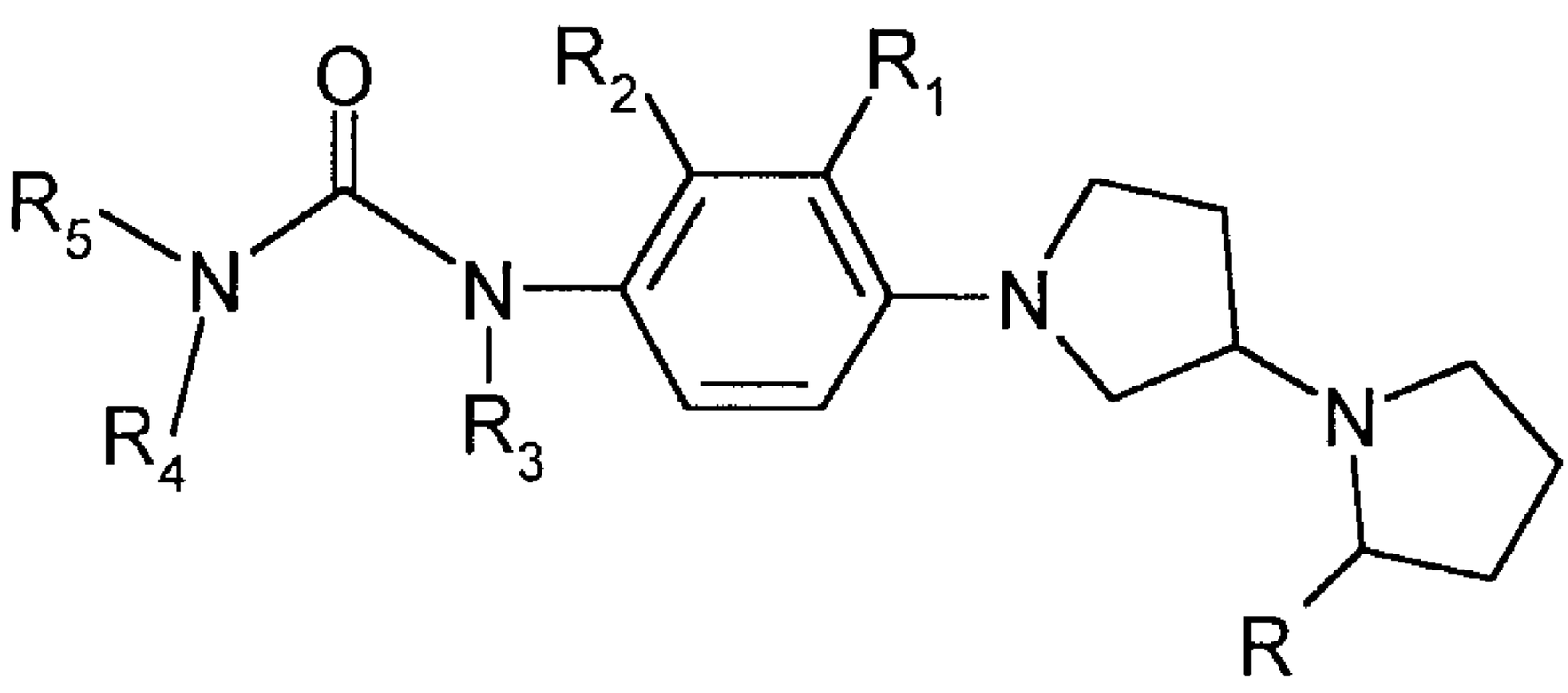
(54) Title: SUBSTITUTED N-PHENYL-BIPYRROLIDINE UREAS AND THERAPEUTIC USE THEREOF



(I)

(57) Abrégé/Abstract:
The present invention discloses and claims a series of substituted N-phenyl-bipyrrolidine ureas of formula (I) as described herein. More specifically, the compounds of this invention are modulators of H3 receptors and are, therefore, useful as pharmaceutical agents, especially in the treatment and/or prevention of a variety of diseases modulated by H3 receptors including diseases associated with the central nervous system. Additionally, this invention also discloses methods of preparation of substituted N-phenyl- bipyrrolidine ureas and intermediates therefor.

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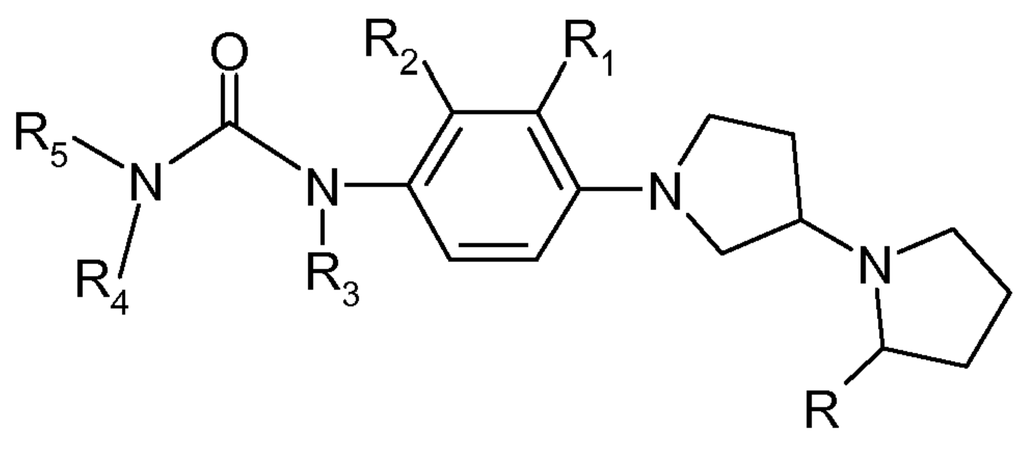
(54) Title: SUBSTITUTED N-PHENYL-BIPYRROLIDINE UREAS AND THERAPEUTIC USE THEREOF



(I)

(57) Abstract: The present invention discloses and claims a series of substituted N-phenyl-bipyrrolidine ureas of formula (I) as described herein. More specifically, the compounds of this invention are modulators of H3 receptors and are, therefore, useful as pharmaceutical agents, especially in the treatment and/or prevention of a variety of diseases modulated by H3 receptors including diseases associated with the central nervous system. Additionally, this invention also discloses methods of preparation of substituted N-phenyl-bipyrrolidine ureas and intermediates therefor.

WO 2009/052068 A1

# SUBSTITUTED N-PHENYL-BIPYRROLIDINE UREAS AND THERAPEUTIC USE THEREOF

## BACKGROUND OF THE INVENTION

### Field of the Invention

The present invention relates to a series of substituted N-phenyl-bipyrrolidine ureas. The compounds of this invention are modulators of H3 receptors and are, therefore, useful as pharmaceutical agents, especially in the treatment and/or prevention of a variety of diseases modulated by H3 receptors including diseases associated with the central nervous system. Additionally, this invention also relates to methods of preparation of substituted N-phenyl-bipyrrolidine ureas and intermediates therefor.

### Description of the Art

Histamine is a ubiquitous messenger molecule released from mast cells, enterochromaffin-like cells, and neurons. The physiological actions of histamine are mediated by four pharmacologically defined receptors (H1, H2, H3 and H4). All histamine receptors exhibit seven transmembrane domains and are members of the G-protein-coupled receptor superfamily (GPCRs).

The H1 receptor was the first member of the histamine receptor family to be pharmacologically defined, with the development of classical antihistamines (antagonists), such as diphenhydramine and fexofenadine. While antagonism of the H1 receptor of the immune system is commonly used for the treatment of allergic reactions, the H1 receptor is

also expressed in various peripheral tissues and the central nervous system (CNS). In the brain, H1 is involved in the control of wakefulness, mood, appetite and hormone secretion.

The H2 receptor is also expressed in the CNS, where it may modulate several processes, including cognition. However, H2 receptor antagonists have primarily been developed to ameliorate gastric ulcers by inhibiting histamine-mediated gastric acid secretion by parietal cells. Classic H2 antagonists include cimetidine, ranitidine, and famotidine.

It should further be noted that H4 receptor function remains poorly defined, but may involve immune regulation and inflammatory processes.

H3 receptors have also been pharmacologically identified in the CNS, heart, lung, and stomach. The H3 receptor differs significantly from other histamine receptors, exhibiting low sequence homology (H1: 22%, H2: 21%, H4: 35%). H3 is a presynaptic autoreceptor on histamine neurons in the brain and a presynaptic heteroreceptor in nonhistamine-containing neurons in both the central and peripheral nervous systems. In addition to histamine, H3 also modulates the release and/or synthesis of other neurotransmitters, including acetylcholine, dopamine, norepinepherin and serotonin. Of particular note, presynaptic modulation of histamine release by H3 allows significant regulation of H1 and H2 receptors in the brain. Modulating multiple neurotransmitter signalling pathways, H3 may contribute to varied physiological processes. Indeed, extensive preclinical evidence indicates that H3 plays a role in cognition, sleep-wake cycle and energy homeostasis.

Modulators of H3 function may be useful in the treatment of obesity and central nervous system disorders (Schizophrenia, Alzheimer's disease, attention-deficit hyperactivity disorder, Parkinson's disease, depression, and epilepsy), sleep disorders (narcolepsy and insomnia), cardiovascular disorders (acute myocardial infarction), respiratory disorders (asthma), and gastrointestinal disorders. See generally, Hancock, Biochem. Pharmacol. 2006 Apr 14;71(8):1103-13 and Esbenshade et al. Mol Interv. 2006 Apr;6(2):77-88, 59.

Recently, compounds that are somewhat structurally related to the compounds of the present invention have been disclosed to be melanin concentrating hormone (MCH) receptor antagonists, see specifically U.S. Patent 7,223,788. It should however be pointed out that there is no disclosure as to the activity of the compounds disclosed therein at the H3 receptor site.

Accordingly, it is an object of this invention to provide a series of substituted N-phenyl-bipyrrolidine ureas as selective H3 receptor ligands for treatment of H3 receptor regulated CNS disorders.

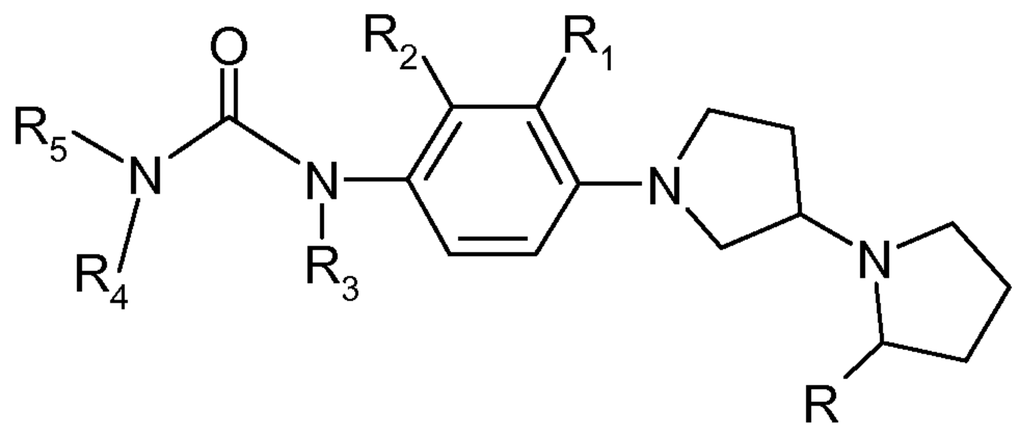
It is also an object of this invention to provide processes for the preparation of the substituted N-phenyl-bipyrrolidine ureas as disclosed herein.

Other objects and further scope of the applicability of the present invention will become apparent from the detailed description that follows.

## SUMMARY OF THE INVENTION

Surprisingly, it has now been found that the compounds of formula (I) are useful as H3 receptor antagonists and/or inverse agonists. The compounds of formula I are not specifically disclosed, nor exemplified, nor are their activity as H3 receptor antagonists/ inverse agonists suggested, in U.S. Patent 7,223,788 as mentioned hereinabove. Moreover, unexpectedly it has now been found that the compounds of formula (I) are selectively active only at H3 receptors and exhibit low activity at the MCH-1 receptor site, which aspect becomes even more apparent from the detailed description that follows.

Thus in accordance with the practice of this invention there is provided a compound of formula (I):



(I)

wherein

R, $R_1$, $R_2$ and $R_3$ are the same or different and independently of each other chosen from hydrogen, $(C_1\text{-}C_4)$alkyl or $CF_3$;

$R_4$ and $R_5$ are the same or different and independently of each other selected from the group consisting of hydrogen, n-hexyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl and thiophen-2-ylmethyl; wherein said $R_4$ and $R_5$ are optionally substituted one or more times with a substituent selected from halogen or CN; provided that both $R_4$ and $R_5$ are not simultaneously hydrogen; or

$R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine,

piperazine, morpholine, 1,3-dihydro-isoindolyl, wherein said heterocyclic ring is optionally substituted one or more times with a substituent selected from the group consisting of methyl, ethyl, phenyl, N-acetyl and N-acetyl-methylamino.

This invention further includes various salts of the compounds of formula (I) including various enantiomers or diastereomers of compounds of formula (I).

In other aspects of this invention there are also provided various pharmaceutical compositions comprising one or more compounds of formula (I) as well as their therapeutic use in alleviating various diseases which are mediated in-part and/or fully by H3 receptors.

## DETAILED DESCRIPTION OF THE INVENTION

The terms as used herein have the following meanings:

As used herein, the expression "($C_1$-$C_6$)alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and tert-butyl. Derived expressions such as "($C_1$-$C_4$)alkoxy", "($C_1$-$C_4$)thioalkyl" "($C_1$-$C_4$)alkoxy($C_1$-$C_4$)alkyl", "hydroxy($C_1$-$C_4$)alkyl", "($C_1$-$C_4$)alkylcarbonyl", "($C_1$-$C_4$)alkoxycarbonyl($C_1$-$C_4$)alkyl", "($C_1$-$C_4$)alkoxycarbonyl", "amino($C_1$-$C_4$)alkyl", "($C_1$-$C_4$)alkylamino", "($C_1$-$C_4$)alkylcarbamoyl($C_1$-$C_4$)alkyl", "($C_1$-$C_4$)dialkylcarbamoyl($C_1$-$C_4$)alkyl" "mono- or di-($C_1$-$C_4$)alkylamino($C_1$-$C_4$)alkyl", "amino($C_1$-$C_4$)alkylcarbonyl" "diphenyl($C_1$-$C_4$)alkyl", "phenyl($C_1$-$C_4$)alkyl", "phenylcarboyl($C_1$-$C_4$)alkyl" and "phenoxy($C_1$-$C_4$)alkyl" are to be construed accordingly.

As used herein, the expression “cycloalkyl” includes all of the known cyclic radicals. Representative examples of “cycloalkyl” include without any limitation cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Derived expressions such as “cycloalkoxy”, “cycloalkylalkyl”, “cycloalkylaryl”, “cycloalkylcarbonyl” are to be construed accordingly.

As used herein, the expression "($C_2$-$C_6$)alkenyl" includes ethenyl and straight-chained or branched propenyl, butenyl, pentenyl and hexenyl groups. Similarly, the expression "($C_2$-$C_6$)alkynyl" includes ethynyl and propynyl, and straight-chained or branched butynyl, pentynyl and hexynyl groups.

As used herein the expression “($C_1$-$C_4$)acyl” shall have the same meaning as “($C_1$-$C_6$)alkanoyl”, which can also be represented structurally as “R-CO-,” where R is a ($C_1$-$C_3$)alkyl as defined herein. Additionally, “($C_1$-$C_3$)alkylcarbonyl” shall mean same as ($C_1$-$C_4$)acyl. Specifically, “($C_1$-$C_4$)acyl” shall mean formyl, acetyl or ethanoyl, propanoyl, n-

butanoyl, etc. Derived expressions such as "($C_1$-$C_4$)acyloxy" and "($C_1$-$C_4$)acyloxyalkyl" are to be construed accordingly.

As used herein, the expression "($C_1$-$C_6$)perfluoroalkyl" means that all of the hydrogen atoms in said alkyl group are replaced with fluorine atoms. Illustrative examples include trifluoromethyl and pentafluoroethyl, and straight-chained or branched heptafluoropropyl, nonafluorobutyl, undecafluoropentyl and tridecafluorohexyl groups. Derived expression, "($C_1$-$C_6$)perfluoroalkoxy", is to be construed accordingly.

As used herein, the expression "($C_6$-$C_{10}$)aryl" means substituted or unsubstituted phenyl or naphthyl. Specific examples of substituted phenyl or naphthyl include o-, p-, m-tolyl, 1,2-, 1,3-, 1,4-xylyl, 1-methylnaphthyl, 2-methylnaphthyl, etc. "Substituted phenyl" or "substituted naphthyl" also include any of the possible substituents as further defined herein or one known in the art. Derived expression, "($C_6$-$C_{10}$)arylsulfonyl," is to be construed accordingly.

As used herein, the expression "($C_6$-$C_{10}$)aryl($C_1$-$C_4$)alkyl" means that the ($C_6$-$C_{10}$)aryl as defined herein is further attached to ($C_1$-$C_4$)alkyl as defined herein. Representative examples include benzyl, phenylethyl, 2-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl and the like.

As used herein, the expression "heteroaryl" includes all of the known heteroatom containing aromatic radicals. Representative 5-membered heteroaryl radicals include furanyl, thienyl or thiophenyl, pyrrolyl, isopyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isothiazolyl, and the like. Representative 6-membered heteroaryl radicals include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and the like radicals. Representative examples of bicyclic heteroaryl radicals include, benzofuranyl, benzothiophenyl, indolyl, quinolinyl, isoquinolinyl, cinnolyl, benzimidazolyl, indazolyl, pyridofuranyl, pyridothienyl, and the like radicals.

As used herein, the expression "heterocycle" includes all of the known reduced heteroatom containing cyclic radicals. Representative 5-membered heterocycle radicals include tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, 2-thiazolinyl, tetrahydrothiazolyl, tetrahydrooxazolyl, and the like. Representative 6-membered heterocycle radicals include piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, and the like. Various other heterocycle radicals include, without limitation, aziridinyl, azepanyl, diazepanyl, diazabicyclo[2.2.1]hept-2-yl, and triazocanyl, and the like.

"Halogen" or "halo" means chloro, fluoro, bromo, and iodo.

As used herein, "patient" means a warm blooded animal, such as for example rat, mice, dogs, cats, guinea pigs, and primates such as humans.

As used herein, the expression "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with the compound of the present invention in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is pharmaceutically acceptable oil typically used for parenteral administration.

The term "pharmaceutically acceptable salts" as used herein means that the salts of the compounds of the present invention can be used in medicinal preparations. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfamic acid, sulfuric acid, methanesulfonic acid, 2-hydroxyethanesulfonic acid, p-toluenesulfonic acid, fumaric acid, maleic acid, hydroxymaleic acid, malic acid, ascorbic acid, succinic acid, glutaric acid, acetic acid, propionic acid, salicylic acid, cinnamic acid, 2-phenoxybenzoic acid, hydroxybenzoic acid, phenylacetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, carbonic acid or phosphoric acid. The acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate can also be formed. Also, the salts so formed may present either as mono- or di- acid salts and can exist substantially anhydrous or can be hydrated. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts, and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

As used herein, the term “prodrug” shall have the generally accepted meaning in the art. One such definition includes a pharmacologically inactive chemical entity that when metabolized or chemically transformed by a biological system such as a mammalian system is converted into a pharmacologically active substance.

