(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 November 2007 (29.11.2007)

PCT

(10) International Publication Number
WO 2007/136668 A3

(51) International Patent Classification:
C07D 207/12 (2006.01) *A61K 31/52* (2006.01)
C07D 473/34 (2006.01) *A61P 25/00* (2006.01)
C07D 495/04 (2006.01) *C07D 403/12* (2006.01)
C07D 401/12 (2006.01) *C07D 407/12* (2006.01)
A61K 31/4025 (2006.01) *C07D 409/12* (2006.01)
A61K 31/404 (2006.01) *C07D 413/12* (2006.01)
A61K 31/433 (2006.01) *C07D 417/12* (2006.01)
A61K 31/517 (2006.01)

(21) International Application Number: PCT/US2007/011765

(22) International Filing Date: 16 May 2007 (16.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/801,905 19 May 2006 (19.05.2006) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

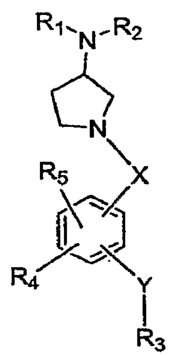
Published:
— *with international search report*

(88) Date of publication of the international search report: 24 January 2008

(48) Date of publication of this corrected version: 27 March 2008

(15) Information about Correction: see Notice of 27 March 2008

(54) **Title:** N-BENZOYL-AND N-BENZYLPYRROLIDIN-3-YLAMINES AS HISTAMINE-3 ANTAGONISTS



(I)

(57) **Abstract:** The present invention provides a compound of Formula (I) and the use thereof for the treatment of a central nervous system disorder related to or affected by the histamine-3 receptor.

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N-BENZOYL- AND N-BENZYLPYRROLIDIN-3-YLAMINES AS HISTAMINE-3 ANTAGONISTS

BACKGROUND OF THE INVENTION

The histamine-3 (H3) receptor is one of four histamine receptor subtypes (H1-H4), all of which are members of the larger G-protein-coupled receptor (GCPR) superfamily of receptors. The H3 receptor is predominantly expressed in the central nervous system. In the brain, it is located in regions associated with learning and memory such as the cerebral cortex, hippocampus and striatum. The H3 receptor acts as both auto- and hetero-receptor to regulate the release of histamine and other neurotransmitters. Within the cortex, the H3 receptor appears to directly modify GABA release from cortical interneurons. Antagonism of the H3 receptor produces a decrease in GABA release and disinhibition of the cortical cholinergic system, resulting in increased acetylcholine levels (Bacciottini, L. *et al*, Behavioral Brain Research, 124, 2001, 183-194). In addition to direct regulation of cholinergic neurotransmission, the H3 receptor has been shown to modulate the release of dopamine, serotonin and norepinephrine (Leurs, R., *et al*, Trends in Pharmacological Sciences, 19, 1998, 177-183). A postmortem study in humans suggests that a decrease in brain histamine levels may contribute to the cognitive decline which occurs in Alzheimer's diseae, directly or through the cholinergic system (Panula, P., *et al*, Neuroscience, 82, 1998, 993-997). H3 agonists have been reported to impair memory in various tasks, such as object recognition, passive avoidance (Blandina, P., et al, British Journal of Pharmacology, 119(8), 1996, 1656-1664) and social olfactory memory (Prast, H., *et al*, 734, 1996, 316-318), whereas H3 antagonists have been reported to rescue impairments produced pharmacologically or genetically; i.e. Miyazaki, S., *et al*, Life Sciences, 61, 1997, 355-361; Meguro, K., et al, Pharmacology, Biochemistry and Behavior, 50, 1995, 321-325; Fox, G. B., et. al, Behavioral Brain Research, 131, 2002, 151-161; and Komater, V. A., et al, Psychopharmacology, 167, 2003, 363-372.

Accumulating neuroanatomical, neurochemical, pharmacological and behavioral data support the concept that H3 receptor antagonists may improve cognitive performance in disease states such as mild cognitive impairment and Alzheimer's disease and may have therapeutic value in the treatment of attention deficit hyperactivity disorder (ADHD), schizophrenia, obesity and sleep disorders.

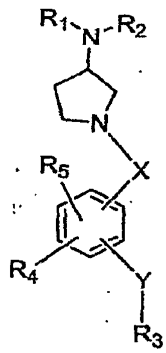
Therefore, it is an object of this invention to provide compounds which are inhibitors of the H3 receptor and are useful as therapeutic agents in the treatment of a variety of central nervous system disorders related to or affected by the H3 receptor.

It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment of central nervous system disorders related to or affected by the H3 receptor.

It is a feature of this invention that the compounds provided may also be useful to further study and elucidate the H3 receptor.

SUMMARY OF THE INVENTION

The present invention provides an N-benzoyl- or N-benzylpyrrolidin-3-ylamine compound of formula I



(I)

wherein

X is CO, CH_2 or SO_m;

Y is NR_6, NR_6CO, O or SO_p;

m and p are each individually 0 or an integer of 1 or 2;

R_1 and R_2 are each independently H or an optionally substituted alkyl group or R_1 and R_2 may be taken together with the atom to which they are attached to form an optionally substituted 4- to 7-membered ring optionally containing one or two additional heteroatoms selected from N, O or S

R_3 is NR_7R_8 or an aryl or heteroaryl group each group optionally substituted with the proviso that when Y is NR_6, O or SO_p then R_3 must be an aryl or heteroaryl group each group optionally substituted;

R_4 and R_5 are each independently H, halogen, OR_9 or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_6 and R_9 are each independently H or an optionally substituted alkyl group; and

R_7 and R_8 are taken together with the atom to which they are attached to form an optionally substituted fused bicyclic or tricyclic 9- to 13-membered ring system optionally containing one to three additional heteroatoms selected from N, O or S; or

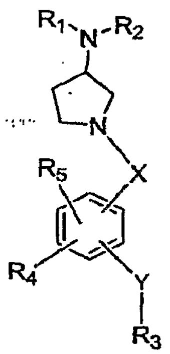
a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

The present invention also provides methods and compositions useful for the therapeutic treatment of central nervous system disorders related to or affected by the Histamine-3 receptor.

DETAILED DESCRIPTION OF THE INVENTION

Alzheimer's disease (AD) is characterized by a progressive loss of memory and cognitive function and is the most common cause of dementia in the elderly. AD is believed to affect approximately 15-20 million people worldwide. The goal of treatment in AD, in addition to reversing the disease process, is to improve or at least slow the loss of memory and cognition and to maintain independent function in patients with mild to moderate disease. AD is characterized by numerous deficits in neurotransmitter function (Möller, H-J., European Neuropsychopharmacology, 9, 1999, S53-S59), further a postmortem study in humans suggests that a decrease in brain histamine levels may contribute to the cognitive decline associated with AD, directly or through the cholinergic system (Panula, P., *et al*, Neuroscience, 82, 1998, 993-997). Histamine-3 (H3) receptor antagonists have been reported to rescue impairments produced pharmacologically or genetically (Miyazaki, S., *et al*, Life Sciences, 61, 1997, 355-361; Meguro, K., et al, Pharmacology, Biochemistry and Behavior, 50, 1995, 321-325; Fox, G. B., et. al, Behavioral Brain Research, 131, 2002, 151-161; and Komater, V. A., et al, Psychopharmacology, 167, 2003, 363-372). Neuroanatomical, neurochemical, pharmacological and behavioral data support the belief that H3 receptor antagonists may improve cognitive performance in disease states such as mild cognitive impairment and Alzheimer's disease and may have therapeutic value in the treatment of attention deficit hyperactivity disorder (ADHD), schizophrenia, obesity and sleep disorders. To that end, compounds which inhibit the H3 receptor and act as H3 antagonists are earnestly sought.