The expression "stereoisomers" is a general term used for all isomers of the individual molecules that differ only in the orientation of their atoms in space. Typically it includes mirror image isomers that are usually formed due to at least one asymmetric center,

(enantiomers). Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers, also certain individual molecules may exist as geometric isomers (cis/trans). Similarly, certain compounds of this invention may exist in a mixture of two or more structurally distinct forms that are in rapid equilibrium, commonly known as tautomers. Representative examples of tautomers include keto-enol tautomers, phenol-keto tautomers, nitroso-oxime tautomers, imine-enamine tautomers, etc. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

As used herein, 'R' and 'S' are used as commonly used terms in organic chemistry to denote specific configuration of a chiral center. The term 'R' (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term 'S' (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon sequence rules wherein prioritization is first based on atomic number (in order of decreasing atomic number). A listing and discussion of priorities is contained in *Stereochemistry of Organic Compounds*, Ernest L. Eliel, Samuel H. Wilen and Lewis N. Mander, editors, Wiley-Interscience, John Wiley & Sons, Inc., New York, 1994.

In addition to the (R)-(S) system, the older D-L system may also be used herein to denote absolute configuration, especially with reference to amino acids. In this system a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix 'D' is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon at the chiral center and 'L', that of the isomer in which it is on the left.

The term “solvate” as used herein means that an aggregate that consists of a solute ion or molecule with one or more solvent molecules. Similarly, a “hydrate” means that a solute ion or molecule with one or more water molecules.

In a broad sense, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a few of the specific embodiments as disclosed herein, the term "substituted" means substituted with one or more substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$perfluoroalkyl, phenyl, hydroxy, $-CO_2H$, an ester, an amide, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$thioalkyl, $(C_1\text{-}C_6)$perfluoroalkoxy,

-$NH_2$, Cl, Br, I, F, -NH-lower alkyl, and -N(lower alkyl)$_2$. However, any of the other suitable substituents known to one skilled in the art can also be used in these embodiments.

"Therapeutically effective amount" means an amount of the compound which is effective in treating the named disease, disorder or condition.

The term "neurodegenerative diseases" includes Alzheimer's disease, Parkinson's disease, and Huntington's disease.

The term "nervous insult" refers to any damage to nervous tissue and any disability or death resulting therefrom. The cause of nervous insult may be metabolic, toxic, neurotoxic, iatrogenic, thermal or chemical, and includes without limitation, ischemia, hypoxia, cerebrovascular accident, trauma, surgery, pressure, mass effect, hemorrhage, radiation, vasospasm, neurodegenerative disease, infection, Parkinson's disease, amyotrophic lateral sclerosis (ALS), myelination/demyelination process, epilepsy, cognitive disorder, glutamate abnormality and secondary effects thereof.

The term "neuroprotective" refers to the effect of reducing, arresting or ameliorating nervous insult, and protecting, resuscitating, or reviving nervous tissue that has suffered nervous insult.

The term "preventing neurodegeneration" includes the ability to prevent neurodegeneration in patients diagnosed with a neurodegenerative disease or who are at risk of developing a neurodegenerative disease. The term also encompasses preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease.

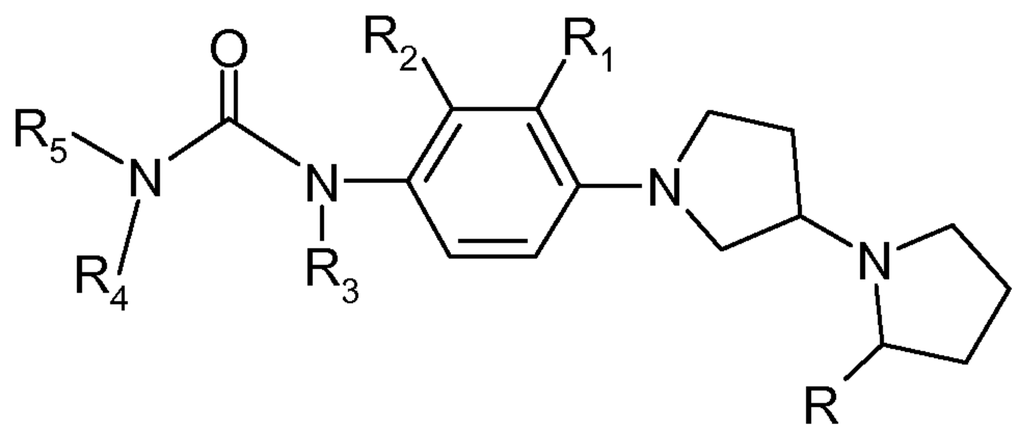
The term "treating" refers to:

(i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder and/or condition, but has not yet been diagnosed as having it;

(ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and

(iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

Thus, in accordance with the practice of this invention there is provided a compound of the formula I:



(I)

wherein

R, $R_1$, $R_2$ and $R_3$ are the same or different and independently of each other chosen from hydrogen, ($C_1$-$C_4$)alkyl or $CF_3$;

$R_4$ and $R_5$ are the same or different and independently of each other selected from the group consisting of hydrogen, n-hexyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl and thiophen-2-ylmethyl; wherein said $R_4$ and $R_5$ are optionally substituted one or more times with a substituent selected from halogen or CN; provided that both $R_4$ and $R_5$ are not simultaneously hydrogen; or

$R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, 1,3-dihydro-isoindolyl, wherein said heterocyclic ring is optionally substituted one or more times with a substituent selected from the group consisting of methyl, ethyl, phenyl, N-acetyl and N-acetyl-methylamino.

This invention further includes various salts of the compounds of formula (I) including various enantiomers or diastereomers of compounds of formula (I). As noted hereinabove and by way of specific examples hereafter all of the salts that can be formed including pharmaceutically acceptable salts are part of this invention. As also noted hereinabove and hereafter all of the conceivable enantiomeric and diastereomeric forms of compounds of formula (I) are part of this invention.

In one of the embodiments, the compound of formula (I) of this invention, wherein R and $R_2$ are methyl; $R_1$ is methyl or hydrogen and $R_3$ is hydrogen is disclosed.

In another embodiment of this invention there is disclosed the compound of formula (I), wherein $R_4$ is hydrogen and $R_5$ is phenyl or benzyl, wherein phenyl or benzyl is optionally substituted with one or more groups selected from chlorine or CN.

In yet another embodiment of this invention there is disclosed the compound of formula (I), wherein $R_4$ is hydrogen and $R_5$ is selected from n-hexyl, cyclohexyl, cyclohexylmethyl or thiophen-2-ylmethyl.

In yet another embodiment there are disclosed compounds of formula (I), wherein $R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form pyrrolidine which is optionally substituted once with N-acetyl-methylamino.

In yet another embodiment of this invention there is disclosed the compound of formula (I), wherein $R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form piperidine, piperazine or morpholine, which are optionally substituted one or more times with methyl, ethyl, phenyl or acetyl.

In another embodiment of this invention there is disclosed the compound of formula (I), wherein $R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form 1,3-dihydro-isoindolyl.

In a further aspect of this invention the following compounds encompassed by the scope of this invention without any limitation may be enumerated:

1-(3-cyano-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3-cyano-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-benzyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-benzyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-2-trifluoromethyl-phenyl]-urea;

1-hexyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexyl-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexyl-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexyl-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'S)]bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea;

1-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea;

3-(acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

3-(acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

piperidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

piperidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-methyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-methyl-piperazine-1-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-methyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-phenyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-acetyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-acetyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-ethyl-piperazine-1-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide;

morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3' (3'S)]bipyrrolidinyl-1'-yl)-phenyl]-amide;

morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide;

1,3-dihydro-isoindole-2-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

1,3-dihydro-isoindole-2-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide; and

1,3-dihydro-isoindole-2-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide.

All of the above compounds may also include corresponding salts wherever possible including the pharmaceutically acceptable salts thereof.

In another aspect of this invention the following compounds encompassed by compound of formula (I) of this invention without any limitation may be enumerated:

1-(3-cyano-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3-cyano-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-(3,5-dichloro-benzyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-(3,5-dichloro-benzyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-2-trifluoromethyl-phenyl]-urea;
1-hexyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-cyclohexyl-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-cyclohexyl-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-cyclohexyl-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'S)]bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea;
1-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea; and
1-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea.

Again all of the conceivable salts of the above noted compounds including the pharmaceutically acceptable salts are part of this invention.

In a further aspect of this invention the following compounds within the scope of this invention may be enumerated:
3-(acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
3-(acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
piperidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
piperidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
4-methyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
4-methyl-piperazine-1-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
4-methyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
4-phenyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
4-acetyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
4-acetyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-ethyl-piperazine-1-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide;

morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3' (3'S)]bipyrrolidinyl-1'-yl)-phenyl]-amide;

morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide;

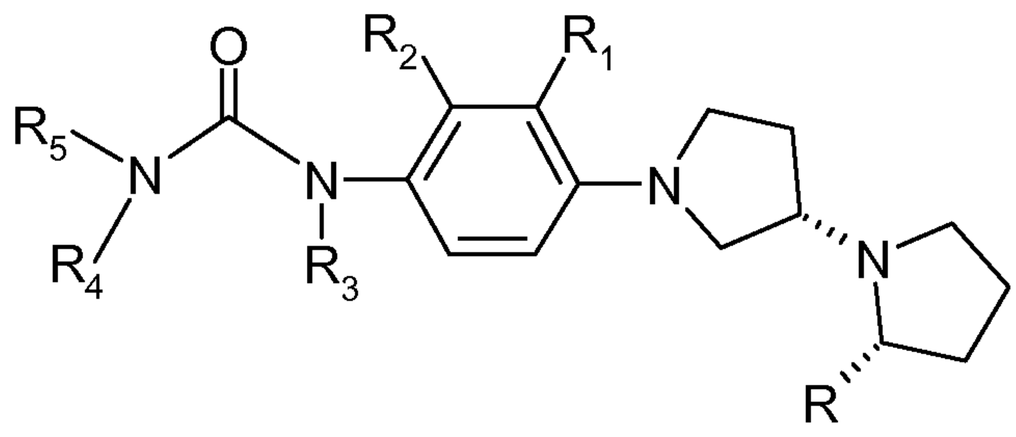
1,3-dihydro-isoindole-2-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

1,3-dihydro-isoindole-2-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide; and

1,3-dihydro-isoindole-2-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide.

Again all of the conceivable salts of the above noted compounds including the pharmaceutically acceptable salts are part of this invention.

In another aspect of this invention the compound of this invention may be represented by a specific stereoisomeric form of formula (II):



(II)

wherein R, $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ are as defined hereinabove.

The compounds of this invention can be synthesized by any of the procedures known to one skilled in the art. Specifically, several of the starting materials used in the preparation of the compounds of this invention are known or are themselves commercially available. The compounds of this invention and several of the precursor compounds may also be prepared by methods used to prepare similar compounds as reported in the literature and as further described herein. For instance, as stated hereinabove a few of the structurally similar compounds have been disclosed in U. S. Patent No. 7,223,788. Also, see R. C. Larock, "Comprehensive Organic Transformations," VCH publishers, 1989.

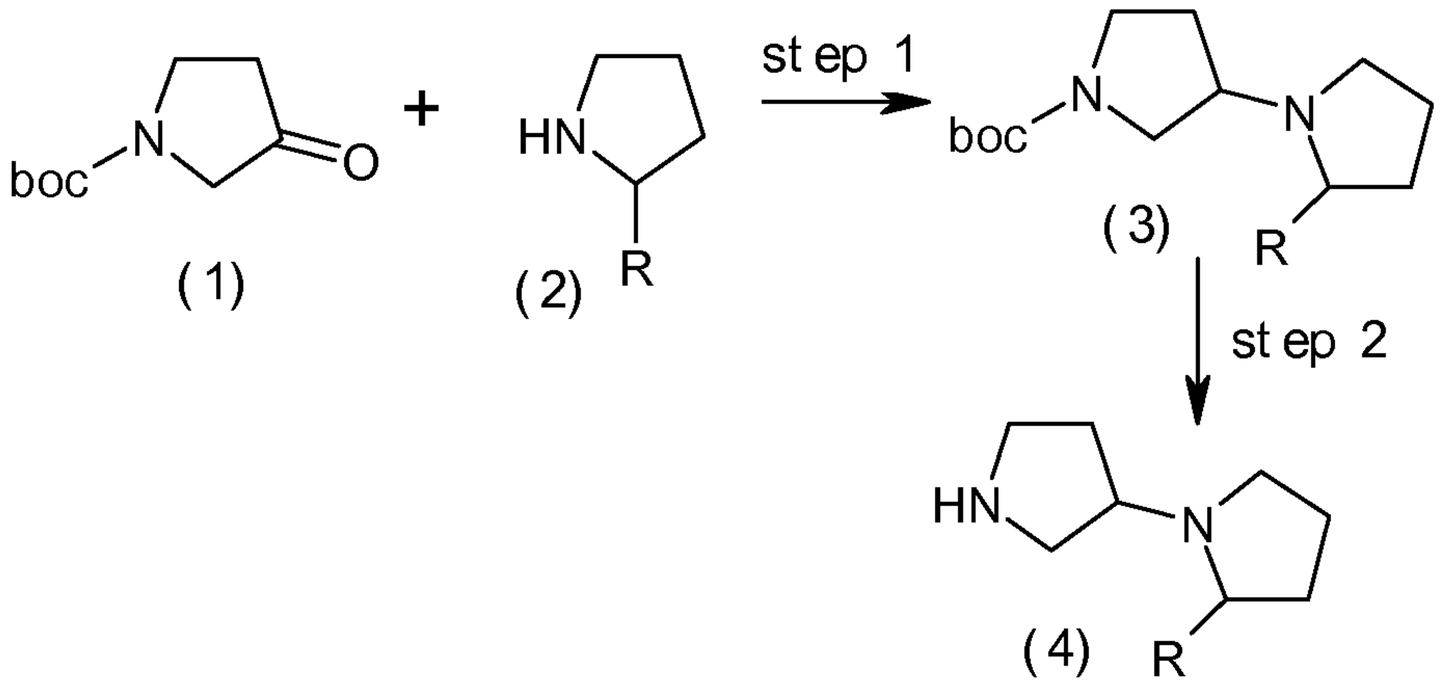
It is also well known that in various organic reactions it may be necessary to protect reactive functional groups, such as for example, amino groups, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice and known to one of skilled in the art, for example, see T. W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, Inc., 1991. For example, suitable amine protecting groups include without any limitation sulfonyl (e.g., tosyl), acyl (e.g., benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g., benzyl), which may be removed subsequently by hydrolysis or hydrogenation as appropriate. Other suitable amine protecting groups include trifluoroacetyl [-C(=O)$CF_3$] which may be removed by base catalyzed hydrolysis, or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker) or a 2,6-dimethoxy-4-[2-(polystyrylmethoxy)ethoxy]benzyl, which may be removed by acid catalyzed hydrolysis, for example with TFA.

More specifically, the compounds disclosed herein and various precursors used therefor can be synthesized according to the following procedures of Schemes 1 - 4, wherein R, $R_1$, $R_2$, $R_3$ and $R_4$ are as defined for Formula I unless otherwise indicated.

For instance, Scheme 1 illustrates the preparation of the intermediate [1, 3']-pyrrolidinyl-pyrrolidine of formula (4), wherein R is as defined herein. First, in step 1, Scheme 1, suitably protected (for example tert-butyloxycarbonyl (boc)) pyrrolidinone of formula (1) is condensed with a desired substituted pyrrolidine of formula (2) by any of the known reductive amination procedures to from an intermediate of formula (3). For instance, such condensation reactions are generally carried out in the presence of reducing agents such as triacetoxyborohydride in an inert atmosphere, such as nitrogen atmosphere. The reaction can be carried out either at sub-ambient, ambient or super-ambient reaction temperatures and pressures. Typically, such reactions are carried out at room temperature at atmospheric pressure of nitrogen. The reaction mixture is then worked-up using procedures known to skilled in the art to isolate the intermediate of formula (3).

In step 2, Scheme 1, the intermediate (3) is then de-protected to form the desired [1, 3']-pyrrolidinyl-pyrrolidine of formula (4). Such deprotection reactions are generally carried out under acidic conditions, for example, in the presence of hydrochloric acid at sub-ambient to ambient temperatures, for example in the temperature range of about -10°C to room temperature. However, other suitable reaction temperatures can also be used depending upon the nature of the intermediate of formula (3).

Scheme 1

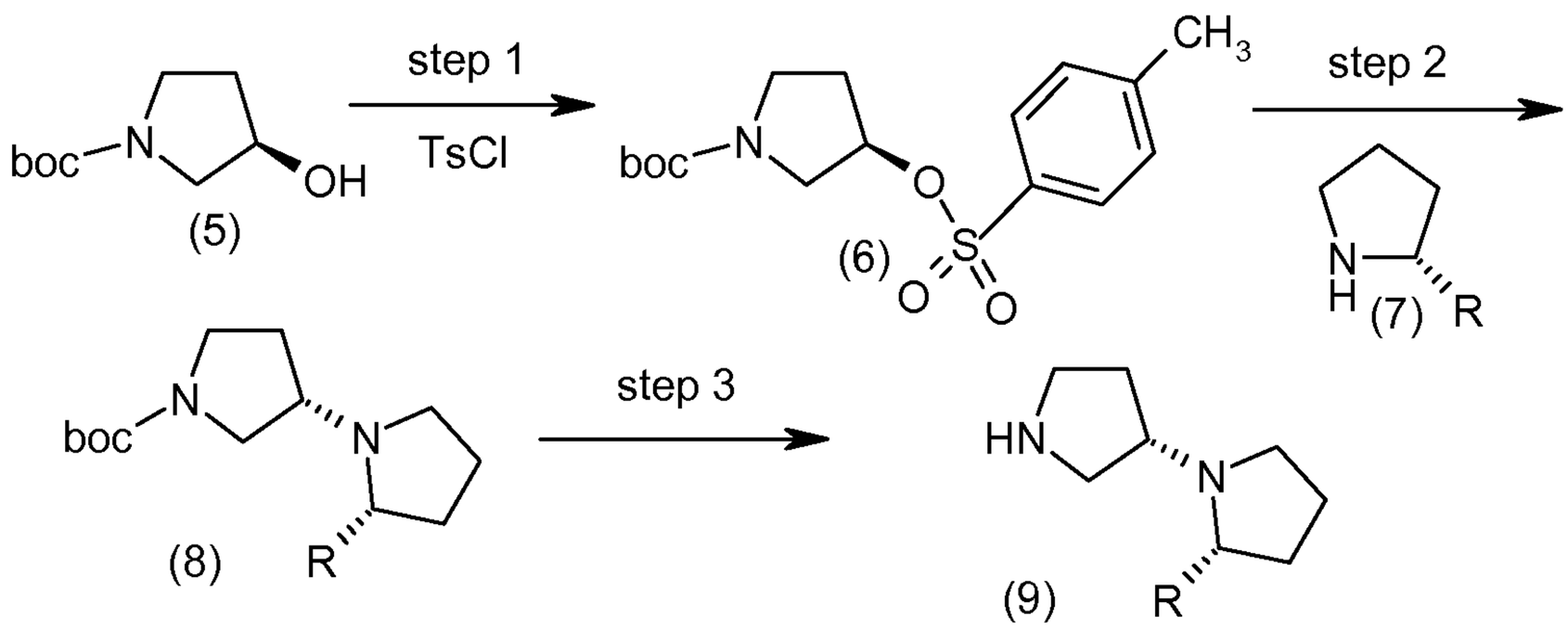



Scheme 2 illustrates preparation of enantiomerically pure isomers of the [1,3'] pyrrolidinyl-pyrrolidine of formula (9), wherein R is as defined herein. In step 1, Scheme 2, suitably protected (for example boc) pyrrolidine alcohol of formula (5) is treated with p-toluene sulfonyl chloride to form intermediate of formula (6). This reaction can be carried out using any of the procedures known to one skilled in the art, such as for example carrying out the reaction in the presence of a suitable base such as triethylamine and DMAP in a suitable organic solvent, preferably an aprotic solvent such as dichloromethane at sub-ambient or ambient temperature conditions.

In step 2, Scheme 2, the intermediate of formula (6) is condensed with a desired pyrrolidine of formula (7). Again, such condensation reactions can be carried out using any of the procedures known to one skilled in the art in order to obtain the intermediate of formula (8). Typically, such condensation reactions are carried out in the presence of a base such as potassium carbonate in the presence of solvents such as acetonitrile at ambient to super-ambient temperature conditions.

In step 3, Scheme 2, the intermediate of formula (8) is then reacted with an acid, such as hydrochloric acid in a suitable solvent, such as dioxane, to form the desired stereospecific isomer of [1,3'] pyrrolidinyl-pyrrolidine intermediate of formula (9). It has now been found that the intermediates of formula (9) can be readily formed in accordance with the process of this invention with high enantiomeric purity, specific details of which are provided hereinbelow by way of various examples. In general, the enantiomeric purity can be determined by chiral HPLC.

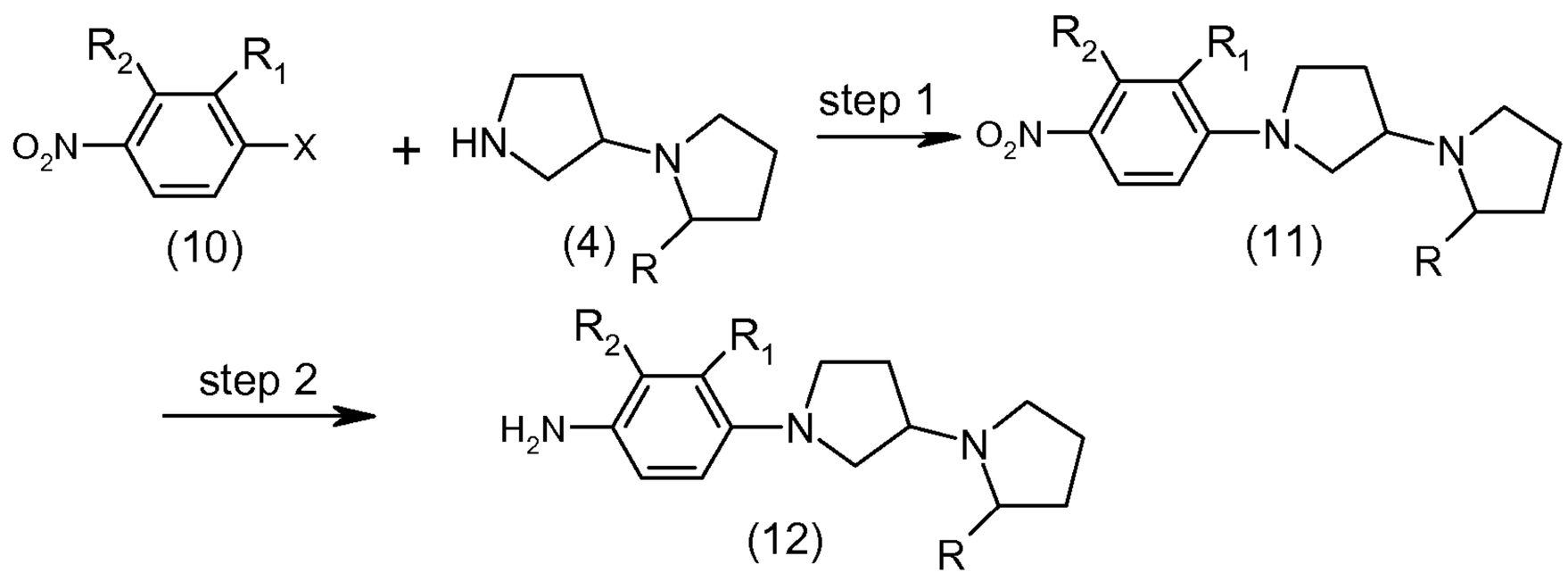
Scheme 2




Scheme 3 illustrates the preparation of amino-phenyl-pyrrolidinyl-pyrrolidine intermediate of formula (12), wherein R, $R_1$ and $R_2$ are as defined herein. In step 1, Scheme 3, suitably substituted nitrobenzene of formula (10), wherein X is a suitable leaving group, such as Cl, F, Br, or triflate (OTf) is condensed with the [1,3'] pyrrolidinyl-pyrrolidine of formula (4) in order to form an intermediate of formula (11). Such condensation reactions can again be carried out using any of the procedures known to one skilled in the art. For example, such condensation reaction can be carried out in a polar solvent such as DMSO in the presence of a base such as potassium carbonate at ambient to super-ambient temperature conditions.

In step 2, Scheme 3, intermediate of formula (11) is reduced by hydrogenation or other known chemical methods, such as using tin dichloride in hydrochloric acid, to form the key intermediate (12).

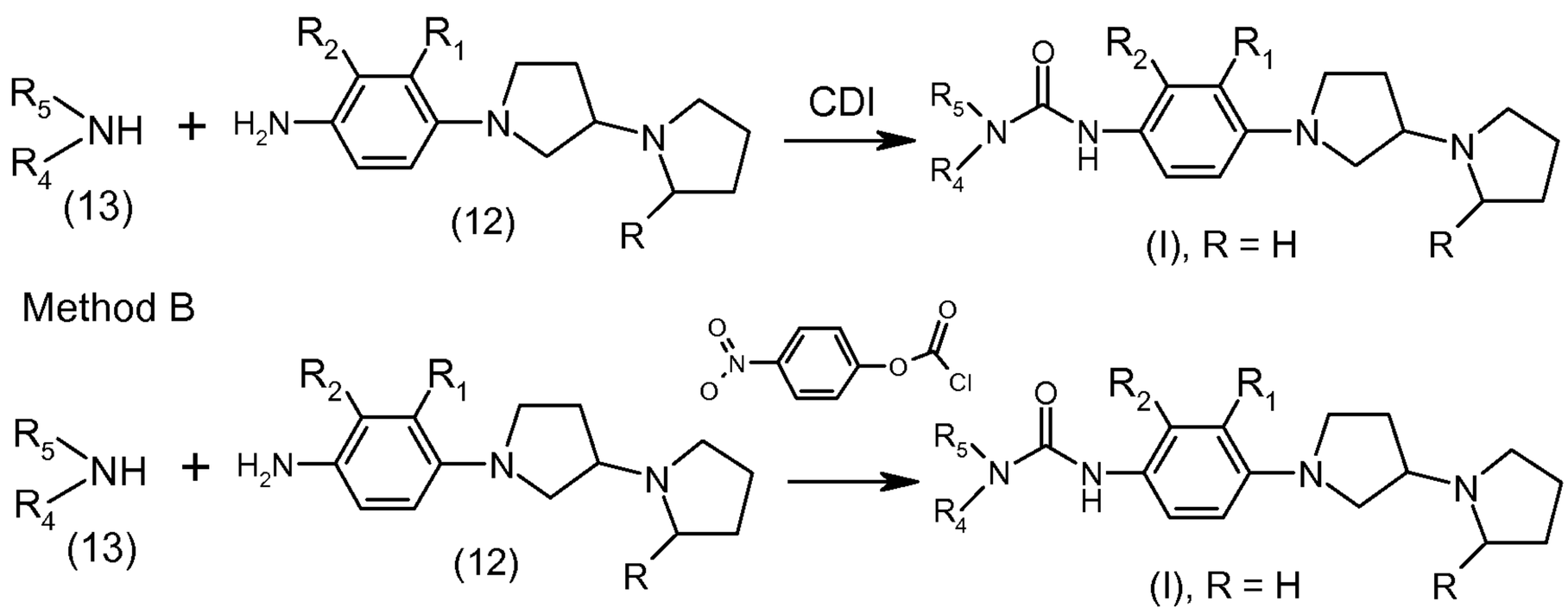
Scheme 3




Scheme 4 illustrates the preparation of compounds of formula (I) of this invention. In Method A, the intermediate of formula (12) is reacted with an amine of formula (13) in the presence of a suitable carbonyl containing coupling agent such as for example carbonyl diimidazole in the presence of a suitable solvent. Again such reactions can be carried out

using any of the procedures known to one skilled in the art. For example, such coupling reaction can be carried out in a polar solvent such as DMF at ambient to super-ambient temperature conditions. Generally such reactions are carried out at a temperature range of from about 60°C to 120°C.

Scheme 4




Alternatively, the compound of formula (I) can also be prepared in accordance with Method B, Scheme 4. In this approach, intermediate of formula (12) is reacted with an amine of formula (13) in the presence of p-(chlorocarbonyloxy)-nitro-benzene. This reaction can again be carried out using any of the methods known to one skilled in the art. Generally such reactions are carried out in a suitable solvent at sub-ambient to ambient temperature conditions. However, super-ambient temperature conditions can also be used under certain situations depending upon the nature of the intermediates of formula (12) and (13) employed.

As already noted hereinabove, the compounds of this invention can readily be converted into salts. More particularly, the compounds of the present invention are basic, and as such compounds of this invention are useful in the form of the free base or in the form of a pharmaceutically acceptable acid addition salt thereof. Acid addition salts may be a more convenient form for use; and, in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compound is preferred, all acid addition salts are useful as sources of the free

base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.

In another aspect of this embodiment, a specific disease, a disorder or a condition that can be treated with the compound of this invention include, without any limitation the following: sleep-related disorders (specific examples include without any limitation narcolepsy, circadian rhythm sleep disorders, obstructive sleep apnea, periodic limb movement and restless leg syndrome, excessive sleepiness and drowsiness due to medication side-effect, etc.), neurological disorders (specific examples that may be enumerated include but not limited to dementia, Alzheimer's disease, multiple sclerosis, epilepsy and neuropathic pain), neuropsychological and cognitive disorders (a few of the specific examples include without any limitation include schizophrenia, attention deficit/hyperactivity disorder, Alzheimer's disease, depression, seasonal affective disorder, and cognitive impairment).

As described hereinbelow by way of specific examples, the compounds of formula (I) bind to the H3 receptors and demonstrate inverse agonism versus H3 functional activity. Therefore, the compounds of this invention may have utility in the treatment of diseases or conditions ameliorated with H3 receptor ligands. More specifically, the compounds of the present invention are H3 receptor ligands that modulate function of the H3 receptor by antagonizing the activity of the receptor. Further, the compounds of this invention may be inverse agonists that inhibit the basal activity of the receptor or they may be antagonists that completely block the action of receptor-activating agonists. Additionally, the compounds of this invention may also be partial agonists that partially block or partially activate the H3 receptor or they may be agonists that activate the receptor. Thus the compounds of this invention may act differentially as antagonists, inverse agonists and/or partial agonists depending on functional output, histamine tone and or tissue context. Accordingly, the differential activities of these compounds may allow for utility to ameliorate multiple disease states as specifically enumerated above.

Thus in one aspect of this invention there is provided a method of treating a disease in a patient, said disease selected from the group consisting of sleep related disorder, dementia, Alzheimer's disease, multiple sclerosis, cognitive disorder, attention deficit hyperactivity disorder and depression, comprising administering to said patient a therapeutically effective amount of a compound of formula (I).

One of skill in the art readily appreciates that the pathologies and disease states expressly stated herein are not intended to be limiting rather to illustrate the efficacy of the compounds of the present invention. Thus it is to be understood that the compounds of this invention may be used to treat any disease caused by the effects of H3 receptors. That is, as noted above, the compounds of the present invention are modulators of H3 receptors and may be effectively administered to ameliorate any disease state which is mediated all or in part by H3 receptors.

All of the various embodiments of the compounds of this invention as disclosed herein can be used in the method of treating various disease states as described herein. As stated herein, the compounds used in the method of this invention are capable of inhibiting the effects of H3 receptor and thereby alleviating the effects and/or conditions caused due to the activity of H3.

In another embodiment of the method of this invention, the compounds of this invention can be administered by any of the methods known in the art. Specifically, the compounds of this invention can be administered by oral, intramuscular, subcutaneous, rectal, intratracheal, intranasal, intraperitoneal or topical route.

Finally, in yet another embodiment of this invention, there is also provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula (I), including enantiomers, stereoisomers, and tautomers of said compound and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in formula I as described herein.

As described herein, the pharmaceutical compositions of this invention feature H3 inhibitory activity and thus are useful in treating any disease, condition or a disorder caused due to the effects of H3 in a patient. Again, as described above, all of the preferred embodiments of the compounds of this invention as disclosed herein can be used in preparing the pharmaceutical compositions as described herein.

Preferably the pharmaceutical compositions of this invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for

intramuscular injection. An erodible polymer containing the active ingredient may be envisaged. 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 unit 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 the active ingredient of the present invention. Flavored unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition 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 materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored 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, polyvinyl-pyrrolidone or gelatin.

The pharmaceutical compositions of this invention can be administered by any of the methods known in the art. In general, the pharmaceutical compositions of this invention can be administered by oral, intramuscular, subcutaneous, rectal, intratracheal, intranasal, intraperitoneal or topical route. The preferred administrations of the pharmaceutical

composition of this invention are by oral and intranasal routes. Any of the known methods to administer pharmaceutical compositions by an oral or an intranasal route can be used to administer the composition of this invention.

In the treatment of various disease states as described herein, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 20 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

This invention is further illustrated by the following examples which are provided for illustration purposes and in no way limit the scope of the present invention.

Examples (General)

As used in the examples and preparations that follow, the terms used therein shall have the meanings indicated: "kg" refers to kilograms, "g" refers to grams, "mg" refers to milligrams, "μg" refers to micrograms, "pg" refers to picograms, "lb" refers to pounds, “oz” refers to ounces, "mol" refers to moles, "mmol" refers to millimoles, "μmole" refers to micromoles, "nmole" refers to nanomoles, "L" refers to liters, "mL" or "ml" refers to milliliters, "μL" refers to microliters, "gal" refers to gallons, "°C" refers to degrees Celsius, "$R_f$ " refers to retention factor, "mp" or "m.p." refers to melting point, "dec" refers to decomposition, "bp" or "b.p." refers to boiling point, "mm of Hg" refers to pressure in millimeters of mercury, "cm" refers to centimeters, "nm" refers to nanometers, “abs.” refers to absolute, “conc.” refers to concentrated, "c" refers to concentration in g/mL, “DMSO” refers to dimethyl sulfoxide, “DMF” refers to N,N-dimethylformamide, “CDI” refers to 1,1'-carbonyldiimidazole, “DCM” or “$CH_2Cl_2$” refers to dichloromethane, “DCE” refers to 1,2-dichloroethane, “HCl” refers to hydrochloric acid, “EtOAc” refers to ethyl acetate, “PBS” refers to Phosphate Buffered Saline, “IBMX” refers to 3-isobutyl-1-methylxanthine, “PEG” refers to polyethylene glycol, “MeOH” refers to methanol, “$MeNH_2$” refers to methyl amine, “$N_2$” refers to nitrogen gas, “iPrOH” refers to isopropyl alcohol, “$Et_2O$” refers to ethyl ether, “LAH” refers to lithium aluminum hydride, “heptane” refers to n-heptane, “HMBA-AM” resin refers to 4-hydroxymethylbenzoic acid amino methyl resin, “$PdCl_2(dppf)_2$” refers to 1,1′-bis(diphenylphosphino)ferrocene-palladium (II) dichloride DCM complex, “HBTU” refers to 2-(1H-benzotriazol-1yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, “DIEA” refers to diisopropylethylamine, “CsF” refers to cesium fluoride, “MeI” refers to methyl iodide, “AcN,” “MeCN” or “$CH_3CN$”refers to acetonitrile, “TFA” refers to trifluoroacetic

acid, "THF" refers to tetrahydrofuran, "NMP" refers to 1-methyl-2-pyrrolidinone, "$H_2O$" refers to water, "BOC" refers to t-butyloxycarbonyl, "brine" refers to a saturated aqueous sodium chloride solution, "M" refers to molar, "mM" refers to millimolar, "μM" refers to micromolar, "nM" refers to nanomolar, "N" refers to normal, "TLC" refers to thin layer chromatography, "HPLC" refers to high performance liquid chromatography, "HRMS" refers to high resolution mass spectrum, "L.O.D." refers to loss on drying, "μCi" refers to microcuries, "i.p." refers to intraperitoneally, "i.v." refers to intravenously, anhyd = anhydrous; aq = aqueous; min = minute; hr = hour; d = day; sat. = saturated; s = singlet, d = doublet; t = triplet; q = quartet; m = multiplet; dd = doublet of doublets; br = broad; LC = liquid chromatograph; MS = mass spectrograph; ESI/MS = electrospray ionization/mass spectrograph; RT = retention time; M = molecular ion, "~" = approximately.

Reactions generally are run under a nitrogen atmosphere. Solvents are dried over magnesium sulfate and are evaporated under vacuum on a rotary evaporator. TLC analyses are performed with EM Science silica gel 60 F254 plates with visualization by UV irradiation. Flash chromatography is performed using Alltech prepacked silica gel cartridges. The $^1H$ NMR spectra are run at 300 MHz on a Gemini 300 or Varian Mercury 300 spectrometer with an ASW 5 mm probe, and usually recorded at ambient temperature in a deuterated solvent, such as $D_2O$, DMSO-$D_6$ or $CDCl_3$ unless otherwise noted. Chemical shifts values (δ) are indicated in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard.

High Pressure Liquid Chromatography-Mass Spectrometry (LCMS) experiments to determine retention times ($R_T$) and associated mass ions are performed using one of the following methods:

Mass Spectra (MS) are recorded using a Micromass mass spectrometer. Generally, the method used was positive electro-spray ionization, scanning mass m/z from 100 to 1000. Liquid chromatography was performed on a Hewlett Packard 1100 Series Binary Pump & Degasser; Auxiliary detectors used were: Hewlett Packard 1100 Series UV detector, wavelength = 220 nm and Sedere SEDEX 75 Evaporative Light Scattering (ELS) detector temperature = 46°C, $N_2$ pressure = 4 bar.

LCT: Grad (AcN+0.05% TFA):($H_2O$+0.05% TFA) = 5:95 (0 min) to 95:5 (2.5 min) to 95:5 (3 min). Column: YMC Jsphere 33x2 4 μM, 1 ml/min

MUX: Column: YMC Jsphere 33x2, 1 ml/min

Grad (AcN+0.05% TFA):(H2O+0.05% TFA) = 5:95 (0 min) to 95:5 (3.4 min) to 95:5 (4.4 min).

LCT2: YMC Jsphere 33x2 4 μM, (AcN+0.05%TFA):(H2O+0.05%TFA) = 5:95 (0 min) to 95:5 (3.4 min) to 95:5 (4.4 min)

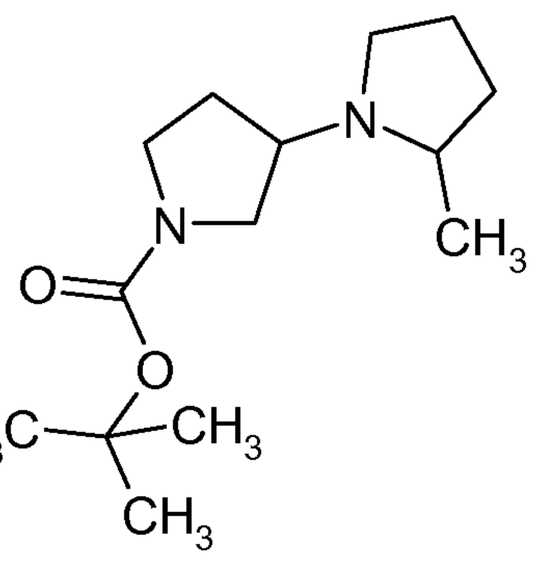
QU: YMC Jsphere 33x2 1ml/min, (AcN+0.08% formic acid):(H2O+0.1% formic acid) = 5:95 (0 min) to 95:5 (2.5min) to 95:5 (3.0min)

The following examples describe the procedures used for the preparation of various starting materials employed in the preparation of the compounds of this invention.