Surprisingly it has now been found that N-benzoyl- and N-benzylpyrrolidin-3-ylamine compounds of formula I demonstrate H-3 affinity along with significant sub-type selectivity and function as H-3 antagonists. Advantageously, said formula I compounds are effective therapeutic agents for the treatment of central nervous system (CNS) disorders associated with or affected by the H-3 receptor. Accordingly, the present invention provides an N-benzoyl- or N-benzylpyrrolidin-3-ylamine compound of formula I



(I)

wherein

X is CO, CH_2 or SO_m;

Y is NR_6, NR_6CO, O or SO_p;

m and p are each individually 0 or an integer of 1 or 2;

R_1 and R_2 are each independently H or an optionally substituted alkyl group or R_1 and R_2 may be taken together with the atom to which they are attached to form an optionally substituted 4- to 7-membered ring optionally containing one or two additional heteroatoms selected from N, O or S;

R_3 is NR_7R_8 or an aryl or heteroaryl group each group optionally substituted with the proviso that when Y is NR_6, O or SO_p then R_3 must be an aryl or heteroaryl group each group optionally substituted;

R_4 and R_5 are each independently H, halogen, OR_9 or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_6 and R_9 are each independently H or an optionally substituted alkyl group; and

R_7 and R_8 are taken together with the atom to which they are attached to form an optionally substituted fused bicyclic or tricyclic 9- to 13-membered ring system optionally containing one to three additional heteroatoms selected from N, O or S; or

a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

It is understood that the claims encompass all possible stereoisomers and prodrugs. Moreover, unless stated otherwise, each alkyl, alkenyl, alkynyl, cycloalkyl cycloheteroalkyl, aryl or heteroaryl group is contemplated as being optionally substituted.

An optionally substituted moiety may be substituted with one or more substituents. The substituent groups, which are optionally present, may be one or more of those customarily employed in the development of pharmaceutical compounds or the modification of such compounds to influence their structure/activity, persistence, absorption, stability or other beneficial property. Specific examples of such substituents include halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsuphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocyclyl or cycloalkyl groups, preferably halogen atoms or lower alkyl or lower alkoxy groups. Unless otherwise specified, typically, 0-4 substituents may be present. When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12 carbon atoms, preferably up to 6 carbon atoms, more preferably up to 4 carbon atoms.

As used herein, the term alkyl includes both (C_1-C_{10}) straight chain and (C_3-C_{12}) branched-chain (unless defined otherwise) monovalent saturated hydrocarbon moiety. Preferably, alkyl is lower alkyl, i.e., C_1-C_6 straight-chain alkyl or C_3-C_6 branched-chain alkyl, more preferably C_1-C_4 straight-chain alkyl or C_3-C_4 branched-chain alkyl. Examples of saturated hydrocarbon alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as *n*-pentyl, *n*-hexyl, and the like. Specifically included within the definition of alkyl are those alkyl groups that are optionally substituted. Suitable alkyl substitutions include, but are not limited to, CN, OH, $NR_{10}R_{11}$, halogen, phenyl, carbamoyl, carbonyl, alkoxy or aryloxy.

As used herein, the term haloalkyl designates a C_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different. Examples of haloalkyl groups include CF_3, CH_2Cl, C_2H_3BrCl, $C_3H_5F_2$, or the like.

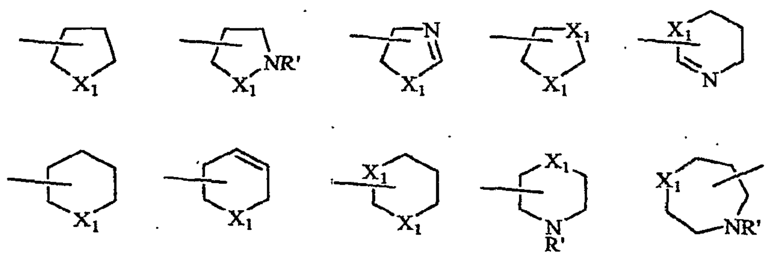
The term halogen, as used herein, designates fluorine, chlorine, bromine, and iodine.

The term alkenyl, as used herein, refers to either a (C_2-C_{10}) straight chain or (C_3-C_{10}) branched-chain monovalent hydrocarbon moiety containing at least one double bond. Such hydrocarbon alkenyl moieties may be mono or polyunsaturated, and may exist in the E or Z configurations. The compounds of this invention are meant to include all possible E and Z configurations. Preferably, alkenyl is C_2-C_6 straight-chain alkenyl or C_3-C_6 branched-chain alkenyl, more preferably C_2-C_4 straight-chain alkenyl or C_3-C_4 branched-chain alkenyl. Examples of mono or polyunsaturated hydrocarbon alkenyl moieties include, but are not limited to, chemical groups such as vinyl, 2-propenyl, isopropenyl, crotyl, 2-isopentenyl, butadienyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), and higher homologs, isomers, or the like.

The term alkynyl, as used in the specification and claims, designates either a (C_2-C_{10}) straight chain or (C_3-C_{10}) branched chain monovalent hydrocarbon moiety having at least one triple bond. Such hydrocarbon alkynyl moieties may be mono or polyunsaturated, and may exist in the E or Z configurations. The compounds of this invention are meant to include all possible E and Z configurations. Preferably, alkynyl is lower alkynyl, i.e., C_1-C_6 straight-chain or C_3-C_6 branched-chain alkynyl, more preferably C_1-C_4 straight-chain or C_3-C_4 branched-chain alkynyl. Examples of mono or polyunsaturated hydrocarbon alkynyl moieties include, but are not limited to, propynyl, butynyl, 1,3-butadiynyl, pentynyl, hexynyl, or the like.

The term cycloalkyl, as used herein, refers to a monocyclic, bicyclic, tricyclic, fused, bridged, or spiro monovalent saturated hydrocarbon moiety of 3-10 carbon atoms, for example 3-6 carbon atoms. Examples of cycloalkyl moieties include, but are not limited to, chemical groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, spiro[4.5]decanyl, or the like.

The term cycloheteroalkyl, as used herein, designates a 5- to 7- membered cycloalkyl ring system containing 1, 2 or 3 heteroatoms, which may be the same or different, selected from N, O or S and optionally containing one double bond. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the following rings wherein X_1 is NR', O or S and R' is H or an optional substituent as defined hereinabove.



The term aryl, as used herein, refers to an aromatic carbocyclic moiety of up to 20 carbon atoms, which may be a single ring (monocyclic) or multiple rings (bicyclic, up to three rings) fused together or linked covalently. Preferred are aryl groups having from 6 to 12 carbon atoms. Examples of aryl moieties include, but are not limited to, chemical groups such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, anthryl, phenanthryl, fluorenyl, indanyl, acenaphthenyl, or the like. Particularly preferred aryl groups are phenyl and naphthyl.

Aryl groups may be unsubstituted or substituted, as indicated above. Preferably, substituted aryl groups are substituted with up to four, more preferably one or two, substituents selected from halogen, cyano, alkyl, haloalkyl, alkoxy, phenyl, phenoxy, heterocycle or cycloalkyl. Specific halo-substituents include chloro, fluoro and bromo. A specific haloalkyl substituent is trifluoromethyl. Specific alkoxy substituents include methoxy and ethoxy, particularly methoxy. Cyclohexyl is an example of a specific cycloalkyl substituent. Heterocycle substituents include heteroaryl groups, for example monocyclic heteroaryl groups, particularly 5-membered heteroaryl groups. A specific example is imidazole. Most preferred aryl substituents are alkyl, alkoxy, halo, heterocycle, cyano, cycloalkyl, and phenoxy.

The term heteroaryl as used herein designates an aromatic heterocyclic ring system, which may be a single ring (monocyclic) or multiple rings (bicyclic, up to three rings) fused together or linked covalently. Preferably, heteroaryl is a 5- to 6-membered monocyclic ring or a 9- to 10-membered bicyclic ring system. The rings may contain from one to four hetero atoms selected from nitrogen, oxygen, or sulfur, wherein the nitrogen or sulfur atoms are optionally oxidized, or the nitrogen atom is optionally quarternized. Examples of heteroaryl moieties include, but are not limited to, heterocycles such as furan, thiophene, pyrrole, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, triazole, pyridine, pyrimidine, pyrazine, pyridazine, benzimidazole, benzoxazole, benzisoxazole, benzothiazole, benzofuran, benzothiophene, thianthrene, dibenzofuran, dibenzothiophene, indole, indazole, quinoline, isoquinoline, quinazoline, quinoxaline, purine, or the like.

Heteroaryl groups may be unsubstituted or substituted, as indicated above. Preferably, substituted aryl groups are substituted with up to four, more preferably one or two, substituents selected from halogen, cyano, alkyl, haloalkyl, alkoxy, phenyl, phenoxy, heterocycle or cycloalkyl. Specific halo-substituents include chloro, fluoro and bromo. A specific haloalkyl substituent is trifluoromethyl. Specific alkoxy substituents include methoxy and ethoxy, particularly methoxy. Cyclohexyl is an example of a specific cycloalkyl substituent. Heterocycle substituents include heteroaryl groups, for example monocyclic heteroaryl groups, particularly 5-membered heteroaryl groups. A specific example is imidazole. Most preferred heteroaryl substituents are phenyl,, haloalkyl, alkyl, alkoxy and halo.