INTERMEDIATES

Intermediate (i)

2-Methyl-[1,3']bipyrrolidinyl-1'-carboxylic acid tert-butyl ester

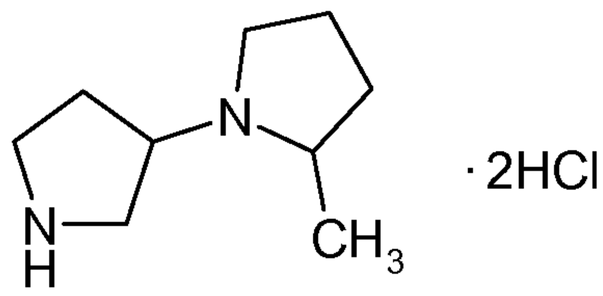


To a solution of N-BOC-3-pyrrolidinone (4.22g, 22.9 mmol) and 2-methylpyrroline (1.95 g, 22.9 mmol) (HCl salt was made by addition of 22.9 mL of 1 M HCl in ether into the DCM solution of 2-methylpyrroline, then evaporated) in DCE (60 mL) was added powdered sodium triacetoxyborohydride slowly under $N_2$ at r.t. The yellowish milky solution was stirred at r.t. overnight. LC/MS - m/z 255 and 199 (base and M-tBu).

The reaction was quenched with aq. $NaHCO_3$ solution. The two layers were separated, and the aqueous layer was extracted with DCM (20 mLx2). The combined DCM extracts were washed with sodium bicarbonate (10 mL), and brine (5 mLx2), dried (anhydrous potassium carbonate), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column, eluted with DCM and 7.5% MeOH in DCM to get the title compound as a liquid 5.50 g (yield: 94%). MS: 255 ($M+H^+$); TLC: 0.5 (10% MeOH in DCM).

Intermediate (ii)

2-Methyl-[1,3']bipyrrolidinyl hydrochloride



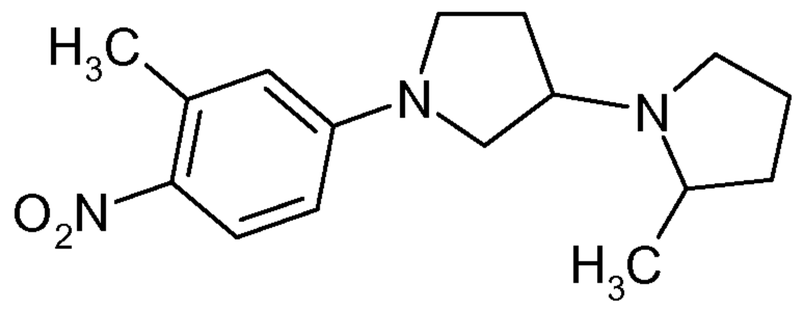
·2HCl

2-Methyl-[1,3']bipyrrolidinyl-1'-carboxylic acid tert-butyl ester (Intermediate (i) obtained above, 5.50 g , 21.62 mmol) was treated with 20 mL of 4 M HCl in dioxane at 0°C. The solution was stirred under nitrogen at r.t. overnight. TLC (10% MeOH in DCM) did not detect the starting material. $N_2$ was passed through the solution with stirring. The outlet was passed though KOH solution to absorb HCl for 30 min. The solvent was removed by evaporation to dryness to get the title compound as a hygroscopic gummy material, 5.3 g (~100 %). This material was used without further purification in subsequent steps as illustrated below. LCMS: $R_T$ = 0.35 minutes, MS: 155 (M+H).

$^1$H NMR ($D_2O$, 300MHz): 4.30 (m), 3.85 (m), 3.76 (s), 3.5 (m), 3.46 (m), 3.32 (m), 2.66 (m), 2.28 (m), 2.10 (m), 1.46 (bs).

Intermediate (iii)

2-Methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3']bipyrrolidinyl

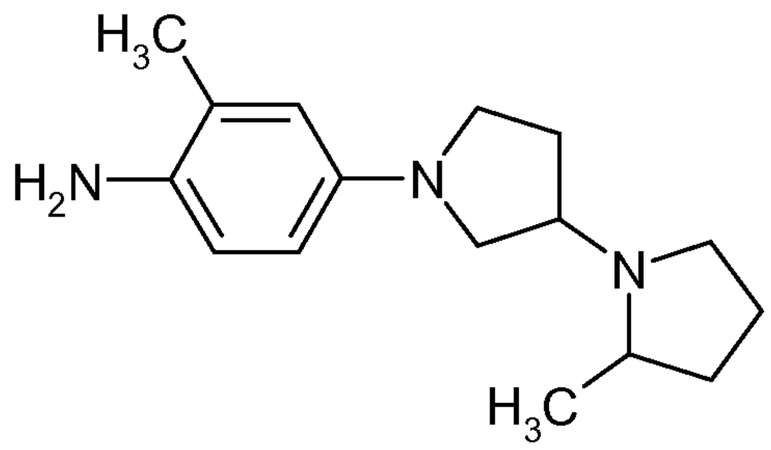


2-Methyl-[1,3']bipyrrolidinyl hydrochloride (Intermediate (ii) obtained above, 5.3 g, 21.6 mmol, 1.12 equiv.) was dissolved in anhydrous DMSO (30 mL). To this solution was added 5-fluoro-2-nitrotoluene (3.00 g, 18.78 mmol, 1 equiv.), followed by powdered potassium carbonate (8.9 g, 65 mmol). The suspension was heated on an oil bath to 85°C for 4h when the starting material was consumed as determined by TLC (5% MeOH in DCM) and LC/MS. To the suspension were added 20 mL of water and 50 mL of DCM. The two layers were separated, and the aqueous layer was extracted with DCM (20 mLx2). The combined DCM extracts were washed with sodium bicarbonate (20 mL), and brine (15 mLx2), dried (anhydrous potassium carbonate), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column, eluted with 5% MeOH in DCM to get the title compound as a yellow solid after drying, 5.47 g (100%). MS: 290 ($M+H^+$).

$^1$H NMR (300 MHz, $CDCl_3$): 8.10 (d, 9Hz, 1H), 6.36 (bd, 9 Hz, 1H), 6.28 (bs, 1H), 3.4-3.2 (m, 5H), 3.00-2.78 (m, 2H), 2.64 (s, 3H), 1.7-2.2 (m, 6H), 1.5 (m, 1H), 1.06 (m, 3H).

Intermediate (iv)

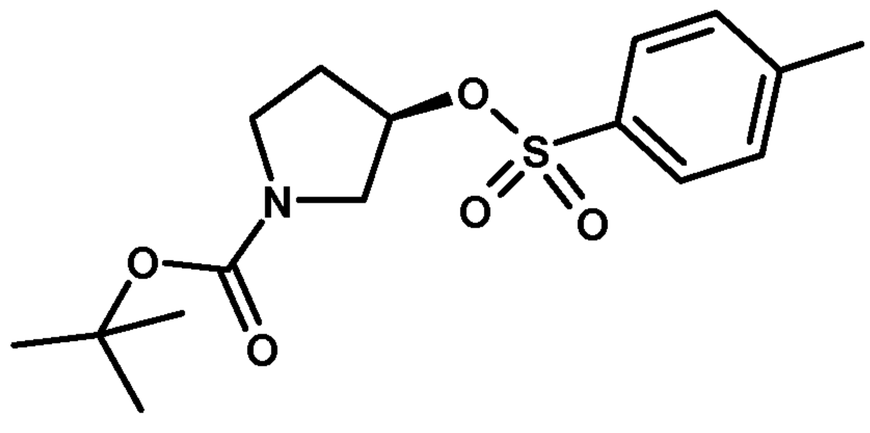
4-(2-Methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine



A solution of 2-methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3']bipyrrolidinyl (Intermediate (iii) obtained above, 2.23 g, 7.7 mmol) in MeOH was de-aerated and nitrogen was introduced. To this solution was added Pd-C (10%). This mixture was stirred under $H_2$ atmosphere at r.t. for 8h. TLC (10% MeOH in DCM) and LC/MS showed the reaction was complete. The mixture was passed through a Celite pad, rinsed with methanol. The filtrate was concentrated to dryness, and further dried under high vacuum to yield a reddish brown liquid after drying under high vacuum to obtain the title compound as a gummy black liquid, 1.73 g (86%). This material was used in the next step without further purification and storage. MS: 260 ($M+H^+$).

Intermediate (v)

3-(3R)-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester



A round-bottomed flask was charged with p-toluenesulfonyl chloride (16.01 g, 83.98 mmol, 1.5 equiv.) and 150 ml of anhydrous DCM. The solution was cooled to an ice-water bath and evacuated and purged with nitrogen. To this solution was added a solution of (3R)-(-)-N-BOC-3-hydroxypyrrolidine (purchased from Aldrich, 10.47 g, 55.99 mmol) in 50 mL of DCM, followed by DMAP (0.66 g) and triethylamine (16.2 mL). The solution was stirred under nitrogen overnight at a temperature from about 0 °C to rt. TLC (5% MeOH in DCM for SM and DCM for product) showed the completion of the reaction. The reaction was quenched by addition of polymer-supported amine (8 g), stirred for 30 min. and 100 mL of DCM was added. The organic layer was washed with $H_3PO_4$ (1M, 2 x 50mL), followed by

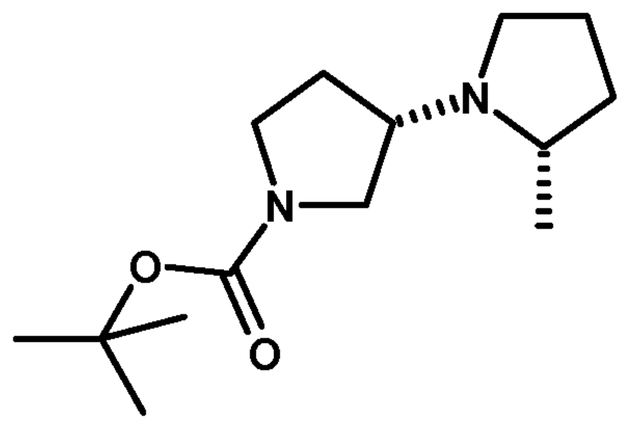
$NaHCO_3$ (50 mL), brine (50 mL), dried ($K_2CO_3$), filtered through a silica gel pad, and concentrated to obtain the title compound as a liquid, 15.82 g (82.8 %).

MS: 363 ($M+Na^+$); TLC (DCM) Rf = 0.3.

$^1H$ NMR ($CDCl_3$, 300MHz), δ (ppm): 7.80 (d, 9.0Hz, 2H), 7.35 (d, 7.8Hz, 2H), 5.04 (bs, 1H), 3.45 (m, 4H), 2.46 (bs, 3H), 2.05 (m, 2H), 1.43 (s, 9H).

Intermediate (vi)

2-(2S)-Methyl-[1,3'(3'S)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester



3-(3R)-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (Intermediate (v) obtained above, 15.82 g, 46.4 mmol, 1 equiv.) and S-(+)-2-methyl-piperindine (purchased from Advanced Asymmetrics, 7.88 g, 92.79 mmol, 2 equiv.) were dissolved in anhydrous $CH_3CN$ (150 mL). To this colorless solution was added powdered $K_2CO_3$ (325 mesh, 98+%, 14.11g, 102.08 mmol, 2.2 equiv.) at r.t. The suspension was heated in an oil bath maintained at 80°C for 24h. TLC (3% MeOH in DCM for SM 7.5% MeOH in DCM for product) showed the SM was consumed almost completely. LC/MS showed very little amount of SM at m/z 363, and the product at 255.

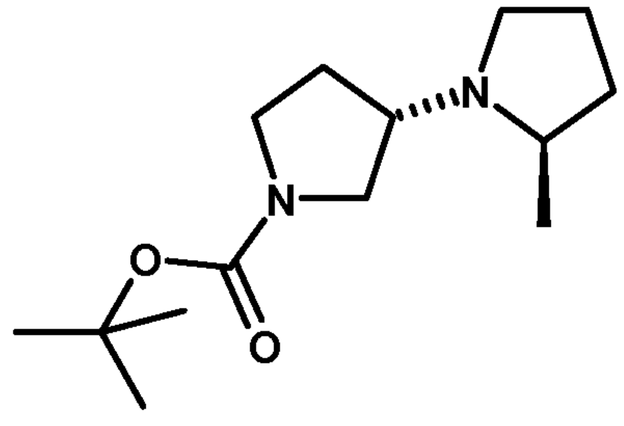
The suspension was concentrated to dryness. The residue was taken in water (25 mL) and DCM (80 mL), the two layers were separated, and the aqueous layer was extracted with DCM (20 mL x 2). The combined DCM extracts were washed successively with sodium bicarbonate (25 mL) and brine (25 mL), dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The crude product was purified on a silica gel column, eluted with MeOH in DCM (0 to 7.5%) to obtain the title compound as a gummy product, 7.91 g (67%).

LCMS: $R_T$ = 1.27 minutes, MS: 255 (M+H).

$^1H$ NMR (300 MHz, $CDCl_3$), δ (ppm): 3.15 (m, 2H), 3.3 (m, 3H), 2.97 (m, 1H), 2.71 (m, 1H), 2.47 (m, 1H), 1.98 (m, 2H), 1.96-1.67 (m, 4H), 1.46 (s, 9H), 1.06 (d, 6.2Hz, 3H).

Intermediate (vii)

2-(2R)-Methyl-[1,3'(3'S)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester

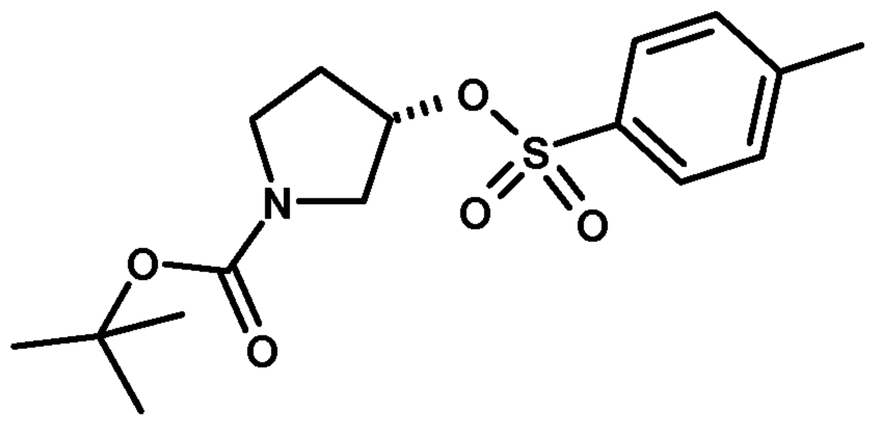


The title compound is prepared in a manner substantially the same as intermediate (vi) by condensing 3-(3R)-(toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (Intermediate (v) obtained above) and R-(-)-2-methylpiperindine (purchased from Advanced Asymmetrics). LCMS: $R_T$ = 1.05 minutes, MS: 255 (M+H).

$^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.30 (m, 1H), 3.14 (bs, 2H), 2.91 (m, 1H), 2.75 (m, 1H), 2.51 (m, 1H), 2.07-1.69 (m, 6H), 1.46 (s, 9H), 1.10 (d, 6.0Hz, 3H).

Intermediate (viii)

3-(3S)-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester



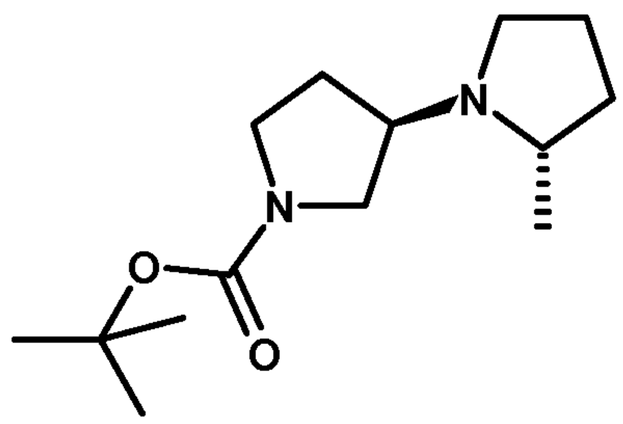
A round bottomed flask was charged with 80 mL of anhydrous DCM. The solvent was evacuated and purged with nitrogen. To this solvent was added (3S)-1-BOC-3-pyrrolidinol (purchased from Astatech, 16.32 g, 33.8 mmol) and DMAP (0.4g). The solution was cooled in an ice-water bath. To this cold solution was transferred a solution of p-toluene-sulfonyl chloride (9.67 g, 50.87 mmol, 1.5 equiv.) in 20 mL of DCM. The ice-water bath was removed and the solution was stirred under nitrogen overnight. TLC (5% MeOH in DCM for SM, I2 visualization; DCM for product, UV) showed the completion of the reaction. The reaction was quenched by addition of polymer-supported amine (4.5 g) and stirred for 30 min. 50 mL of DCM was then added and filtered. The filtration pad was washed with DCM. The organic layer was washed with $H_3PO_4$ (1M, 2 x 50mL), followed by $NaHCO_3$ (50 mL), brine (50 mL), dried ($K_2CO_3$), filtered and concentrated to a liquid. This was purified on a 110 g silica gel column on Analogix using 0-2% MeOH in DCM to obtain pure product, 8.82g (77% yield).

TLC (DCM) Rf = 0.3. LC: Rt = 3.55 min, 100% pure based on total ion, MS: 363 (M+Na); 342, 327, 286 (base).

$^1$H NMR (300MHz, $CDCl_3$), δ (ppm): 7.81 (d, 8.7Hz, 2H), 7.37 (d, 8.7Hz, 2H), 5.04 (bs, 1H), 3.45 (m, 4H), 2.46 (s, 3H), 1.44 (s, 9H).

Intermediate (ix)

2-(2S)-Methyl-[1,3'(3'R)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester

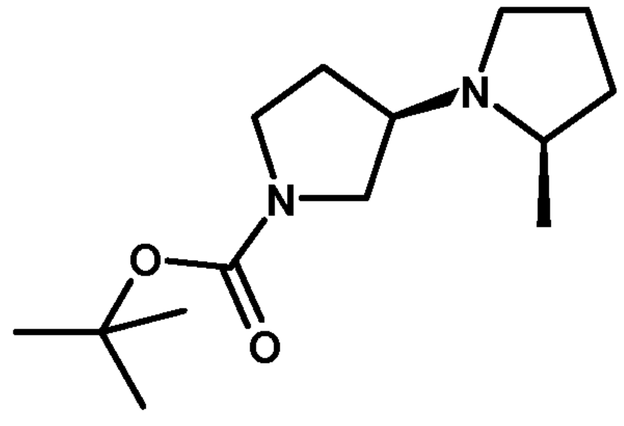


3-(3S)-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (Intermediate (viii) obtained above) (6.82 g, 19.97 mmol, 1 equiv.) and S-(+)-2-methyl-piperindine (purchased from Advanced Asymmetrics, 3.40 g, 40 mmol, 2 equiv.) were dissolved in anhydrous $CH_3CN$ (65 mL). To this colorless solution was added powdered $K_2CO_3$ (325 mesh, 98+%, 6.10g, 44.2 mmol, 2.2 equiv.) at r.t. The suspension was heated with stirring under nitrogen over an oil bath maintained at 80°C for 24h. TLC (3% MeOH in DCM for SM, 7.5% MeOH in DCM for product) showed the SM was consumed almost completely. LC/MS showed very little amount of SM at m/z 363. The suspension was concentrated to dryness. The residue was taken in water (25mL) and DCM (80 mL), the two layers were separated, and the aqueous layer was extracted with DCM (20 mLx2). The combined DCM extracts were washed successively with sodium bicarbonate (25 mL) and brine (25 mL), dried (anhydrous potassium carbonate), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column (70g) on Analogix, eluted with MeOH in DCM (0 to 7.5%) to obtain 4.08g (80.3%) of the title compound as a gummy. LCMS: $R_T$ = 1.14 minutes, MS: 255 (M+H).