Exemplary of the fused bicyclic or tricyclic 9- to 13-membered ring system formed when R_7 and R_8 are taken together with the nitrogen atom to which they are attached are indolyl, indazolyl, benzimidazolyl, tetrahydrocarbazolyl, hexahydroindolizinoindolonyl, tetrahydropyranoindolyl, azaindolyl, imidazopyridinyl, indolinyl, tetrahydroquinolinyl, pyridoindolyl, dihydrodibenzoazepinyl, or the like.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The compounds of the present invention may be converted to salts, in particular pharmaceutically acceptable salts using art recognized procedures. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di-, or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds or their pharmaceutically acceptable salts, are also included. The term "pharmaceutically acceptable salt", as used herein, refers to salts derived from organic and inorganic acids such as, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, napthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, when a compound of this invention contains a carboxylate or phenolic moiety, or similar moiety capable of forming base addition salts.

Compounds of the invention include esters, carbamates or other conventional prodrug forms, which in general, are functional derivatives of the compounds of the invention and which are readily converted to the inventive active moiety *in vivo*. Correspondingly, the method of the invention embraces the treatment of the various conditions described hereinabove with a compound of formula I or with a compound which is not specifically disclosed but which, upon administration, converts to a compound of formula I *in vivo*. Also included are metabolites of the compounds of the present invention defined as active species produced upon introduction of these compounds into a biological system.

Preferred compounds of the invention are those compounds of formula I wherein X is CO or CH_2.

More preferred compounds are compounds in which X is CO.

Another group of preferred compounds is those formula I compounds wherein Y is NR_6, NR_6CO or O, for example, compounds in which Y is O; or compounds in which Y is NH, or compounds in which Y is NHCO.

More preferred compounds are compounds in which Y is O.

Also preferred are those formula I compounds wherein R_1 and R_2 are taken *together with the atom to which they are attached to form an optionally substituted 5-membered ring.* Particularly preferred are those formula I compounds wherein R_1 and R_2 *are taken together with the atom to which they are attached to form* pyrrolidine.

Other preferred formula I compounds are those compounds in which R_1 and R_2 are each alkyl, more preferably methyl.

More preferred compounds of the invention are those compounds of formula I wherein X is CO or CH_2 and R_1 and R_2 are taken together with the atom to which they are attached to form a 5-membered ring. Another group of more preferred compounds is those compounds of formula I wherein X is CO or CH_2 and Y is O. A further group of more preferred compounds are those compounds of formula I wherein X is CO; Y is O; and R_1 and R_2 are taken together with the atom to which they are attached to form a 5-membered ring.

Among the preferred compounds of the invention are:

(3'S)-1'-(4-phenoxybenzoyl)-1,3'-bipyrrolidine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1-naphthamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)quinoline-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1-benzothiophene-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2-phenylquinazolin-4-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-9H-purin-6-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)pyridin-2-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)thieno[3,2-d]pyrimidin- 4-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-7-methylthieno[3,2-d]pyrimidin-4-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)isoquinolin-1-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-5- (trifluoromethyl)pyridin-2-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)pyrimidin-2-amine;

1-[4-(1-benzothien-3-ylamino)benzoyl]-N,N-dimethylpyrrolidin-3-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2,1,3-benzothiadiazol-4-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1H-indol-5-amine;

3-chloro-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)thiophene-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2-naphthamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)isoquinoline-1- carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1-methyl-1H-indole-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-5-methyl-3- phenylisoxazole-4-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-4-methoxyquinoline-2-carboxamide;

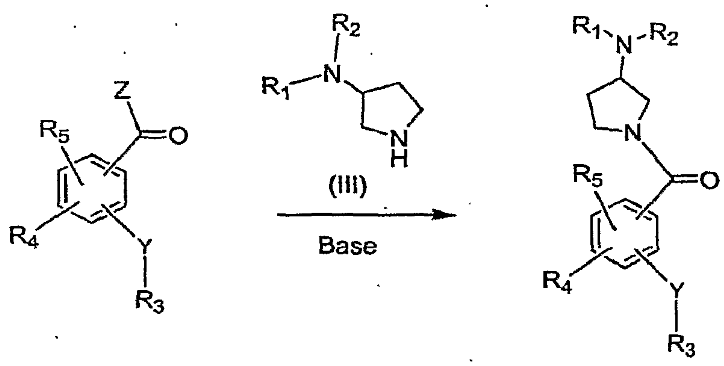
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-7-methoxy-1-benzofuran- 2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)biphenyl-4-carboxamide;
5-bromo-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)thiophene-2-carboxamide;
4-cyclohexyl-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)benzamide;
6-chloro-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2H-chromene-3-carboxamide;
3-chloro-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1- benzothiophene-2-carboxamide;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-4-phenoxybenzamide;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)quinolin-5-amine;
1-[4-(2,3-dihydro-1,4-benzodioxin-6-ylamino)benzoyl]-N,N-dimethylpyrrolidin-3-amine;
1-[4-(1,3-benzodioxol-5-ylamino)benzoyl]-N,N-dimethylpyrrolidin-3-amine;
(3'S)-1'-(4-phenoxybenzoyl)-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-fluoro-2-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(3-chloro-4-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(3-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(2-chloro-4-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;
4-{4-[(3'S)-1,3'-bipyrrolidin-1'-ylcarbonyl]phenoxy}quinoline;
(3'S)-1'-{4-[4-(1H-imidazol-1-yl)phenoxy]benzoyl}-1,3'-bipyrrolidine;
4-{4-[(3'S)-1,3'-bipyrrolidin-1'-ylcarbonyl]phenoxy}benzonitrile;
(3'S)-1'-[4-(3-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(3-methoxyphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-chlorophenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-methoxyphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-chloro-2-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(2-chloro-4-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(2-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-{4-[4-(4-fluorophenoxy)phenoxy]benzoyl}-1,3'-bipyrrolidine;
(3'S)-1'-{4-[3-(3-fluorophenoxy)phenoxy]benzoyl}-1,3'-bipyrrolidine;
(3'S)-1'-{4-[(4-chloro-1-napthyl)oxy]benzoyl}-1;3'-bipyrrolidine; or

a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

Advantageously, the present invention provides a process to prepare compounds of formula I wherein X is CO (Ia) which comprises reacting a benzoic acid or benzoyl chloride compound of formula II with a pyrrolidine of formula III in the presence of a base optionally in the presence of a solvent. The reaction is shown in scheme I wherein Z is OH or Cl.

SCHEME I

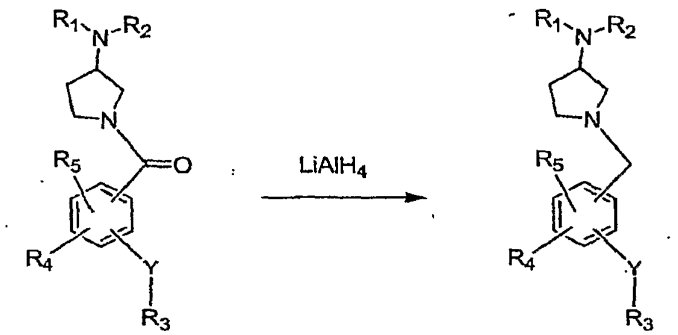


(II) (Ia)

Bases suitable for use in the method of invention are organic amines such as triethylamine, methyldiethylamine, diisopropylethylamine or any suitable organic base useful as an acid scavenger in organic synthetic procedures. Solvents suitable for use in the method of the invention include methylene chloride, chloroform, tetrahydrofuran or the like.

Compounds of formula I wherein X is CH_2 (Ib)may be readily prepared by reacting the formula Ia compound with a suitable reducing agent such as $LiAlH_4$ or Borane to give the desired compound of formula Ib. The reaction is shown in scheme II.

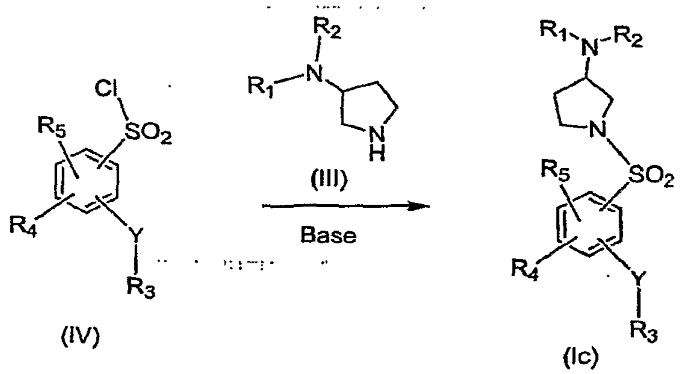
SCHEME II



(Ia) (Ib)

Compounds of formula I wherein X is SO_2 (Ic) may be prepared in a manner similar to that described in reaction scheme I by replacing the benzoic acid or benzoyl chloride of formula II with the corresponding phenyl sulfonyl chloride of formula IV. For example the phenylsulfonyl chloride of formula IV may be reacted with a 3-aminopyrrolidine of formula III to give the desired compound of formula Ic. The reaction is shown in scheme III.

SCHEME III

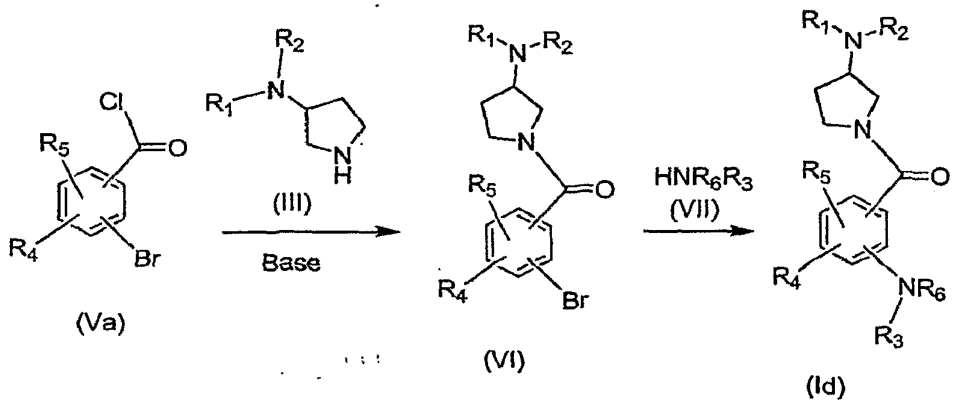


(IV) (Ic)

Similarly, compounds of formula I wherein X is S or SO may be prepared by reducing the compound of formula Ic with a suitable reducing agent to give the corresponding sulfinyl or thio compounds of formula I.

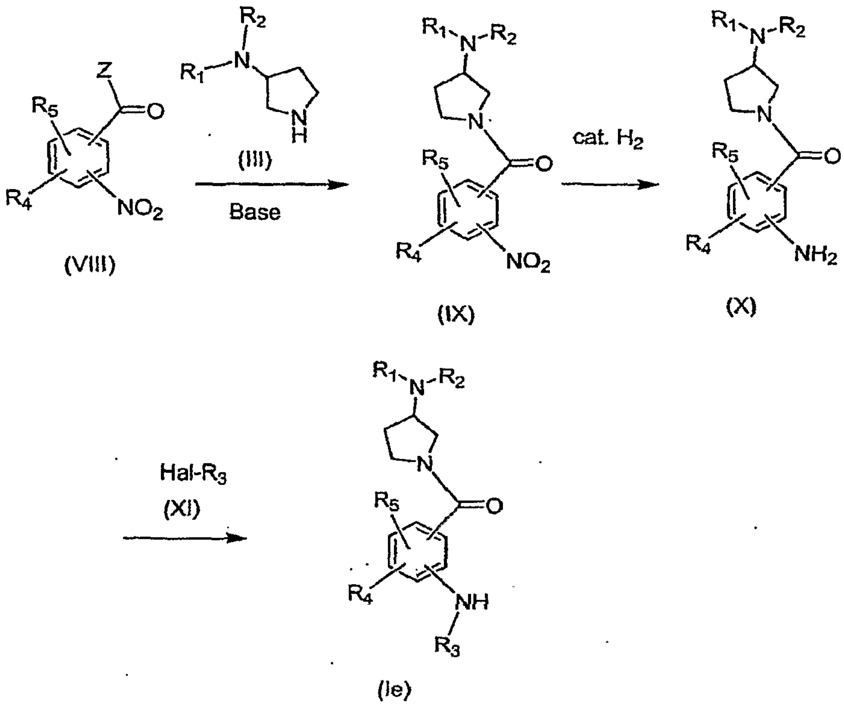
Alternatively, compounds of formula I wherein X is CO and Y is NR_6 (Id) may be prepared by reacting a bromobenzoyl chloride of formula Va with a pyrrolidin-3-ylamine of formula II in the presence of base such as diisopropylethylamine (DIEA) to give the compound of formula VI and reacting said formula VI compound with an amine of formula VII in the presence of a palladium coupling agent to give the desired formula Id compound. The reaction is shown in scheme IV.

SCHEME IV



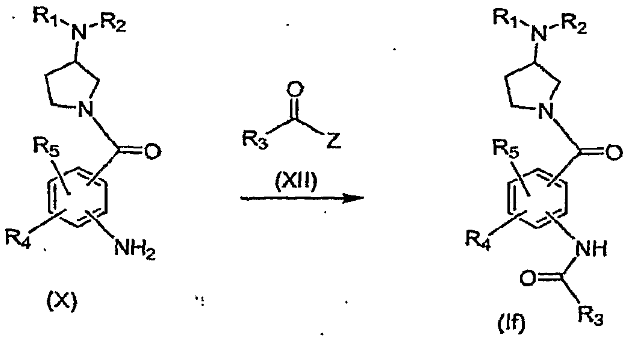
Compounds of formula Id wherein R_6 is H (Ie) may also be prepared by reacting a nitrobenzoyl compound of formula VIII with a pyrrolidin-3-ylamine of formula III in the presence of a DIEA and a solvent such as tetrahydrofuran to give the compound of formula IX; reducing the formula IX compound via catalytic hydrogenation to give the compound of formula X: and reacting the formula X compound with an aryl halide of formula XI in the presence of a catalyst such as pyridine HCl or a palladium catalyst. The reaction is shown in scheme V wherein Z is Cl or OH and Hal represents Cl, Br or I.

SCHEME V



Compounds of formula I wherein X is CO and Y is NHCO (If) may be prepared in a manner similar to that described hereinabove. For example, a compound of formula X may be reacted with an aryl acid or an aryl acid chloride of formula XII in the presence of a base to give the desired compound of formula If. In addition to the aryl acid and aryl acid chloride, a mixed anydride may also be used. The reaction is shown in scheme VI wherein Z is OH or Cl.

SCHEME VI



Advantageously, the formula I compounds of the invention are useful for the treatment of CNS disorders related to or affected by the Histamine-3 receptor including cognitive disorders, for example Alzheimer's disease, mild cognitive impairment, attention deficit hyperactivity disorder, schizophrenia, memory loss, sleep disorders, obesity or the like. Accordingly, the present invention provides a method for the treatment of a disorder of the central nervous system related to or affected by the Histamine-3 receptor in a patient in need thereof which comprises providing said patient a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided by oral or parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The term "providing" as used herein with respect to providing a compound or substance embraced by the invention, designates either directly administering such a compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

The inventive method includes: a method for the treatment of schizophrenia; a method for the treatment of a disease associated with a deficit in memory, cognition or learning or a cognitive disorder such as Alzheimer's disease or attention deficit hyperactivity disorder; a method for the treatment of a mild cognitive disorder, a method for the treatment of a developmental disorder such as schizophrenia; a method for the treatment of a sleep disorder or any other CNS disease or disorder associated with or related to the H3 receptor.

In one embodiment, the present invention provides a method for treating attention deficit hyperactivity disorders (ADHD, also known as Attention Deficit Disorder or ADD) in both children and adults. Accordingly, in this embodiment, the present invention provides a method for treating attention deficit disorders in a pediatric patient.

The present invention therefore provides a method for the treatment of each of the conditions listed above in a patient, preferably in a human, said method comprises providing said patient a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided by oral or parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The present invention also provides the use of a compound of formula I as described herein in the manufacture of a medicament for treating a central nervous system disorder related to or affected by the Histamine-3 receptor. The central nervous system disorder may be for example a cognitive disorder, a developmental disorder, or a sleep disorder, particularly a cognitive disorder. Specific disorders include Alzheimer's disease; a learning disorder; attention deficit disorder; and schizophrenia.

The present invention further provides the use of a compound of formula I as described herein in the manufacture of a medicament for inhibiting the H3 receptor.

The therapeutically effective amount provided in the treatment of a specific CNS disorder may vary according to the specific condition(s) being treated, the size, age and response pattern of the patient, the severity of the disorder, the judgment of the attending physician and the like. In general, effective amounts for daily oral administration may be about 0.01 to 1,000 mg/kg, preferably about 0.5 to 500 mg/kg and effective amounts for parenteral administration may be about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg.