$^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.30 (m, 1H), 3.14 (bs, 2H), 2.91 (m, 1H), 2.75 (m, 1H), 2.51 (m, 1H), 2.07-1.69 (m, 6H), 1.46 (s, 9H), 1.10 (d, 6.0Hz, 3H).

Intermediate (x)

2-(2R)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester

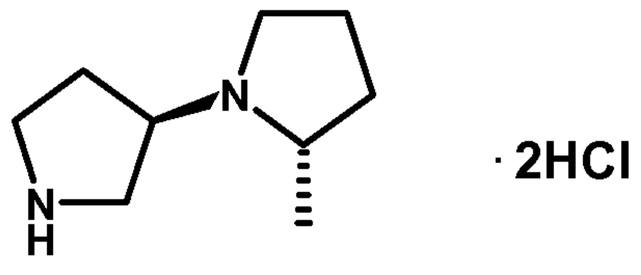


The title compound is prepared in a manner substantially the same as intermediate (ix) by condensing 3-(3S)-(toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (Intermediate (viii) obtained above) and R-(-)-2-methylpiperindine (purchased from Advanced Asymmetrics). LCMS: $R_T$ = 1.09 minutes, MS: 255 (M+H).

$^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.15 (m, 2H), 3.3 (m, 3H), 2.97 (m, 1H), 2.71 (m, 1H), 2.47 (m, 1H), 1.98 (m, 2H), 1.96-1.67 (m, 4H), 1.46 (s, 9H), 1.06 (d, 6.2Hz, 3H).

Intermediate (xi)

2(2S)-Methyl-[1,3'(3'R)]bipyrrolidinyl



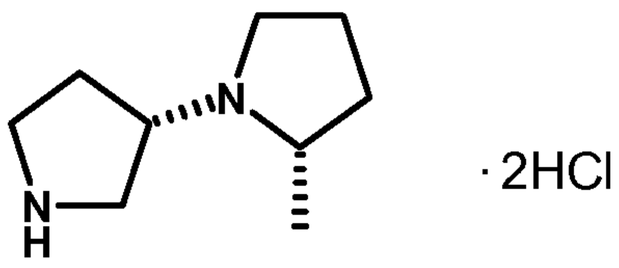
· 2HCl

2-(2S)-Methyl-[1,3'(3'R)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester (7.91 g , 31.14 mmol) was treated with 28.8 mL of HCl in dioxane at 0°C. The solution was stirred under nitrogen at r.t. overnight. Both TLC (10% MeOH in DCM) and LC/MS did not detect the starting material. Nitrogen was purged through the solution with stirring. The outlet was passed through KOH solution to absorb HCl for 1h. The solvent was removed by evaporation to dryness to get the title compound as a hygroscopic thick gummy product (2HCl salt, hydrated. exact composition unknown), 8.07 g (~100 %). MS: 155 (M+H).

$^1$H NMR: ($D_2O$, 300 MHz), δ (ppm): 11.6 (bs, 1H), 9.1 (bs, 1H) 4.12 ( m, 1H) 3.5, (m, 2H), 3.3-3.1 ( m, 3H), 2.4-2.1 (m, 4H), 2.4(m, 2H), 1.6 (m, 1H), 1.4(d, 6.0 Hz,3H).

Intermediate (xii)

2(2S)-Methyl-[1,3'(3'S)]bipyrrolidinyl



· 2HCl

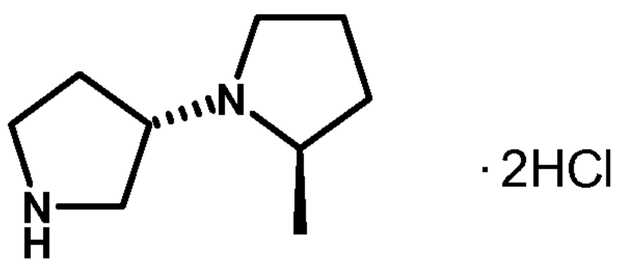
The title compound was prepared in a manner substantially the same as intermediate (xi) by acid hydrolysis of 2-(2S)-methyl-[1,3'(3'S)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester (Intermediate (vi) obtained above).

LCMS: $R_T$ = 0.37 minutes, MS: 155 (M+H).

$^1$H NMR: ($D_2O$, 300 MHz), δ (ppm): 11.6 (bs, 1H), 9.1 (bs, 1H) 4.12 ( m, 1H) 3.5, (m, 2H), 3.3-3.1 ( m, 3H), 2.4-2.1 (m, 4H), 2.4(m, 2H), 1.6 (m, 1H), 1.4(d, 6.0 Hz,3H)

Intermediate (xiii)

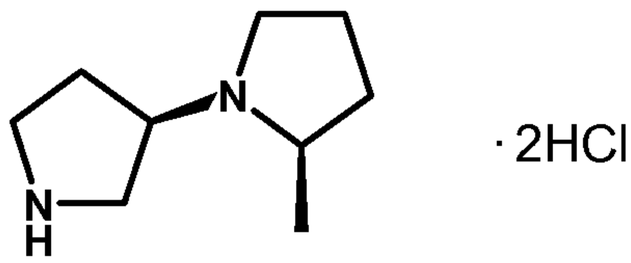
2(2R)-Methyl-[1,3'(3'S)]bipyrrolidinyl



The title compound was prepared in a manner substantially the same as intermediate (xi) by acid hydrolysis of 2-(2R)-methyl-[1,3'(3'S)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester (Intermediate (vii) obtained above).

Intermediate (xiv)

2(2R)-Methyl-[1,3'(3'R)]bipyrrolidinyl

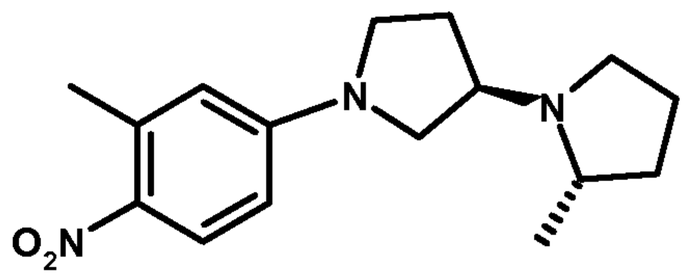


The title compound was prepared in a manner substantially the same as intermediate (xi) by acid hydrolysis of 2-(2R)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-carboxylic acid tert-butyl ester (Intermediate (x) obtained above). MS: 155.

$^1$H NMR: ($D_2O$, 300 MHz), δ (ppm): 11.6 (bs, 1H), 9.1 (bs, 1H) 4.12 ( m, 1H) 3.5, (m, 2H), 3.3-3.1 ( m, 3H), 2.4-2.1 (m, 4H), 2.4(m, 2H), 1.6 (m, 1H), 1.4(d, 6.0 Hz,3H).

Intermediate (xv)

2-(2S)-Methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'R)]bipyrrolidinyl



2(2S)-Methyl-[1,3'(3'R)] bipyrrolidinyl (0.23g, 1.2 mmol) was dissolved in anhydrous DMSO (5 mL) taken in a flask. To this solution was added 5-fluoro-2-nitrotoluene (223 mg, 1.44 mmol), followed by powdered anhydrous potassium carbonate (662 mg, 4.8 mmol). The

suspension was heated on an oil bath to 85°C (bath temperature) for 4h when the starting material was consumed as confirmed by TLC (5% MeOH/DCM) and LC/MS. MS showed 290 (base).

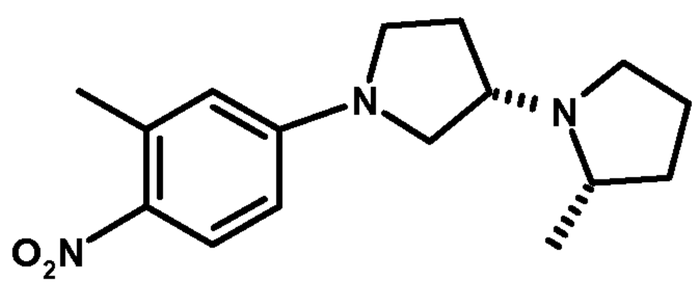
To the suspension were added 2 mL of water and 5 mL of DCM. The two layers were separated, and the aqueous layer was extracted with DCM (10 mLx2). The combined DCM extracts were washed with sodium bicarbonate (5 mL), and brine (5 mLx2), dried (anhydrous potassium carbonate), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column, eluted with 5% MeOH in DCM to obtain the title compound as a yellow solid after drying. LCMS: $R_T$ = 1.38 minutes, MS: 290 (M+H).

$^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.10 (d, 9.1Hz, 1H), 6.36 (dd, 9.2, 2.5 Hz, 1H), 6.28 (d, 2.4 Hz, 1H), 3.654(m, 2H), 3.37 (m, 3H), 2.99 (dt, 3.7Hz, 8.8Hz,1H), 2.84 (sixtet, 6.6Hz, 1H), 2.65 (s, 3H), 2.56 (q , 8.1Hz, 1H), 2.31 (m, 2H), 2.11 (m ,2H) 1.87 (m,1H), 1.08 (d, 6.2Hz, 3H).

The analytical chiral HPLC conditions used were as follows: Isocratic 100% isopropanol with 0.5% IPAmine 5ml/min outlet pressure 150 bar, 200 nM. The results obtained were as follows: $R_T$ = 10.92 min; ee 100%.

Intermediate (xvi)

2-(2S)-Methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'S)]bipyrrolidinyl



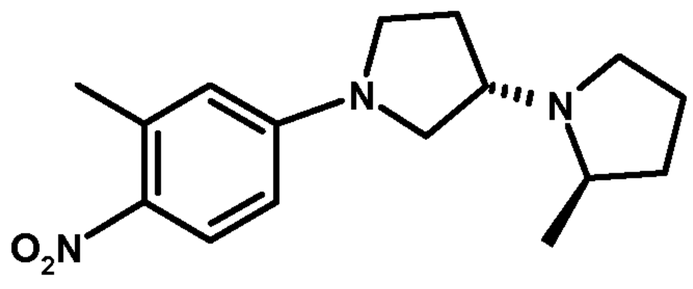

The title compound was prepared in a manner substantially the same as intermediate (xv) by condensing 2(2S)-methyl-[1,3'(3S)]bipyrrolidinyl and 5-fluoro-2-nitrotoluene. LCMS: $R_T$ = 1.43 minutes, MS: 290 (M+H).

$^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.10 (d, 9.2Hz, 1H), 6.36 (dd, 9.2, 2.8 Hz, 1H), 6.28 (d, 2.2 Hz, 1H), 3.6 (m, 2H), 3.3 (m, 3H), 3.00-2.78 (dt, 3.5Hz, 8.8Hz,2H), , 2.79 (m, 1H), 2.64 (s, 3H), 2.56 (m, 1H), 2.03 (m, 2H), 1.98 (m ,2H) 1.45 (m,1H), 1.08 (d, 6.2Hz, 3H).

The analytical chiral HPLC conditions used were as follows: Isocratic 100% isopropanol with 0.5% IPAmine 5ml/min outlet pressure 150 bar, 200 nM. The results obtained were as follows: $R_T$ = 8.16 min; ee 100%.

Intermediate (xvii)

2-(2R)-Methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'S)]bipyrrolidinyl



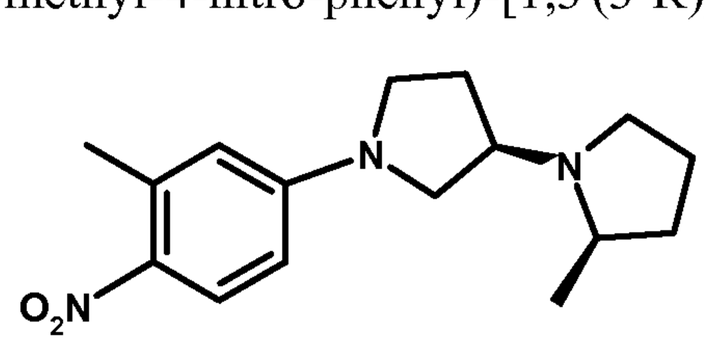
The title compound was prepared in a manner substantially the same as intermediate (xv) by condensing 2(2R)-methyl-[1,3'(3'S)]bipyrrolidinyl and 5-fluoro-2-nitrotoluene. LCMS: $R_T$ = 1.41 minutes, MS: 290 (M+H).

$^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.10 (d, 9.1Hz, 1H), 6.36 (dd, 9.2, 2.5 Hz, 1H), 6.28 (d, 2.4 Hz, 1H), 3.654(m, 2H), 3.37 (m, 3H), 2.99 (dt, 3.7Hz, 8.8Hz,1H), 2.84 (sixtet, 6.6Hz, 1H), 2.65 (s, 3H), 2.56 (q , 8.1Hz, 1H), 2.31 (m, 2H), 2.11 (m ,2H) 1.87 (m,1H), 1.08 (d, 6.2Hz, 3H).

The analytical chiral HPLC conditions used were as follows: Isocratic 100% isopropanol with 0.5% IPAmine 5ml/min outlet pressure 150 bar, 200 nM. The results obtained were as follows: $R_T$ = 11.93 min; ee 100%.

Intermediate (xviii)

2-(2R)-Methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'R)]bipyrrolidinyl



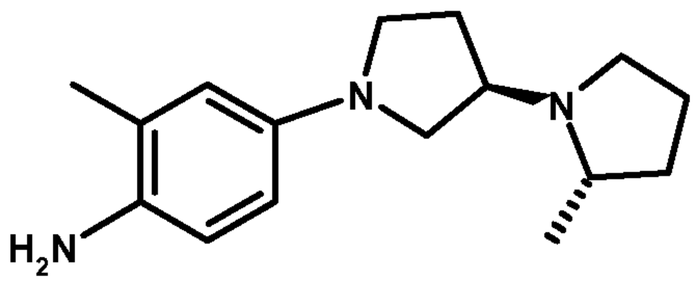
The title compound was prepared in a manner substantially the same as intermediate (xv) by condensing 2(2R)-Methyl-[1,3'(3'R)]bipyrrolidinyl and 5-fluoro-2-nitrotoluene. LCMS: $R_T$ = 1.43 minutes, MS: 290 (M+H).

$^1$H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.10 (d, 9.2Hz, 1H), 6.36 (dd, 9.2, 2.8 Hz, 1H), 6.28 (d, 2.2 Hz, 1H), 3.6 (m, 2H), 3.3 (m, 3H), 3.00-2.78 (dt, 3.5Hz, 8.8Hz,2H), , 2.79 (m, 1H), 2.64 (s, 3H), 2.56 (m, 1H), 2.03 (m, 2H), 1.98 (m ,2H) 1.45 (m,1H), 1.08 (d, 6.2Hz, 3H).

The analytical chiral HPLC conditions used were as follows: Isocratic 100% isopropanol with 0.5% IPAmine 5ml/min outlet pressure 150 bar, 200 nM. The results obtained were as follows: $R_T$ = 8.95 min; ee 100%.

Intermediate (xix)

2-Methyl-4-(2-(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenylamine

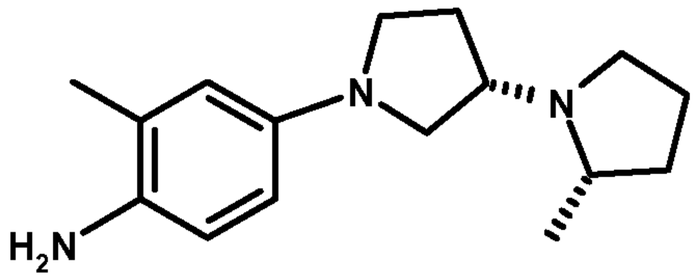


A solution of 2-(2S)-methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'R)]bipyrrolidinyl (2.02 g, 6.98 mmol) in MeOH (40 mL) was de-aerated and nitrogen was introduced. To this solution was added Pd-C (10%, 0.2g). This mixture was stirred under $H_2$ atmosphere at r.t. for 4h at which time the TLC (10% MeOH in DCM) and LC/MS showed that the reaction was complete, and the product was detected by MS at 261. The mixture was passed through a Celite pad, rinsed with methanol. The filtrate was concentrated to dryness, and further dried to yield the title compound as a reddish brown liquid after drying under high vacuum, 1.81g (100%). LC/MS: 260, TLC (10%MeOH/DCM): 0.3 Rf.

This material was used immediately without storage and further purification.

Intermediate (xx)

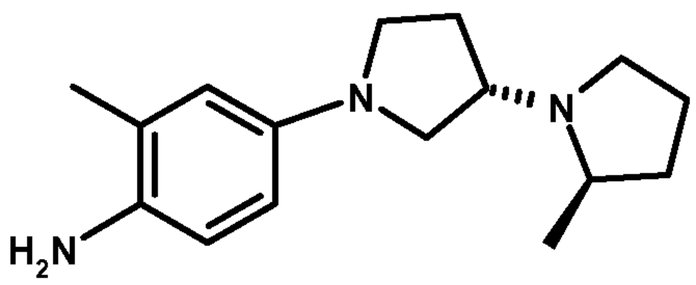
2-Methyl-4-(2-(2S)-methyl-[1,3'(3'S)]bipyrrolidinyl-1'-yl)-phenylamine



The title compound was prepared in a manner substantially the same as intermediate (xx) by hydrogenation of 2-(2S)-methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'S)]bipyrrolidinyl. LC/MS: 260, TLC (10%MeOH/DCM): 0.3 Rf.

Intermediate (xxi)

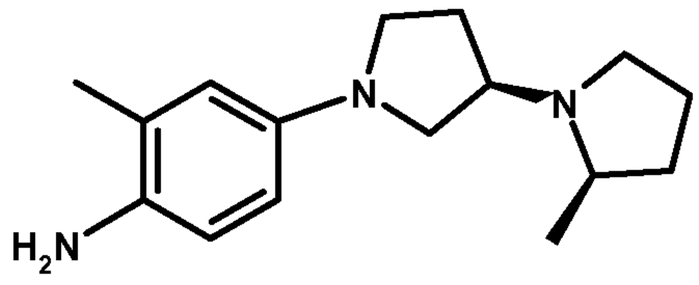
2-Methyl-4-(2-(2R)-methyl-[1,3'(3'S)]bipyrrolidinyl-1'-yl)-phenylamine



The title compound was prepared in a manner substantially the same as intermediate (xx) by hydrogenation of 2-(2R)-methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'S)]bipyrrolidinyl. LC/MS: 260, TLC (10%MeOH/DCM): 0.3 Rf.

Intermediate (xxii)

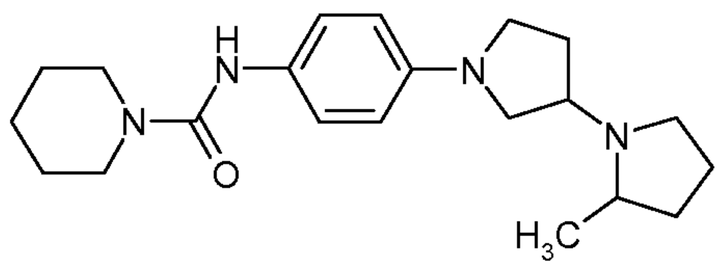
2-Methyl-4-(2(2R)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenylamine



The title compound was prepared in a manner substantially the same as intermediate (xx) by hydrogenation of 2-(2R)-Methyl-1'-(3-methyl-4-nitro-phenyl)-[1,3'(3'R)]bipyrrolidinyl. LC/MS: 260, TLC (10%MeOH/DCM): 0.3 Rf.