In actual practice, the compounds of the invention are provided by administering the compound or a precursor thereof in a solid or liquid form, either neat or in combination with one or more conventional pharmaceutical carriers or excipients. Accordingly, the present invention provides a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as described hereinabove.

In one embodiment, the invention relates to compositions comprising at least one compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such compositions include pharmaceutical compositions for treating or controlling disease states or conditions of the central nervous system. In certain embodiments, the compositions comprise mixtures of one or more compounds of formula I.

In certain embodiments, the invention relates to compositions comprising at least one compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such compositions are prepared in accordance with acceptable pharmaceutical procedures. Pharmaceutically acceptable carriers are those carriers that are compatible with the other ingredients in the formulation and are biologically acceptable.

The compounds of formula I may be administered orally or parenterally, neat, or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances that can also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders, tablet-disintegrating agents, or encapsulating materials. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

In certain embodiments, a compound of formula I is provided in a disintegrating tablet formulation suitable for pediatric administration.

Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or a pharmaceutically acceptable oil or fat. The liquid carrier can contain other suitable pharmaceutical additives such as, for example, solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

In certain embodiments, a liquid pharmaceutical composition is provided wherein said composition is suitable for pediatric administration. In other embodiments, the liquid composition is a syrup or suspension.

Liquid pharmaceutical compositions that are sterile solutions or suspensions can be administered by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration can be in either liquid or solid form.

The compounds of formula I may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of formula I can be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of formula I can also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier can take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments can be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient can also be suitable. A variety of occlusive devices can be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

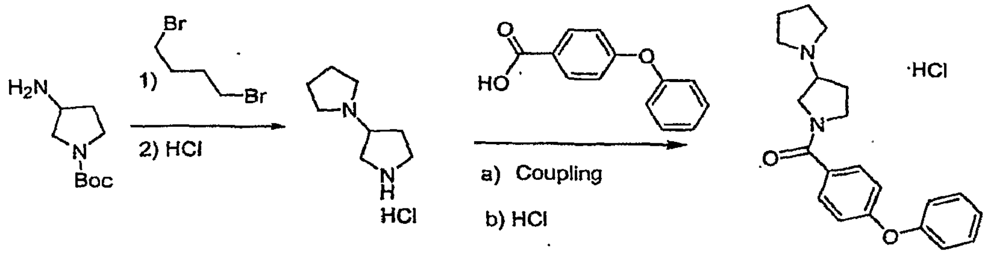
The therapeutically effective amount of a compound of formula I provided to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, or the like. In therapeutic applications, compounds of formula I are provided to a patient suffering from a condition in an amount sufficient to treat or at least partially treat the symptoms of the condition and its complications. An amount adequate to accomplish this is a "therapeutically effective amount" as described previously herein. The dosage to be used in the treatment of a specific case must be subjectively determined by the attending physician. The variables involved include the specific condition and the size, age, and response pattern of the patient. Generally, a starting dose is about 5 mg per day with gradual increase in the daily dose to about 150 mg per day, to provide the desired dosage level in the patient.

In certain embodiments, the present invention is directed to prodrugs of compounds of formula I. The term "prodrug," as used herein, means a compound that is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of formula I. Various forms of prodrugs are known in the art such as those discussed in, for example, Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug Delivery Reviews, 8:1-38(1992), Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975).

For a more clear understanding, and in order to illustrate the invention more clearly, specific examples thereof are set forth hereinbelow. The following examples are merely illustrative and are not to be understood as limiting the scope and underlying principles of the invention in any way. The terms HPLC and NMR designate high performance liquid chromatography and proton nuclear magnetic resonance, respectively. The term MS designates mass spectroscopy with (+) referring to the positive mode which generally gives a M+1 (or M+H) absorption where M = the molecular mass. All compounds are analyzed at least by MS and NMR. The term Boc designates t-butoxycarbonyl. The terms EtOAc, DMSO and THF designate ethyl acetate, dimethylsulfoxide and tetrahydrofuran, respectively. Unless otherwise noted, all parts are parts by weight.

EXAMPLE 1

Preparation of 1'-(4-phenoxybenzoyl)-1,3'-bipyrrolidine Hydrochloride



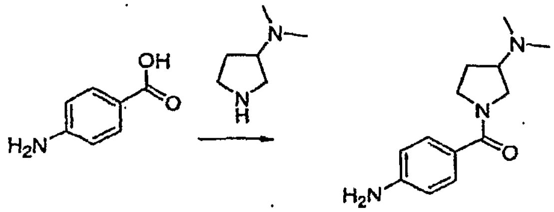
Step 1. Boc-protected 3-aminopyrrolidine (1 mL, 11.6 mmol) is mixed with 1,4-dibromobutane (1.2 eq. 1.7 mL) and K_2CO_3 (2 eq) in toluene and heated to relux temperature for 16 h. The reaction mixture is cooled to room temperature, diluted with EtOAc, washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a residue.

Step 2. The residue (1 g, crude, about 4.2 mmol, theory) is stirred with 2 N HCl in dioxane for 3 h, until the deprotection is complete. The reaction mixture is filtered to give the 3-(pyrrolidino)pyrrolidine HCl salt product in its crystalline form.

Step 3. A stirred mixture of the HCl salt of 3-(pyrrolidino)pyrrolidine (0.44 g, 2.1 mmmol) and 4-phenoxy benzoic acid (0.34 g, 1.6 mmmol) in CH_2Cl_2 is treated with 0.85 mL of triethylamine at room temperature. The reaction mixture is treated with solid benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (1.2 g, 2.4 mmol), stirred overnight under nitrogen, diluted with CH_2Cl_2, washed sequentially with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is chromatographed and treated with HCl in ether to afford the title compound as a white solid, identified by NMR and MS analyses.

EXAMPLE 2

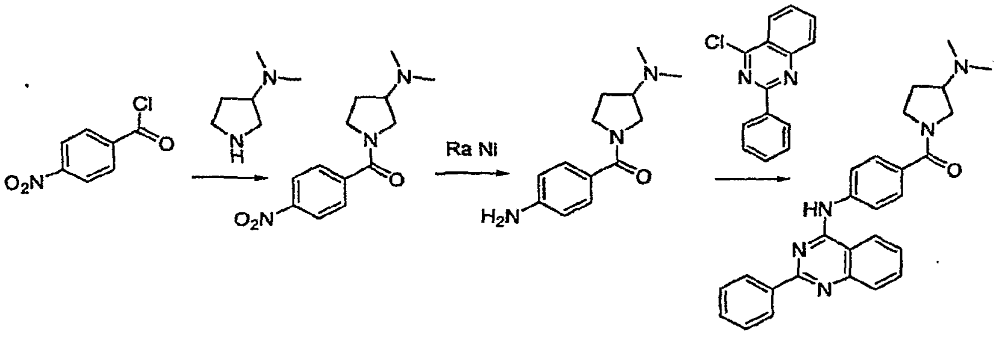
Preparation of 1-(4-Aminobenzoyl)-3-dimethylamino-pyrrolidine



A mixture of 4-aminobenzoic acid (1.4 g, 10 mmol), 3-(dimethylamino)-pyrrolidine (1.5 g, 13 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (2.5 g, 13 mmol) in CH_2Cl_2 is stirred at room temperature for 16 h, diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$ and concentrated in vacuo to give the title compound (1.1 g), identified by NMR analysis.

EXAMPLE 3

Preparation of N-(4-{[3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2-phenylquinazolin-4-amine



Step 1. To a solution of 4-nitrobenzoyl chloride (1.8 g, 10 mmol) and diisopropylethylamine (2.8 mL, 20 mmol) in THF at room temperature is added 3-(dimethylamino)pyrrolidine (1.4 mL, 11 mmol). The reaction is stirred for 2 hours at room temperature and concentrated *in vacuo* to give 3-dimethylamino-1-(4-nitrobenzoyl)pyrrolidine, identified by HPLC and MS [264.3 m/e (M+H)] analyses.

Step 2. The 3-dimethylamino-1-(4-nitrobenzoyl)pyrrolidine (2.4 g, crude), obtained in Step 1, is dissolved in methanol, treated sequentially with hydrazine (5 mL) and Raney-Nickel (suspension in water, approximately 1 g), stirred at room temperature for 4 h and filtered through celite. The filtercake is washed with methanol. The filtrates are combined and concentrated to give 1-(4-aminobenzoyl)-3-dimethylamino-pyrrolidine as a pale brown oil, identified by HPLC and MS [234.5 m/e (M+H)].