Example 1

Piperidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate



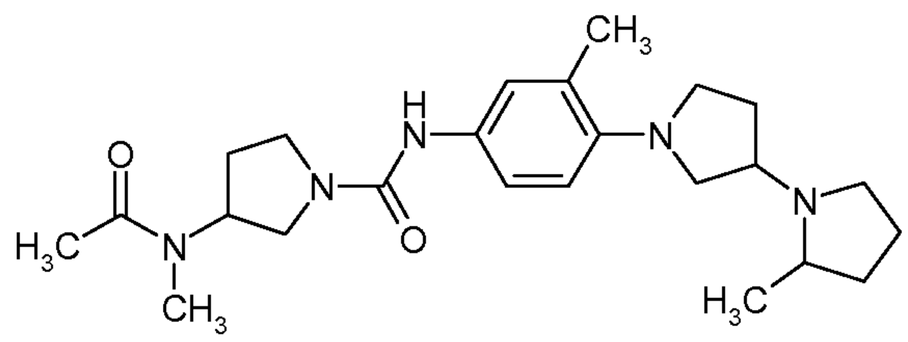
.$CF_3CO_2H$

A mixture of 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine (34 mg, 0.13 mmol, diastereoisomeric mixture), piperidine (12 mg, 0.14 mmol) and carbonyl diimidazole (26 mg, 0.16 mmol) in 3 ml of DMF was heated at 80° for 14h, filtered, and evaporated. RP-HPLC gave 10 mg (16%) of the title compound.

LCMS: $R_T$ = 1.05 minutes, MS: 357.3 (M+H).

Example 2

3-(Acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

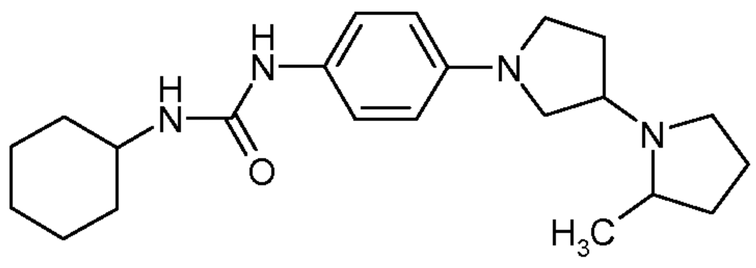


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3-(acetyl-methyl-amino)-pyrrolidine and carbonyl diimidazole. MS: 428.3 (M+H).

Example 3

1-Cyclohexyl-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

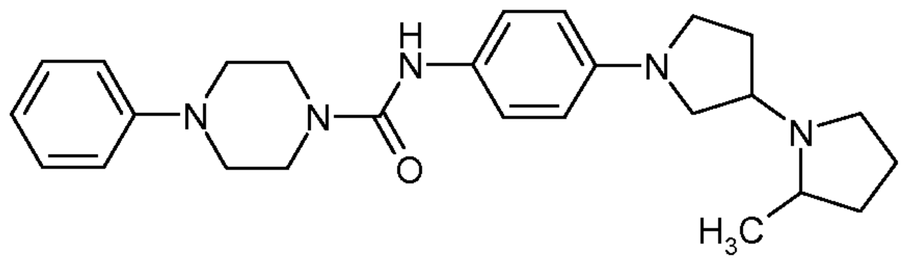


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with cyclohexylamine and carbonyl diimidazole. MS: 371.3 (M+H).

Example 4

4-Phenyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

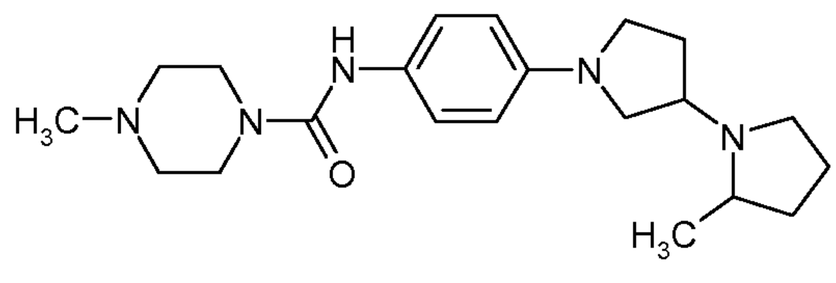


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 4-phenyl-piperazine and carbonyl diimidazole. MS: 434.3 (M+H).

Example 5

4-Methyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

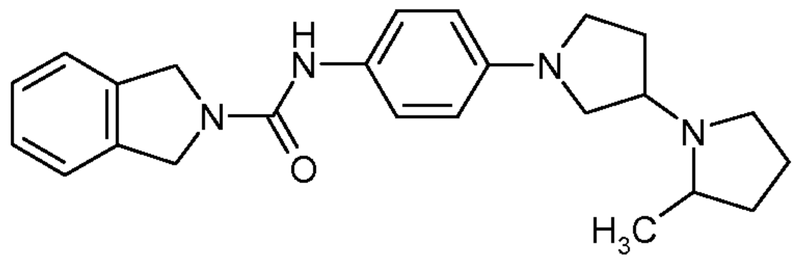


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 4-methyl-piperazine and carbonyl diimidazole. MS: 372.3 (M+H).

Example 6

1,3-Dihydro-isoindole-2-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

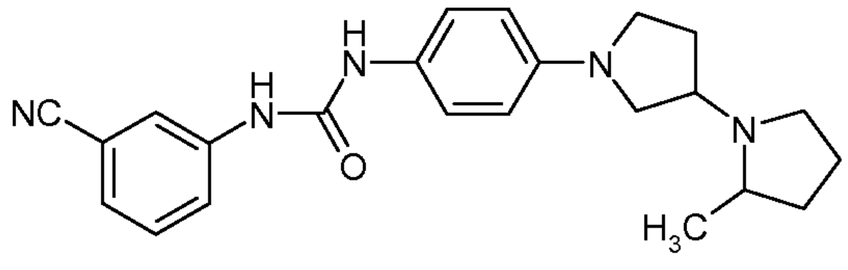


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 1,3-dihydro-isoindole and carbonyl diimidazole. MS: 391.3 (M+H).

Example 7

1-(3-Cyano-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

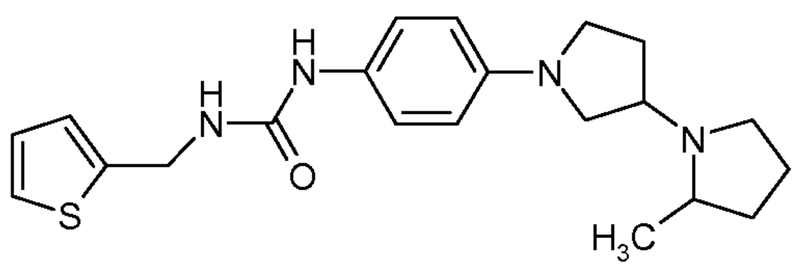


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3-cyano-aniline and carbonyl diimidazole. MS: 390.2 (M+H).

Example 8

1-[4-(2-Methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea trifluoroacetate

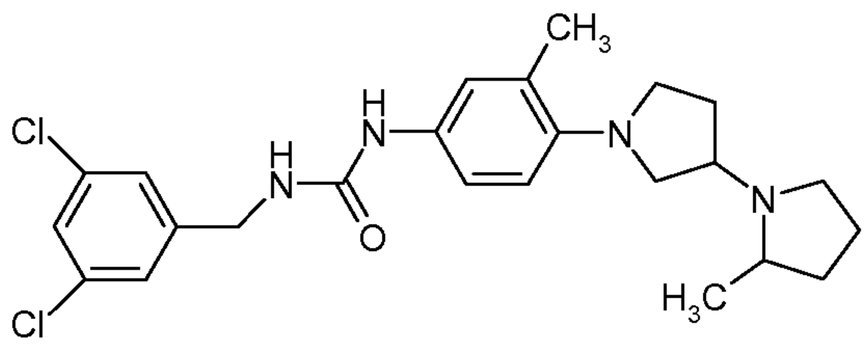


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with thiophen-2-ylmethyl amine and carbonyl diimidazole. MS: 385.2 (M+H).

Example 9

1-(3,5-Dichloro-benzyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

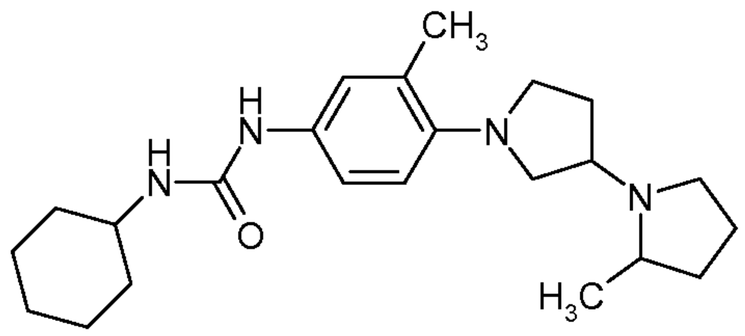


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3,5-dichloro-benzyl amine and carbonyl diimidazole. MS: 461.2 (M+H).

Example 10

1-Cyclohexyl-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

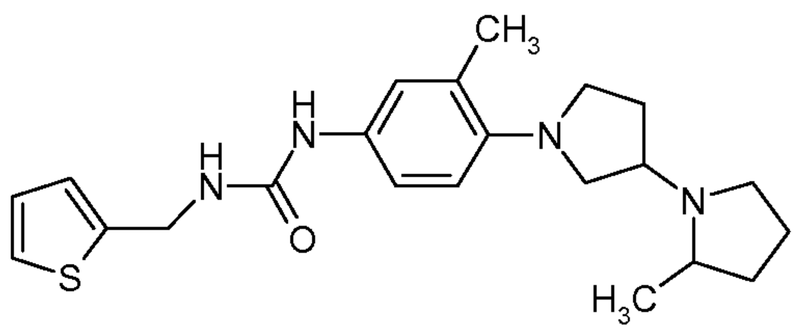


$.CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with cyclohexyl amine and carbonyl diimidazole. MS: 385.3 (M+H).

Example 11

1-[3-Methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea trifluoroacetate

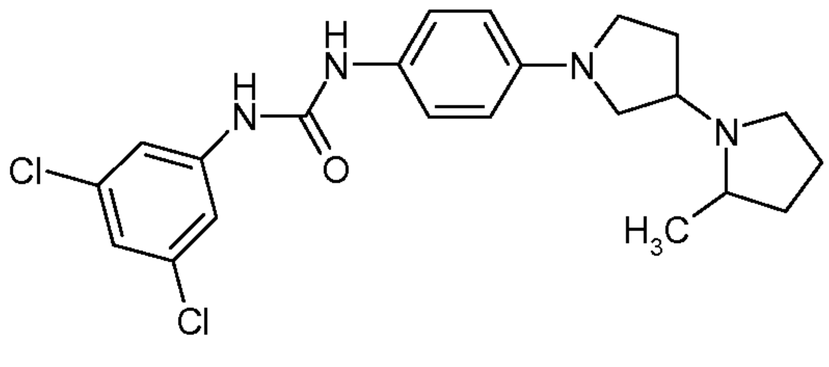


$.CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with thiophen-2-ylmethylamine and carbonyl diimidazole. MS: 399.2 (M+H).

Example 12

1-(3,5-Dichloro-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

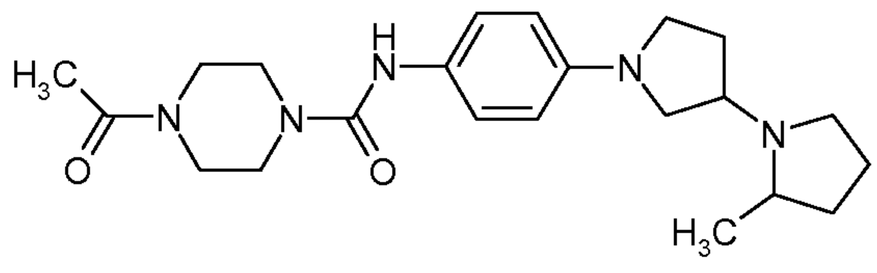


$.CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3,5-dichloro-phenyl amine and carbonyl diimidazole. MS: 433.2 (M+H).

Example 13

4-Acetyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

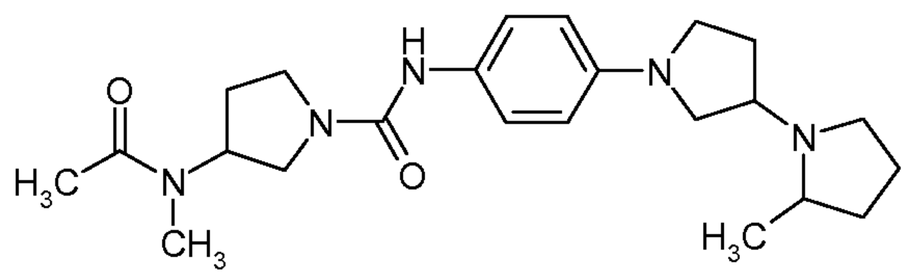


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 1-piperazin-1-yl-ethanone and carbonyl diimidazole. MS: 400.3 (M+H).

Example 14

3-(Acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

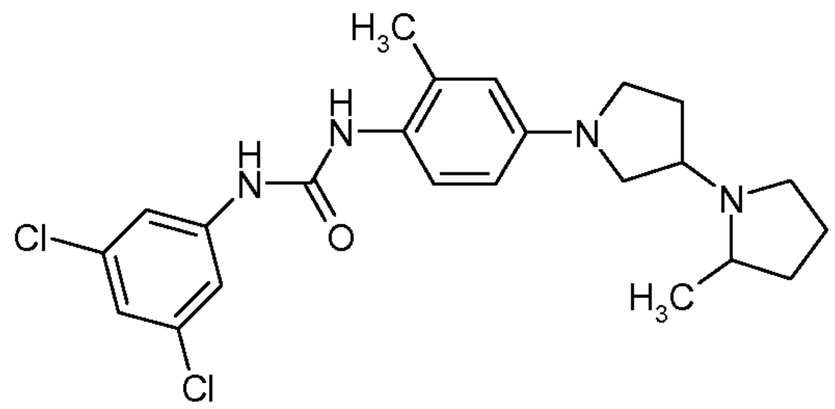


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3-(acetyl-methyl-amino)-pyrrolidine and carbonyl diimidazole. MS: 414.3 (M+H).

Example 15

1-(3,5-Dichloro-phenyl)-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

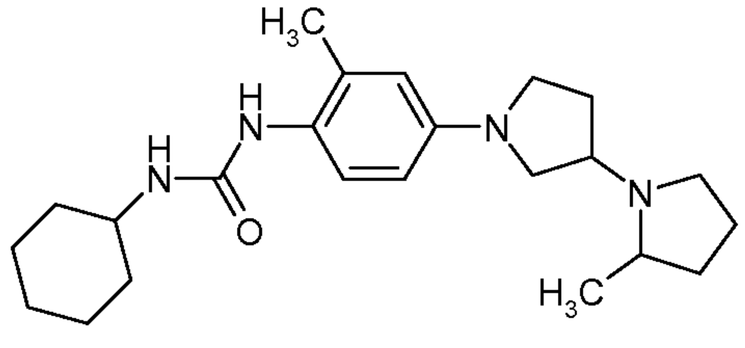


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3,5-dichloro-phenyl amine and carbonyl diimidazole. MS: 447.2 (M+H).

Example 16

1-Cyclohexyl-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

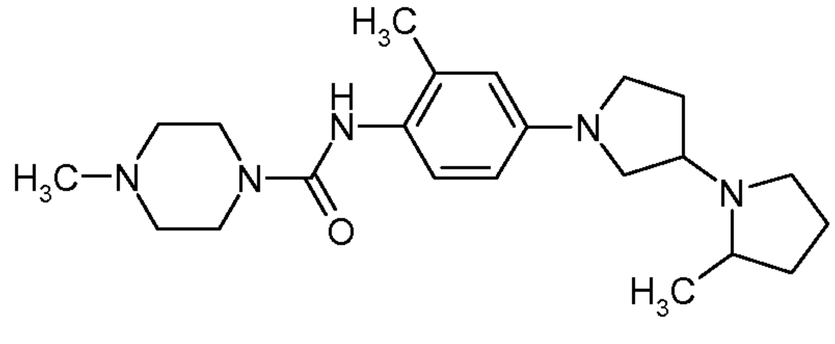


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with cyclohexyl amine and carbonyl diimidazole. MS: 385.3 (M+H).

Example 17

4-Methyl-piperazine-1-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

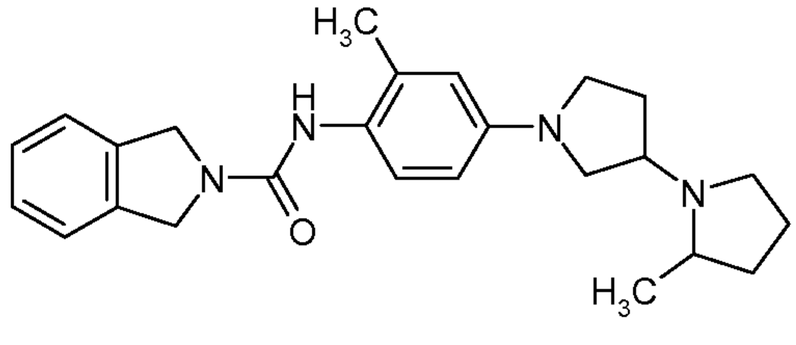


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with N-methyl-piperazine and carbonyl diimidazole. MS: 386.3 (M+H).

Example 18

1,3-Dihydro-isoindole-2-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

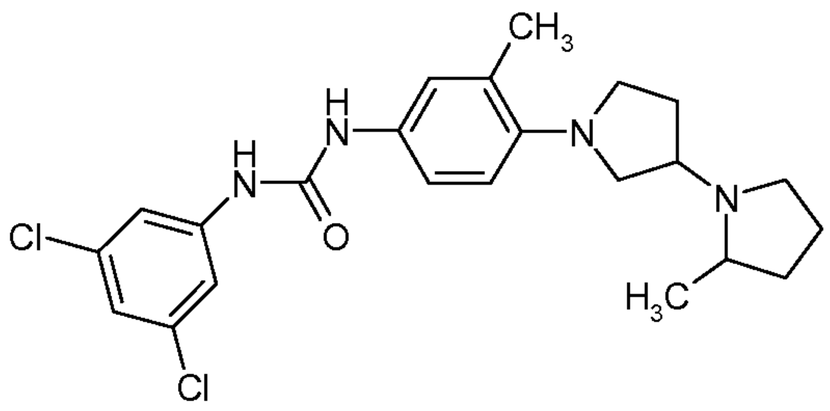


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 1,3-dihydro-isoindole and carbonyl diimidazole. MS: 405.3 (M+H).

Example 19

1-(3,5-Dichloro-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

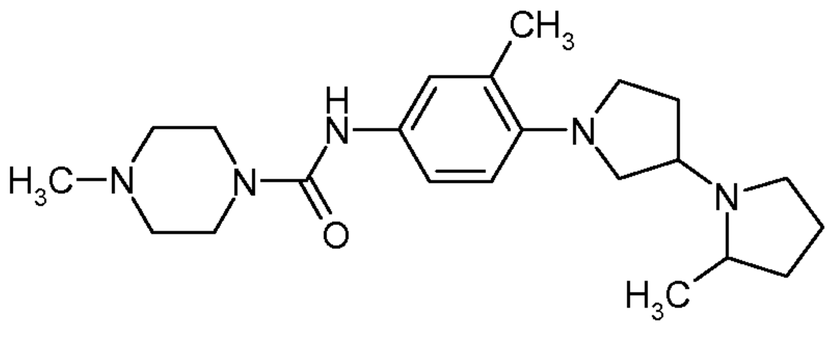


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3,5-dichloro-phenylamine and carbonyl diimidazole. MS: 447.2 (M+H).