Step 3. A mixture of 1-(4-aminobenzoyl)-3-dimethylamino-pyrrolidine (46 mg, 0.2 mmol), 4-chloro-2-phenylquinazoline (48 mg, 0.2 mmol) and pyridine hydrochloride (23 mg, 0.2 mmol) in ethoxyethanol is heated to 135°C overnight, cooled to room temperature and concentrated *in vacuo*. The resultant residue is dissolved in a mixture of DMSO, methanol and water and purified by reverse-phase semi-preparative HPLC[1] to give the title product as a white powder (15 mg), identified by HPLC and mass spectral analyses. Retention Time, 2.69 min.; MS [438.2 m/e (M+H)].

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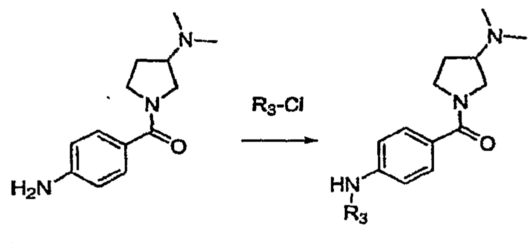
[1]Semi-preparative HPLC Conditions: A = 0.02% TFA in water, B = 0.02% TFA in acetonitrile, 10-95% B in 8 min., 34 mL/min, 50° C, 215 nm detection, Waters Xterra™ 20 x 50 mm column.

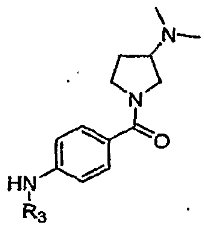
EXAMPLES 4-10

Preparation of N-(4-{[3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-heteroaryl-4-amine Compounds



Using essentially the same procedure described in Example 3, Step 3, and employing the appropriate heteroaryl chloride, R_3-Cl, the compounds shown in Table I areobtained and identified by HPLC and mass spectral analyses. HPLC Conditions are the same as those used in Example 3.

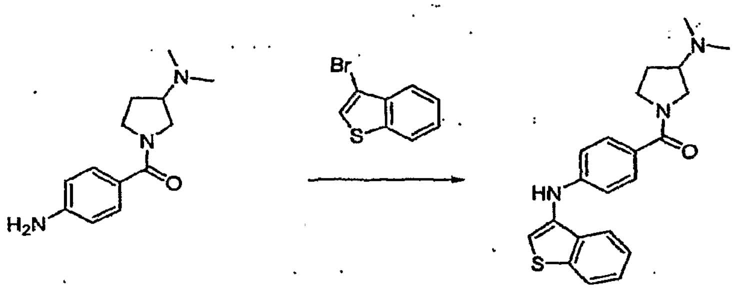
TABLE I



Ex. No.	R3	[M+H]	Time (Min.)
4	9-H-purin-6-yl	350.2	1.70
5	pyridin-2-yl	311.5	1.36
6	thieno[2,3-d]pyrimidin-4-yl	368.1	1.99
7	7-methyl-thieno[2,3-d]pyrimidin-4-yl	382.2	2.13
8	isoquinolin-1-yl	361.2	2.49
9	5-(trifluoromethyl)pyridin-2-yl	377.2	2.62
10	pyrimidin-2-yl	312.2	1.91

EXAMPLE 11

Preparation of 1-[4-(1-Benzothien-3-ylamino)benzoyl]-N,N-dimethylpyrrolidin-3-amine



A mixture of 1-(4-aminobenzoyl)-3-dimethylamino-pyrrolidine (50 mg, 0.21 mmol), 3-bromobenzothiophene (50 mg, 0.23 mmol), sodium tert-butoxide (44 mg, 34 mmmol), tris(dibenzylideneacetone)dipalladium(0) (3 mg, 0.002 mmol), CTC-Q-Phos (6 mg, 0.004 mmol) is heated to 80°C for 16 h and concentrated *in vacuo*. The resultant residue is dissolved in a mixture of DMSO, methanol and water and purified by reverse-phase semi-preparative HPLC[1] to give the title compound as a white powder (11 mg), identified by HPLC and mass spectral analyses. Retention Time, 2.62 min.; MS [366.2 m/e (M+H)].

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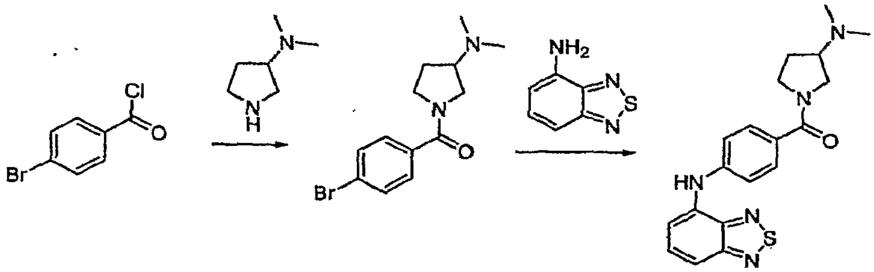
[1]Semi-preparative HPLC Conditions: A = 0.02% TFA in water, B = 0.02% TFA in acetonitrile, 10-95% B in 8 min., 34 mL/min, 50° C, 215 nm detection, Waters Xterra™ 20 x 50 mm column.

EXAMPLE 12

Preparation of N-(4-{[3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2,1,3-benzothiadiazol-4-amine



Step 1. To a solution of 4-bromobenzoyl chloride (2.2 g, 10 mmol) and pyridine (1 mLl) inCH_2Cl_2 at 0°C is added 3-(dimethylamino)pyrrolidine (1.14 mL, 10 mmol). The reaction is stirred at room temperature for 2 h, diluted with ether and filtered. The filtercake is washed with ether, treated with 0.1 N sodium hydroxide, stirred and filtered. This filtercake is washed with ether and recrystallized from petroleum ether to give 1-(4-bromobenzoyl)-3-dimethylaminopyrrolidine as a white powder (1.5 g), identified by NMR analysis.

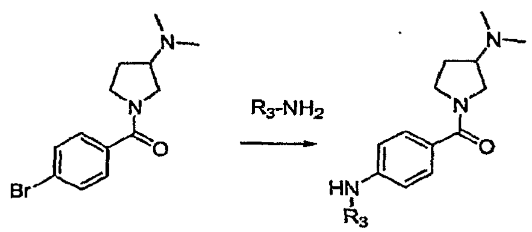
Step 2. A mixture of 1-(4-bromobenzoyl)-3-dimethylaminopyrrolidine (40 mg, 0.13 mmol), 4-amino-2,1,3-benzothiadiazole (23 mg, 0.13 mmol), potassium phosphate (27 mg, 0.13 mmmol), tris(dibenzylideneacetone)dipalladium(0) (3 mg, 0.002 mmol), and CTC-Q-Phos (6 mg, 0.004 mmol) are heated to 80°C for 16 h and concentrated *in vacuo*. The resultant residue is dissolved in a mixture of DMSO, methanol and water and purified by reverse-phase semi-preparative HPLC[1] to give the title compound as a white powder (11 mg), identified by HPLC and mass spectral analyses. Retention Time, 1.74 min.; MS [368.6 m/e (M+H)].

---

[1]Semi-preparative HPLC Conditions: A = 0.02% TFA in water, B = 0.02% TFA in acetonitrile, 10-95% B in 8 min., 34 mL/min, 50° C, 215 nm detection, Waters Xterra™ 20 x 50 mm column.

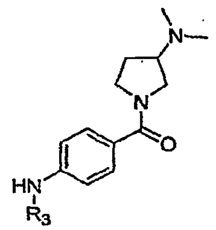
EXAMPLES 13-16

Preparation of N-(4-{[3-(Dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-heteroaryl-4-amine Compounds



Using essentially the same procedure described in Example 12, Step 2, and employing the appropriate heteroarylamine, R_3-NH_2, the compounds shown in Table II are obtained and identified by HPLC and mass spectral analyses. HPLC Conditions are the same as those used in Example 12.

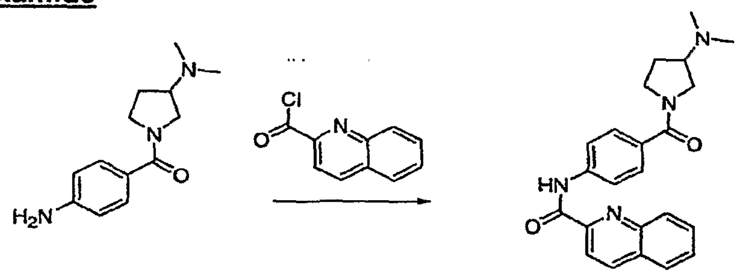
TABLE II



Ex. No.	R3	[M+H]	Time (Min.)
13	1-H-indol-5-yl	349.2	2.51
14	quinolin-5-yl	361.2	2.18
15	2,3-dihydrobenzodioxin-6-yl	368.2	1.68
16	1,3-benzodioxol-5-yl	354.2	2.48

EXAMPLE 17

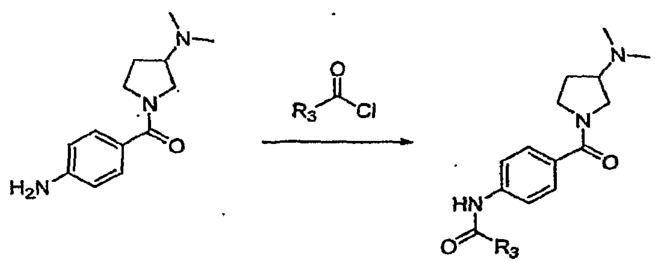
Preparation of N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)quinoline-2-carboxamide



A mixture of 1-(4-aminobenzoyl)-3-dimethylamino-pyrrolidine (46 mg, 0.2 mmol), quinoline-2-carbonyl chloride (38 mg, 0.2 mg) and diisopropyl ethyl amine (0.1 mL, 0.6 mmol) in CH_2Cl_2 is stirred at room temperature for 5 h and concentated *in vacuo*. The resultant residue is dissolved in a mixture of DMSO, methanol and water and purified by reverse-phase semi-preparative HPLC, using the same HPLC conditions described in Example 1, to give the title compound as a white powder (10 mg), identified by HPLC and mass spectral analyses. Retention Time, MS [366.2 m/e (M+H)].

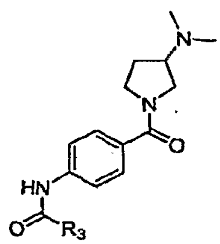
EXAMPLES 18-33

Preparation of N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)aryl- and -heteroaryl-carboxamide Compounds



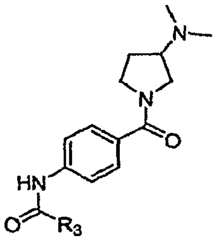
Using essentially the same procedure described in Example 17 and employing the desired aryl or heteroaryl acid chloride, the compounds shown in Table III are obtained and identified by NMR and mass spectral analyses. The HPLC conditions are the same as those described in Example 1.

TABLE III



Ex. No.	R3	[M+H]	Time (Min.)
18	naphth-1-yl	388.6	2.44
19	benzothiophene-2-yl	394.6	2.25
20	thiophene-2-yl	378.1	1.64
21	naphth-2-yl	388.2	1.82
22	isoquin-1-yl	389.2	1.75

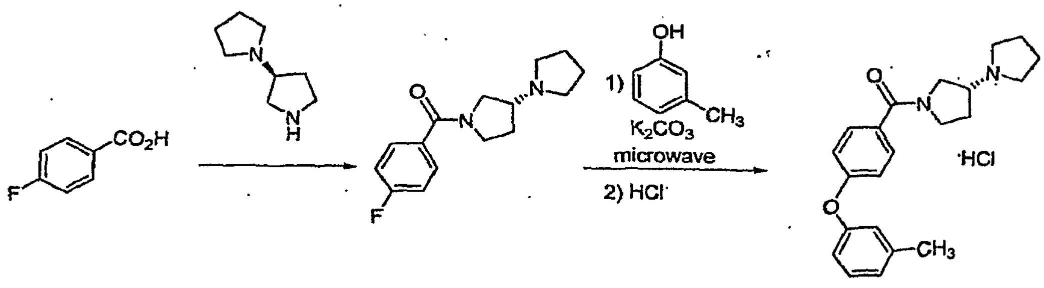
TABLE III, cont.



Ex. No.	R3	[M+H]	Time (Min.)
23	1-H-indol-2-yl	391.2	1.82
24	1,2,3,4-tetrahydronaphth-2-yl	392.2	1.86
25	5-methyl-3-phenyl-isoxazol-4-yl	419.2	1.66
26	4-methoxyquinolin-2-yl	419.2	1.92
27	7-methoxy-benzofuran-2-yl	408.2	1.79
28	4-biphenyl	414.2	1.92
29	5-bromothiophene-2-yl	422	1.77
30	4-cyclohexylphenyl	420.3	2.16
31	6-chloro-2H-chromene-3-yl	426.2	1.92
32	3-chlorobenzothiophene-2-yl	428.1	1.92
33	4-phenoxyphenyl	430.2	1.92

EXAMPLE 34

Preparation of (3'S)-1'-[4-(3-Methylphenoxy)benzoyl]-1,3'-bipyrrolidine Hydrochloride



Step 1) (3'S)-1'-(4-fluorobenzoyl)-1,3'-bipyrrolidine

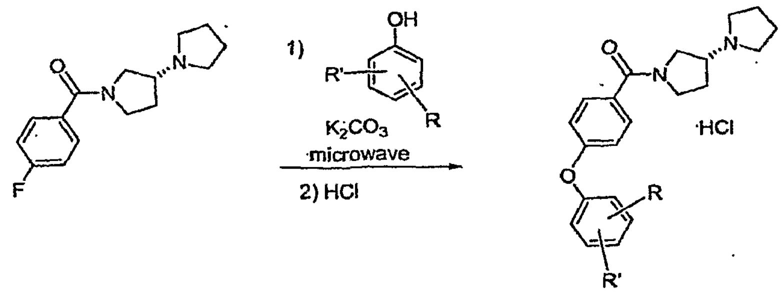
A solution of 4-fluorobenzoic acid (1.5 g, 10.71 mmol) in dichloroethane:DMF (4:1) was treated with *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethlyuronium tetrafluoroborate (4.13 gm 12.85 mmol) and *N*-methylmorpholine (5.41 g, 53.55 mmol) followed by a solution of (3'*S*)-1,3'-bipyrrolidine (2.52 g, 11.77 mmol) in dichloroethane:DMF (4:1). The reaction mixture was stirred at room temperature for 3 h and quenched with saturated sodium hydrogen carbonate. The phases were separated. The aqueous phase was extracted with ethyl acetate. The organic phase and the extracts were combined, washed sequentially with water and saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography to provide (3'*S*)-1'-(4-fluorobenzoyl)-1,3'-bipyrrolidine (57%) as a white solid.

Step 2) (3'S)-1'-[4-(3-methylphenoxy)benzoyl]-1,3'-bipyrrolidine hydrochloride

A solution of (3'*S*)-1'-(4-fluorobenzoyl)-1,3'-bipyrrolidine (0.011 g, 0.381 mmol in dimethylformamide was treated with *m*-cresol (0.127 g, 1.14 mmol) and potassium carbonate (0.105 g, 0.762 mmol), heated to 150°C via microwave radiation for 20 minutes and cooled to room temperature. The reaction mixture was diluted with dichloromethane, washed sequentially with water and saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (silica, methanol:dichloromethane 5:95) to give the free amine of the title product as a yellow oil. This oil was dissolved in isopropanol and diethyl ether (1:10), treated with 1.0N HCl in diethyl ether and filtered. The filter cake was dried to afford the title product as a yellow solid, 0.021 g (16%), identified by NMR and mass spectral analyses. MS [351.3 m/e (M+H)].

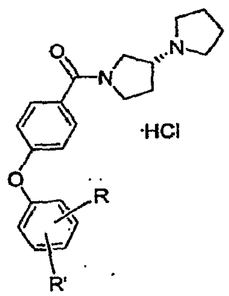
<u>EXAMPLES 35-43</u>

Preparation of (3'S)-1'-[4-(Substituted-phenoxy)benzoyl]-1,3'-bipyrrolidine Hydrochloride Compounds



Using essentially the same procedure described in Example 34, Step 2, and employing the desired phenol, the compounds shown on Table IV were obtained and identified by NMR and mass spectral analyses.