Example 20

4-Methyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

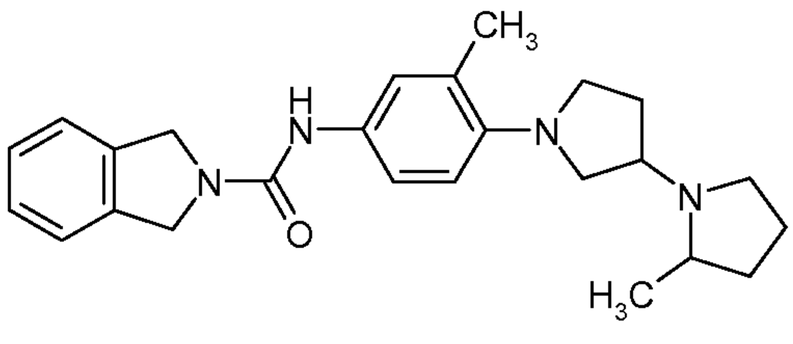


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with N-methyl-piperazine and carbonyl diimidazole. MS: 386.3 (M+H).

Example 21

1,3-Dihydro-isoindole-2-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

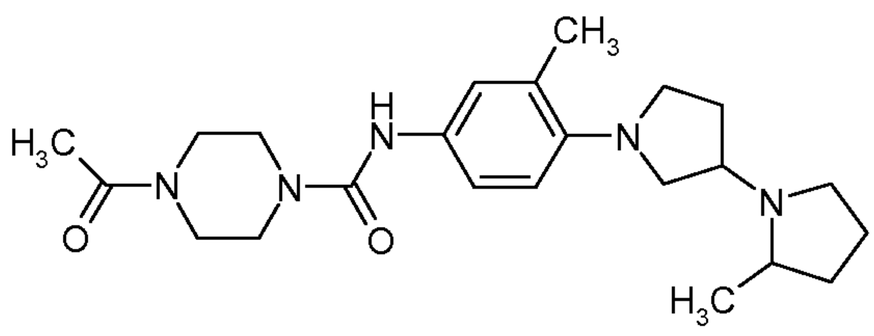


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 1,3-dihydro-isoindole and carbonyl diimidazole. MS: 405.3 (M+H).

Example 22

4-Acetyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

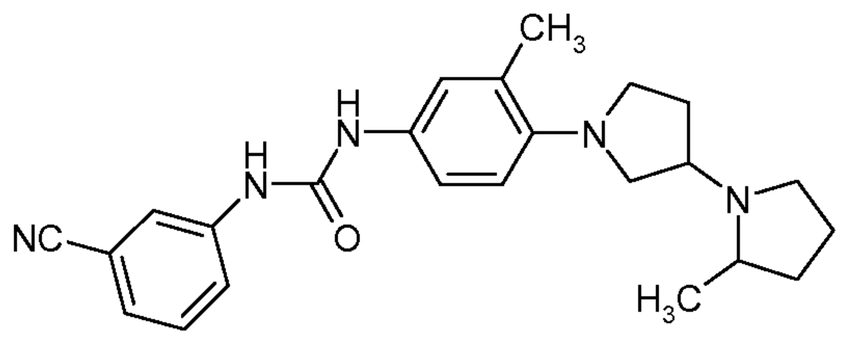


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 1-piperazin-1-yl-ethanone and carbonyl diimidazole. MS: 414.3 (M+H).

Example 23

1-(3-Cyano-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea trifluoroacetate

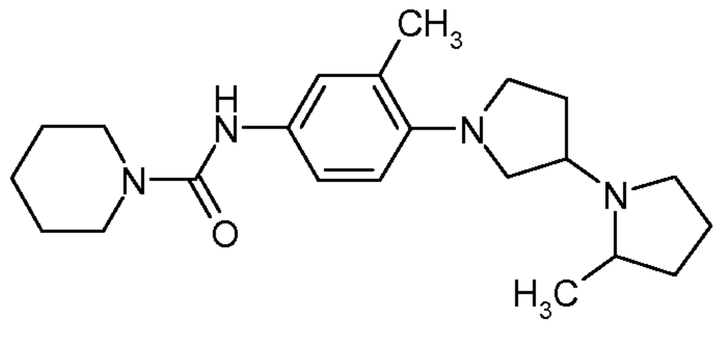


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with 3-cyano-phenylamine and carbonyl diimidazole. MS: 404.3 (M+H).

Example 24

Piperidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide trifluoroacetate

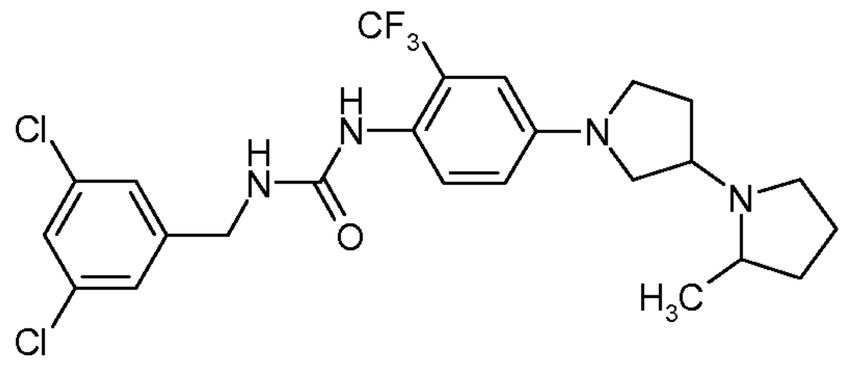


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling 3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenylamine with piperidine and carbonyl diimidazole. MS: 371.3 (M+H).

Example 25

1-(3,5-Dichloro-benzyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-2-trifluoromethyl-phenyl]-urea trifluoroacetate

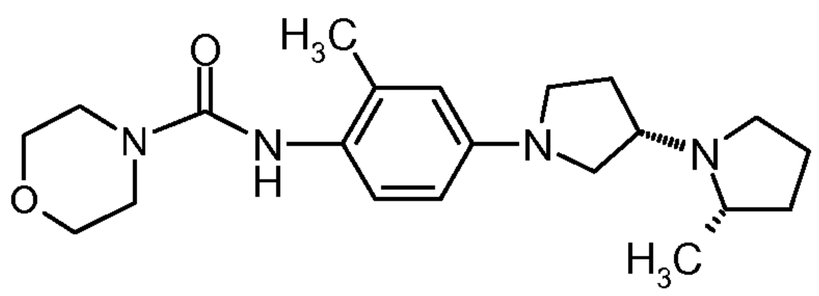


.$CF_3CO_2H$

The title compound was prepared in a manner substantially the same as Example 1 by coupling (2-methyl-[1,3']bipyrrolidinyl-1'-yl)-2-trifluoromethyl-phenylamine with 3,5-dichloro-benzylamine and carbonyl diimidazole. MS: 371.3 (M+H).

Example 26

Morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3' (3'S)]bipyrrolidinyl-1'-yl)-phenyl]-amide



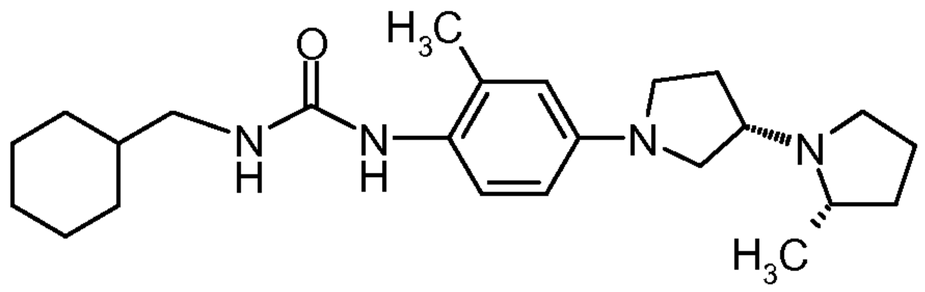
Step 1: 2-Methyl-4-(2-(2S)methyl-[1,3']-(3'S)bipyrrolidinyl-1'-yl)-phenylamine (50 mg, 0.2 mmol) was dissolved in DCM (5 mL). The solution was cooled to an ice-water bath. To this cold solution was added a solution of nitro-phenyl chloroformate (68 mg, 0.34 mmol, 1.8 equiv.) in 1 mL of DCM, followed by 0.5 mL of pyridine. The solution was stirred under nitrogen at 0°C for 30 min., and then at rt for 1.5 h. The intermediate showed Rf 0.75 in TLC (10% Methanol in DCM); LC/MS: retention time: 3.172 min, MS: 425.2. This intermediate in solution was used in the next step without further purification.

Step 2: To the above reaction mixture was added 200 mg of morpholine at rt. The clear brownish solution was stirred at rt overnight. TLC (10% methanol in DCM) showed the disappearance of the intermediate carbamate, and the product at Rf 0.55. MS: 373.3. The reaction was quenched by addition of 3 mL of saturated sodium bicarbonate solution and 3 mL of DCM. The two layers were separated, and the aqueous layer was extracted with DCM (2 mLx2). The combined DCM extracts were washed successively with sodium bicarbonate (2 mL) and brine (2 mLx2), dried (anhydrous potassium carbonate), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column, eluted with 0-10 % MeOH in DCM to obtain the title compound 29.6 mg (32% yield) as a solid after drying. LC/MS: retention time: $T_R$ = 1.32 min., MS = 373.3.

$^1$H NMR ($CDCl_3$, 300MHz), δ (ppm): 7.19 (d, 9.3Hz, 1H), 6.38 (m, 1H), 6.36 (s, 1H), 5.84 (s, 1H), 3.73 (m, 4H), 3.49 (m, 2H), 3.44 (m, 4H), 3.25 (m, 2H), 3.19 (m, 1H), 2.77 (m, 1H), 2.54 (m, 1H), 2.21 (s, 3H), 2.02-1.75 (m, 3H), 1.56-1.40 (m, 4H), 1.14 (d, 5.8Hz, 3H).

Example 27

1-Cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'S)]bipyrrolidinyl-1'-yl)-phenyl]-urea

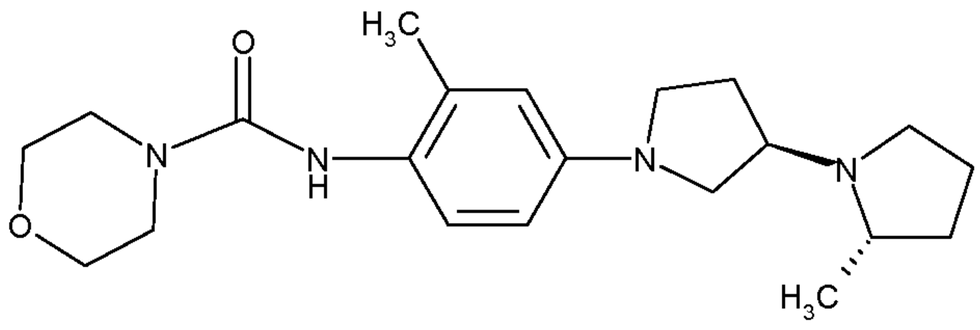


The title compound was prepared in a manner substantially the same as example 26 by coupling 2-methyl-4-(2(2S)-methyl-[1,3'(3'S)]bipyrrolidinyl-1'-yl)-phenylamine with cyclohexyl-methylamine in 52% yield. LCMS: $R_T$ = 2.93 minutes, MS: 399.31 (M+H).

$^1$H NMR ($CDCl_3$, 300MHz), δ (ppm): 7.06 (d, 8.2Hz, 1H), 6.39 (m, 1H), 6.37 (s, 1H), 5.65 (s, 1H), 3.73 (m, 4H), 4.46 (m, 1H), 3.54 (m, 1H), 3.40-3.25 (m, 4H), 3.02 (m, 3H), 2.81 (m, 1H), 2.57 (m, 1H), 2.24 (s, 3H), 2.06-1.96 (m, 4H), 1.85-1.60 (m, 10H), 1.49 (m, 1H), 1.21 (m, 1H), 1.15 (d, 6.2Hz, 3H), 0.85 (m, 1H).

Example 28

Morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide

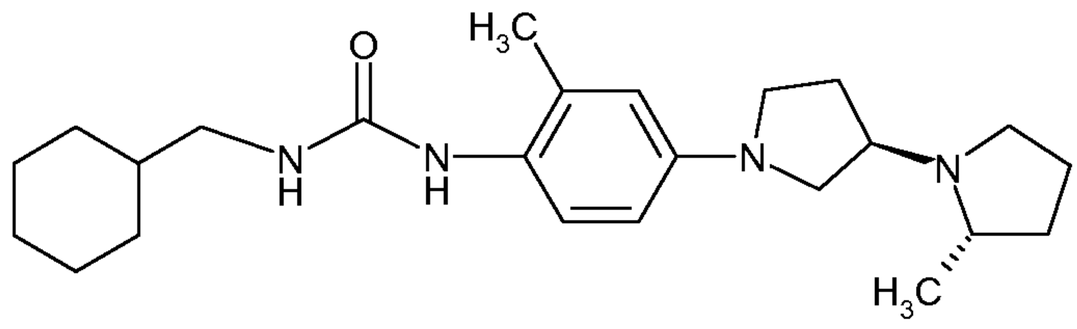


The title compound was prepared in a manner substantially the same as example 26 by coupling 2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenylamine with morpholine in 81% yield. LC/MS: retention time: $T_R$ = 1.27 min., MS = 373.3.

$^1$H NMR ($CDCl_3$, 300MHz), δ (ppm): 7.19 (d, 9.7Hz, 1H), 6.39 (m, 1H), 6.37 (s, 1H), 5.85 (s, 1H), 3.73 (m, 4H), 3.45 (m, 4H), 3.40-3.26 (m, 4H), 3.19 (m, 1H), 2.99 (m, 1H), 2.80 (m, 1H), 2.78 (m, 1H), 2.21 (s, 3H), 2.06-1.73 (m, 4H), 1.56-1.40 (m, 2H), 1.15 (d, 6.2Hz, 3H).

Example 29

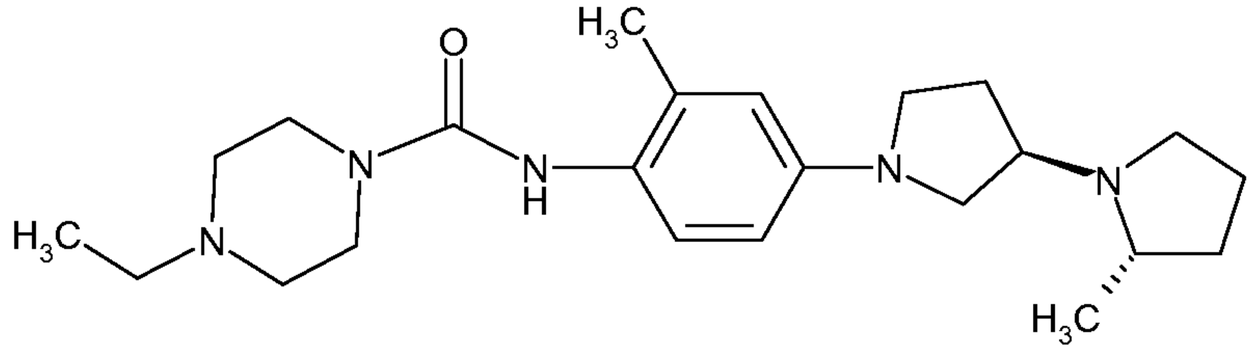
1-Cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea



The title compound was prepared in a manner substantially the same as example 26 by coupling 2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenylamine with cyclohexyl-methylamine in 71 % yield. LCMS: $R_T$ = 3.04 minutes, MS: 399.31 (M+H). $^1$H NMR ($CDCl_3$, 300MHz), δ (ppm): 7.06 (d, 8.3Hz, 1H), 6.39 (m, 1H), 6.37 (s, 1H), 5.63 (s, 1H), 3.73 (m, 4H), 4.45 (m, 1H), 3.43-3.25 (m, 5H), 3.02 (m, 3H), 2.89 (m, 1H), 2.58 (m, 1H), 2.24 (s, 3H), 2.06-1.96 (m, 4H), 1.85-1.60 (m, 10H), 1.49 (m, 1H), 1.21 (m, 1H), 1.16 (d, 6.3Hz, 3H), 0.85 (m, 1H).

Example 30

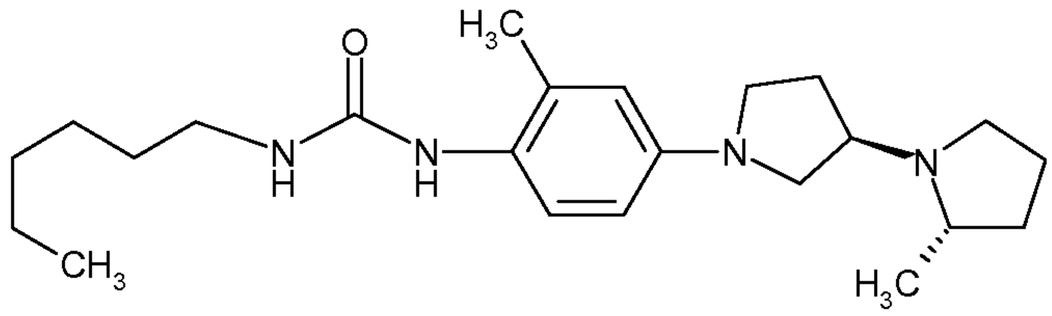
4-Ethyl-piperazine-1-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide



The title compound was prepared in a manner substantially the same as example 26 by coupling 2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenylamine with N-1-ethyl-piperazine in 76 % yield. LCMS: $R_T$ = 2.15 minutes, MS: 400.30 (M+H). $^1$H NMR ($CDCl_3$, 300MHz), δ (ppm): 7.06 (d, 8.3Hz, 1H), 6.39 (m, 1H), 6.37 (s, 1H), 5.83 (s, 1H), 3.58 (m, 4H), 3.43-3.25 (m, 5H), 3.02 (m, 1H), 2.89 (m, 1H), 2.58 (m, 1H), 2.58 (m, 6H), 2.24 (s, 3H), 2.06-1.40 (m, 6H), 1.85-1.60 (m, 5H).

EXAMPLE 31

1-Hexyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea



The title compound was prepared in a manner substantially the same as example 26 by coupling 2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenylamine with hexylamine in 79 % yield. LCMS: $R_T$ = 3.09 minutes, MS: 387.32 (M+H).

$^1$H NMR ($CDCl_3$, 300MHz), δ (ppm): 7.05 (d, 8.3Hz, 1H), 6.39 (m, 1H), 6.37 (m, 1H), 5.66 (m, 1H), 4.40 (s, 1H), 3.43-3.14 (m, 8H), 3.01 (m, 1H), 2.84 (m, 1H), 2.58 (m, 1H), 2.23 (s, 3H), 2.09-1.75 (m, 4H), 1.48 (m, 3H), 1.24 (m, 6H), 1.16 (d, 6.2Hz, 3H), 0.86 (m, 3H).

## Biological Examples

### Example 32

This Example demonstrates the efficacy of compounds of this invention as H3 receptor ligands. The compounds of this invention have been demonstrated to displace [$^3$H]-Methylhistamine radioligand binding to mammalian cell membranes expressing rhesus (Macacca Mulatta) H3 receptor. These compounds display rhesus H3 affinity constants (Ki) in the range of 1 μM to <1 nM. Additionally, the compounds of this invention have been demonstrated by GTPγS radioligand binding assay to inhibit rhesus H3 constitutive functional activity in cell membranes. This inhibition of basal rhesus H3-mediated GTPγS radioligand binding demonstrates that the compounds of this invention find utility as inverse agonists. These compounds decreased rhesus H3 GTPγS radioligand binding by 0-40% below basal levels.

Rhesus H3 membranes were prepared from the Flp-In T-REx 293 Cell Line (Invitrogen) stably transfected with pcDNA5/FRT/TO (Invitrogen) containing the rhesus monkey (Macacca Mulatta) 445 amino acid H3 receptor. (Genbank #AY231164). Stably transfected cultures were amplified in tissue culture flasks by standard tissue culture methods and induced to express rhesus H3 by exposure to 500 ng/ml tetracycline (Cellgro) for 24 hours. After induction, cells were dissociated from flasks utilizing Cell Stripper (Cellgro). Cells were centrifuged (1K x g, 5 min) and pellet frozen in an ethanol-dry ice bath to disrupt cell membranes. Frozen cell pellet was re-suspended in 5 mM HEPES (pH 7.4, Invitrogen) at 10ml/1000 cm2 of harvested cells. The cell suspension was drawn through an 18 gauge needle (2-3x) followed by a 23 gauge needle (2-3x) to further disrupt cell membranes. The cell suspension was centrifuged (40K x g, 30 min). Cell membrane pellet was re-suspended in 5 mM HEPES (pH 7.4, Invitrogen) at a final protein concentration of 10 mg/ml. Rhesus H3 membranes were stored under liquid nitrogen prior to use in [3H]-Methylhistamine and GTPγS radioligand binding assays.

Rhesus H3 radioligand binding assay was performed using rhesus H3 receptor membranes (prepared as described above), [3H]-Methylhistamine (Perkin Elmer) and WGA SPA beads (wheat germ agglutinin scintillation proximity assay) beads (Amersham). The assay was

performed in 96-well Opti-Plates (Packard). Each reaction contained 50 µl rhesus H3 membranes (20-30 µg total protein), 50 µl WGA SPA beads (0.1 µg) and 50 µl of 83Ci/mmol [$^3$H]-Methylhistamine (final concentration 2 nM) and 50 µl of tested compound. The compounds of this invention and/or vehicle were diluted with binding buffer from 10 mM DMSO stocks. Assay plates were sealed with TopSeal (Perkin Elmer) and mixed on shaker (25°C , 1 hour). Assay plates were read on TopCount scintillation counter (Packard). Results were analyzed by Hill transformation and Ki values were determined by Cheng-Prusoff equation. The results are tabulated in Table 1.

Table 1

| Example No. | Rhesus H3 binding ki (nM) | Inverse Agonism: % inhibition of Basal GTPγS binding in Rhesus H3 |
|---|---|---|
| 1 | 6.0 | - |
| 2 | 89.7 | - |
| 3 | 4.1 | - |
| 4 | 10.6 | - |
| 5 | 25.7 | - |
| 6 | 11.1 | - |
| 7 | 7.7 | - |
| 8 | 2.0 | - |
| 9 | 28.9 | - |
| 10 | 11.2 | - |
| 11 | 8.4 | - |
| 12 | 19.1 | - |
| 13 | 34.1 | - |
| 14 | 35.5 | - |
| 15 | 22.2 | - |
| 16 | 4.6 | - |
| 17 | 10.5 | - |
| 18 | 10.8 | - |
| 19 | 43.0 | - |
| 20 | 12.7 | - |

| Example No. | Rhesus H3 binding ki (nM) | Inverse Agonism: % inhibition of Basal GTPγS binding in Rhesus H3 |
|---|---|---|
| 21 | 8.0 | - |
| 22 | 23.0 | - |
| 23 | 6.3 | - |
| 24 | 29.0 | - |
| 25 | 18.1 | - |

Example 33

This Example illustrates selective affinity of the compounds of this invention at H3 receptors and exhibit low activity at the MCH-1 receptor site.

The H3 affinity of the compounds of this invention was measured in accordance with the procedures set forth in Example 32.

The activity of the compounds of this invention at the MCH-1 receptor site, if any was measured by the procedures as set forth below.

Test Compounds: The compounds of this invention were stored in a 96-well microtiter plates (1 μL, 10 mM, 100% DMSO). Each of the test sample was diluted with 249 μL of 100% DMSO (dilution 1:250). The test compounds were further diluted 1:4 (0.1% DMSO) during assay resulting in the final concentration of test compounds of this invention to be 10 μM.

Negative Control: 40 μM of MCH-1 in assay buffer with 0.4% DMSO were transferred to the dilution microtiter plates for control which resulted in final concentration of 10 μM.

Blank: Assay buffer containing 0.4% DMSO were transferred to the dilution microtiter plates for blanks.

Assay Procedure: The filter plates with 250 mL of 0.5% PEI-solution/well were incubated for 2 hours at room temperature. PEI was removed by vacuum filtration just before pipetting (Univac Polyfiltronic/Whatman). The solution of the compound as prepared above (50 μL), or MCH-1 (negative control) or Puffer/DMSO (positive control) were added to 96-well round bottom microtiter plate. Then 50 μl of [$^{125}$J]-ligand solution was added followed by 100 μl of membrane suspension. The plates were closed with the lids, and incubated for 60 min. at 25°C. The samples were transferred to GF/B filter plate. The reaction mixture was removed by vacuum filtration, washed 4 x with 300 μl ice-cold washing buffer and the washing

solution was removed by vacuum filtration. The rubber layer at the bottom of the plate was then removed and the filters were dried over night at room temperature. 25 µl of scintillation cocktail was added and the plates were sealed and, plate frames were added and incubated for 1 hour at room temperature. The radioactivity was then measured, settings $^{125}$J standard, 30 sec./well. From this the percent inhibition of ligand binding was measured.

Results: In general the compounds of this invention exhibited a rhesus H3 binding ki value in the range of from about 90 nM to less than 10 nM, whereas the percent inhibition of ligand binding at MCH-1 receptor was less than 50% at 10 µM concentration. This comparative Example demonstrates that the compounds of this invention can be more than thousand times more selective at H3 receptor site than at MCH-1 receptor site.

Example 34

This Example illustrates the study of efficacy of the compounds of this invention in increasing the wakefulness in animal models.

Male Sprague Dawley rats (Charles River, France) weighing 250 ± 10 g were anaesthetized with Zoletil$^{R}$ 50 (60 mg/kg ip) and mounted in a stereotaxic apparatus. Cortical electrodes (small stainless steel screw electrodes of 0.9 mm in diameter) were screwed into the bone over the sensorimotor cortex (1.5 mm lateral to the median suture and 1.5 mm behind the fronto-parietal suture), the visual cortex (1.5 mm lateral to the median suture and 1.5 mm in front of the parieto-occipital suture) and over the cerebellum (reference electrode). Cortical electrodes were attached to a connector (Winchester, 7-lead) and fixed with dental cement to the cranium.

After three weeks of post-operative recovery, animals were placed in plexiglass cylinders (60 cm diameter) with free access to food and water. The temperature of the room was kept constant (21 ± 1 °C) and lights were on from 7 a.m. to 7 p.m. The rats were recorded from 10 a.m. to 4 p.m. during three consecutive days: control day (D1), drug day (D2) and post drug day (D3). Vehicle (D1 and D3) or drug (D2) were administered 15 min before the recording.

Activity in sensorimotor and visual cortices were recorded by comparison with the reference electrode placed over the cerebellar cortex. Three stages were differentiated:

- wakefulness (W) characterized by low voltage fast electrocortical (ECoG) activity;
- NREM sleep (non rapid eye movement or slow wave sleep: SWS) characterized by an increase in electrocortical activity; development of high-amplitude slow waves with some bursts of sleep spindles;

- REM sleep (rapid eye movement or paradoxical sleep: PS) characterized by hypersynchronization of the theta rhythm in the visual area.

Analysis of the ECoG signal was performed automatically by means of a computerized system discriminating between the various sleep phases using sequential spectral analysis of ten seconds periods (Deltamed's software "Coherence").

The compounds of this invention were dissolved in 0.6% MTC tween and administered by oral route (po). The volume of injection was 0.5ml/100g of body weight.

Two types of analysis were used to quantify the effects of the compounds of this invention on sleep-wakefulness variables: the one hour-period and the six hour-period analysis.

The results are expressed in minutes (one hour-period analysis) or as the percentage of the control values (100%). Statistical analysis of the data was carried out using the Student's t test for paired values to determine significant variations from control values.

Example 35

Stress-induced ultrasonic vocalizations test in adult rats

This Example illustrates the study of efficacy of the compounds of this invention as antidepressive agents in animal models.

The procedure used was adapted from the technique described by Van Der Poel A.M, Noach E.J.K, Miczek K.A (1989) Temporal patterning of ultrasonic distress calls in the adult rat: effects of morphine and benzodiazepines. *Psychopharmacology* 97:147-8. Rats were placed for a training session in a cage with a stainless steel grid floor (MED Associates, Inc., St. Albans, VT). Four electric shocks (0.8 mA, 3s) were delivered every 7s and ultrasonic vocalizations (UV, 22KHz) were subsequently recorded with the Ultravox system (Noldus, Wageningen, The Netherlands) during 2 min. A modified ultrasound detector (Mini-3 bat model) connected to a microphone was used to transform ultrasonic sound into audible sound. The signal was then filtered and sent to a computer where the Ultravox software recorded each bout of UV that lasted more than 10ms. Rats were selected on the basis of their UV duration (>40s) and subjected to the test, 4h after training. For the test, rats were placed in the same cage as that used for training. One electric shock (0.8 mA, 3s) was delivered and UV (duration and frequency) were subsequently recorded with the Ultravox system during 2 min. The compounds of this invention were administered p.o. 60 min before testing.

Example 36

Forced-swimming test in rats

This Example further illustrates the study of efficacy of the compounds of this invention as antidepressive agents in animal models.

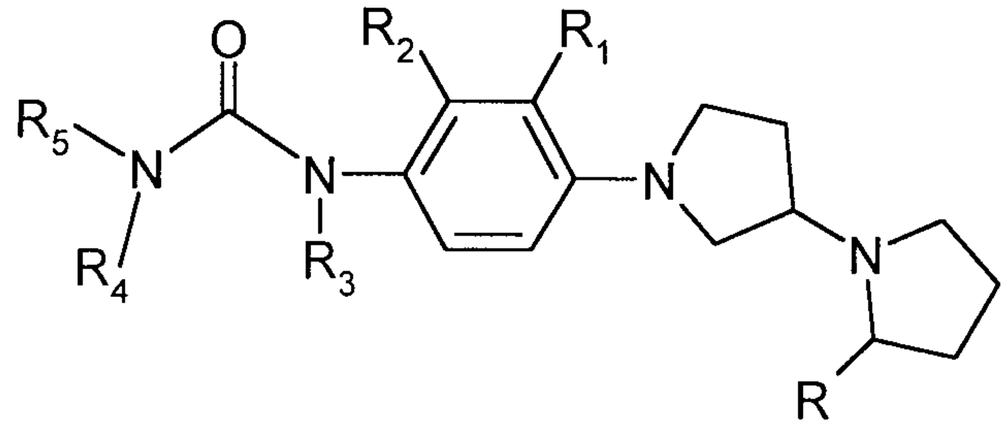
The procedure was a modification of that described by Porsolt et al. (1977) Depression: a new animal model sensitive to antidepressant treatments. *Nature* 266:730-2. Rats were placed in individual glass cylinder (40 cm height, 17 cm diameter) containing water (21°C) to a height of 30 cm. Two swimming sessions were conducted (a 15-min training session followed 24h later by a 6-min test). After each swimming session, rats were placed under a heating lamp to avoid hypothermia. The duration of immobility was measured during the 6-min test. The compounds of this invention were administered p.o. twice (15 min after training session and 60 min before the test).

Although the invention has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby; but rather, the invention encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof.

# CLAIMS

What is claimed is:

1. A compound of formula (I):



(I)

wherein

R, $R_1$, $R_2$ and $R_3$ are the same or different and independently of each other chosen from hydrogen, $(C_1$-$C_4)$alkyl or $CF_3$;

$R_4$ and $R_5$ are the same or different and independently of each other selected from the group consisting of hydrogen, n-hexyl, phenyl, benzyl, cyclohexyl, cyclohexylmethyl and thiophen-2-ylmethyl; wherein said $R_4$ and $R_5$ are optionally substituted one or more times with a substituent selected from halogen or CN; provided that both $R_4$ and $R_5$ are not simultaneously hydrogen; or

$R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, 1,3-dihydro-isoindolyl, wherein said heterocyclic ring is optionally substituted one or more times with a substituent selected from the group consisting of methyl, ethyl, phenyl, N-acetyl and N-acetyl-methylamino; or

a pharmaceutically acceptable salt thereof or an enantiomer or a diastereomer thereof.

2. The compound according to claim 1, wherein

R and $R_2$ are methyl;

$R_1$ is methyl or hydrogen:

$R_3$ is hydrogen;

$R_4$ is hydrogen; and

$R_5$ is phenyl or benzyl, wherein phenyl or benzyl is optionally substituted with one or more groups selected from chlorine or CN; or

$R_5$ is selected from n-hexyl, cyclohexyl, cyclohexylmethyl or thiophen-2-ylmethyl; or

$R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form pyrrolidine which is optionally substituted once with N-acetyl-methylamino; or

$R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form piperidine, piperazine or morpholine, which are optionally substituted one or more times with methyl, ethyl, phenyl or acetyl; or

$R_4$ and $R_5$ taken together with the nitrogen atom to which they are attached form 1,3-dihydro-isoindolyl.

3. The compound of claim 1 selected from the group consisting of:

1-(3-cyano-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3-cyano-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-phenyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-benzyl)-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-(3,5-dichloro-benzyl)-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-2-trifluoromethyl-phenyl]-urea;

1-hexyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexyl-3-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexyl-3-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexyl-3-[2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'S)]bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-cyclohexylmethyl-3-[2-methyl-4-(2(2S)-methyl-[1,3' (3'R)]bipyrrolidinyl-1'-yl)-phenyl]-urea;

1-[4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea;

1-[3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-3-thiophen-2-ylmethyl-urea;

3-(acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

3-(acetyl-methyl-amino)-pyrrolidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

piperidine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

piperidine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-methyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-methyl-piperazine-1-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-methyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

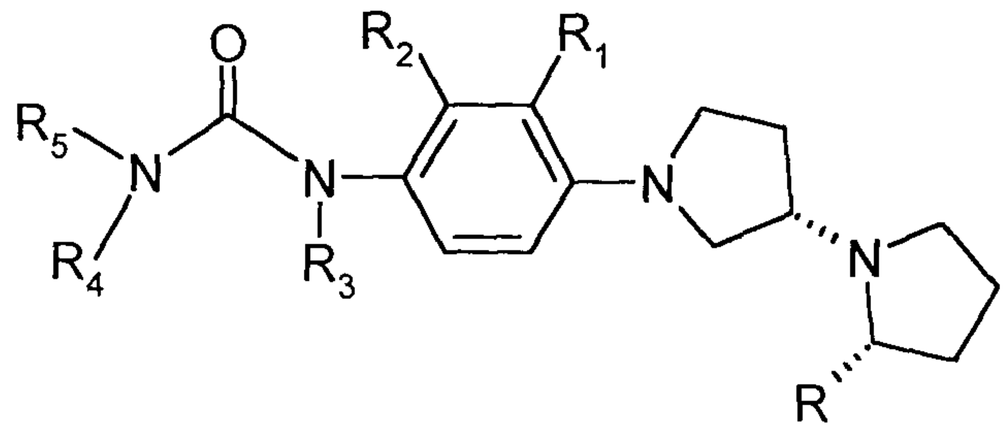
4-phenyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-acetyl-piperazine-1-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-acetyl-piperazine-1-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;

4-ethyl-piperazine-1-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide;
morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3'(3'S)]bipyrrolidinyl-1'-yl)-phenyl]-amide;
morpholine-4-carboxylic acid [2-methyl-4-(2(2S)-methyl-[1,3'(3'R)]bipyrrolidinyl-1'-yl)-phenyl]-amide;
1,3-dihydro-isoindole-2-carboxylic acid [4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
1,3-dihydro-isoindole-2-carboxylic acid [2-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide; and
1,3-dihydro-isoindole-2-carboxylic acid [3-methyl-4-(2-methyl-[1,3']bipyrrolidinyl-1'-yl)-phenyl]-amide;
or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 which is having the formula (II):



(II)

wherein R, $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ are as defined in claim 1.

5. A pharmaceutical composition comprising a compound of formula (I) or formula (II) according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof or an enantiomer or a diastereomer thereof in combination with at least one pharmaceutically acceptable excipient, diluent or a carrier.

6. Use of a compound of formula (I) according to any one of claims 1 to 4, optionally in combination with a pharmaceutically acceptable carrier, for the

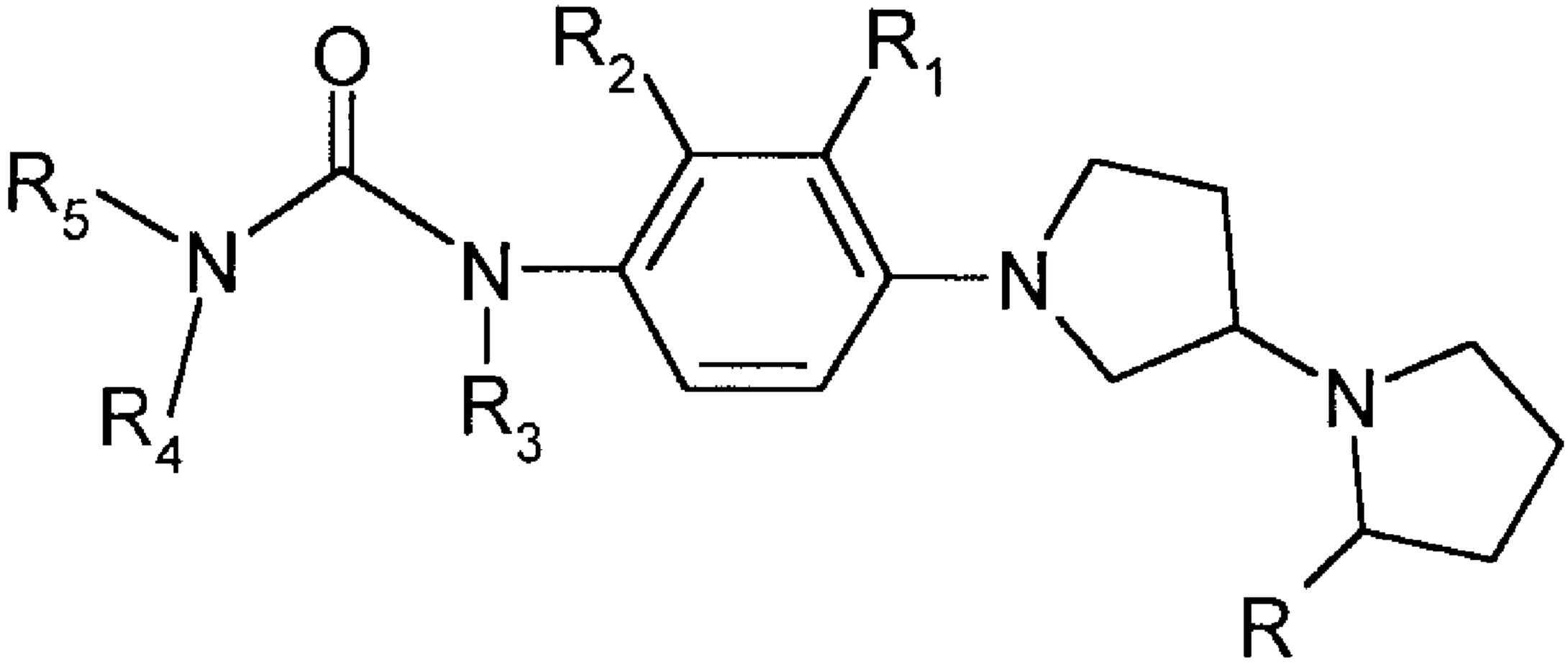
preparation of a pharmaceutical composition for the treatment of a disease selected from the group consisting of sleep related disorder, dementia, Alzheimer's disease, multiple sclerosis, cognitive disorder, attention deficit hyperactivity disorder and depression.

7. The use according to claim 6, wherein the sleep disorder is selected from the group consisting of narcolepsy, circadian rhythm sleep disorder, obstructive sleep apnea, periodic limb movement and restless leg syndrome, excessive sleepiness and drowsiness due to medication side-effect.

8. The use according to claim 6, wherein the disease is cognitive disorder.

9. The use according to claim 6, wherein the disease is Alzheimer's disease.

10. The use according to claim 6, wherein the disease is depression or dementia.




(I)