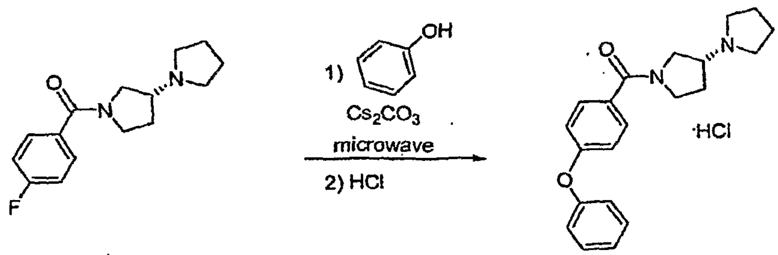
TABLE IV



Ex. No.	R	R'	% Yield	mp °C	[M+H]
35	H	4-CH_3	34	98-100	351.3
36	H	3-OCH_3	34	82-84	367.2
37	H	4-Cl	21	--	371.2
38	H	4-OCH_3	16	--	367.2
39	2-CH_3	4-Cl	35	123-125	385.2
40	2-Cl	4-CH_3	33	124-126	385.2
41	2-CH_3	H	9	--	351.3
42	H	4-imidazol-1-yl	28	--	403.2
43	H	4-CN	12	--	362.3

EXAMPLE 44

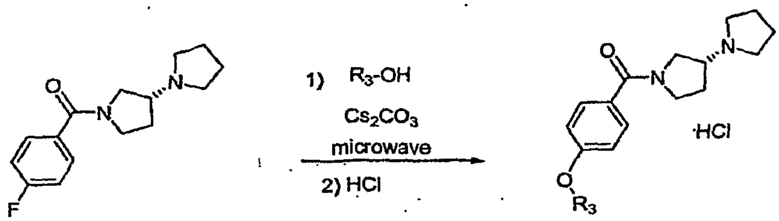
Preparation of (3'S)-1'-(4-phenoxybenzoyl)-1,3'-bipyrrolidine Hydrochloride



A mixture of 100 mg of (3'*S*)-1'-(4-fluorobenzoyl)-1,3'-bipyrrolidine (0.4mmol), 1.5 equivalents of phenol and 2.0 equivalents of cesium carbonate in 1 mL of DMF is irradiated in a CEM Microwave vessel for 10 minutes. The reaction mixture is cooled to room temperature and purified by Gilson reverse phase chromatography to afford the free amine of the title product. The free amine is treated with ethereal HCl and evaported to dryness *in vacuo* to give the title product, identified by NMR and mass spectral analyses. [M+H] 337.4

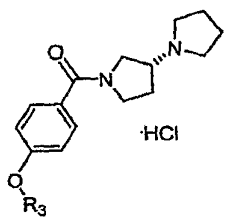
EXAMPLES 45-53

Preparation of (3'S)-1'-(4-phenoxybenzoyl)-1,3'-bipyrrolidine



Using essentially the same procedure described in Example 44 and employing the desired substituted phenol reagent, the compounds shown on Table V were obtained and identified by NMR and mass spectral analyses.

TABLE V



Ex. No.	R3	[M+H]
45	4-fluorophenyl	355.2
46	4-fluoro-2-methylphenyl	369.4
47	3-chloro-4- fluorophenyl	389.9
48	3-fluorophenyl	355.4
49	2-chloro-4- fluorophenyl	389.9
50	quinolin-4-yl	388.5
51	4-chloronaphth-1-yl	421.9
52	4-(4-fluorophenoxy)phenyl*	447.5
53	3-(3-fluorophenoxy)phenyl*	447.5

*Isolated as a byproduct when displacement of fluoride occurred more than once.

Example 54

Evaluation of Methyl histamine binding in human histamine H3 receptor cell line

The affinity of test compounds for the histamine 3 (H3) receptor is evaluated in the following manner. Stably transfected HEK293T cells are grown in DMEM containing 10% heat inactivated FBS and G-418 (500ug/ml). Cells are scraped from the plate, transferred to centrifuge tubes, washed one time in PBS by centrifugation in a Sorvall RT7 Plus centrifuge (2000rpm 10 minutes, 4°C). The resulting pellets are stored at -80°C until ready for use. Cells are re-suspended in buffer (50mM Tris pH=7.5) and placed in a Dounce homogenizer, douncing ten times to homogenize cells. The homogenate is spun down by centrifugation (Sorvall RT7 Plus, 1800rpm

10 minutes, 4°C). The supernatant is placed in a Corex tube and spun down by centrifugation (Sorvall RC 5c Plus, 17,000 rpm 20 minutes, 4°C). The pellet is resuspended in buffer (50mM Tris, pH 7.5). Protein concentration (ug/ul) is determined using the Micro-BCA Protein Determination. The binding assay is set up in a 96 well microtiter plate in a total volume of 250 uL. Non-specific binding is determined in the presence of 10 uM clobenpropit. The final radioligand concentration is 1 nM. The test compound is serially diluted using the Beckman Biomek2000 to a final approximate range of 100 uM to 100 pM. Membranes are suspended in buffer, homogenized in 2 bursts of ten seconds using a Vitris mechanical homogenizer set at power setting 5. Ten μg of membranes are added to each well. Following a one hour incubation at 30°C, the reaction is terminated by the addition of ice cold buffer and rapid filtration with a Packard Filtermate Harvester through a GF/B filter pre-soaked with 1% PEI for one hour. The plate is dried for one hour at 37°C and 60 μL Microscint Scintillant is added to each well. The CPM per well is measured on a Packard Top Count NXT. Ki values are determined in nM. The Ki is calculated from the IC_{50} (i.e. the concentration of competing ligand which displaces 50% of the specific binding of the radioligand). CPM values are expressed as % specific binding and plotted vs compound concentration. A curve is fitted using a four-parameter logistic fit and the IC_{50} value is determined. The Ki is calculated from this using the Cheng-Prusoff equation: $pKi = IC_{50}/1+(L/Kd)$ where L = concentration of free radioligand used in the assay, and Kd is the dissociation constant of the radioligand for the receptor. L is determined for each experiment by counting an aliquot of the diluted radioligand (corresponding to that added to each well) and the Kd has previously been determined under identical conditions for this cell line / radioligand.

Cyclic AMP assay for histamine receptor H3 antagonism activity.

Stable H3 cells are maintained in tissue culture flask in DMEM with high glucose, 10 % FBS, 1X pen/strep, 500 ug/ml GY18, until experiment. Culture media is removed and cells are washed twice with PBS w/ Ca^{++} and Mg^{++} plus 500 μM IBMX. Cells are then detached by tapping on the side of the flask and resuspend in the same buffer. Two thousand cells/well are incubated with 1 μM histamine plus 10 μM forskolin plus various concentrations of compounds in a total volume of 30 μL in 96 well plates for 30 min at 30°C. Final test compound concentrations range from

10-4M to 10-9.5M at full log dilutions. Cyclic AMP levels are measured using HitHunter cAMP kit from Discoverx, cat# 900041 according to manufacturer's instruction. Chemiluminescence signals are detected using Top Count (Packard). Cyclic AMP levels in control cells receiving 10 μM forskolin plus 100 nM histamine are considered 0%, and in cells receiving 10 uM forskolin plus 100 nM histamine plus 1 μM clobenpropit are considered 100%. Data are expressed as % control and analyzed using Prizm soft ware. The Kb values are calculated using the following equation, KB = EC_{50} or IC_{50}/[1 + (ligand/Kd)]. The data are shown in Table VI, below.

For Table VI

A = ≤ 10 nM
B = 10.1 nM -50.0 nM
C = 50.1 nM - 100 nM
D = > 100 nM

TABLE VI

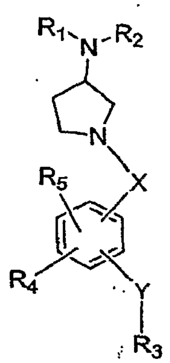
Ex No	H3 Binding Ki (nM)	cAMP Kb (nM)
1	A	--
3	--	--
4	D	--
5	--	--
6	D	10.8
7	D	14
8	--	--
9	--	--
10	--	--
11	D	--
12	--	--
13	D	--
14	--	--
15	D	--
16	D	--

Ex No	H3 Binding Ki (nM)	cAMP Kb (nM)
17	D	57
18	--	--
19	D	--
20	--	--
21	D	--
22	D	--
23	D	--
24	D	--
25	D	--
26	D	--
27	D	--
28	D	--
29	D	--
30	D	--
31	D	--
32	D	--
33	D	--
34	B	--
35	B	--
36	B	--
37	B	--
38	B	--
39	A	--
40	A	--
41	A	--
42	A	--
43	A	--
44	A	--
45	A	--
46	A	--
47	A	--

Ex No	H3 Binding Ki (nM)	cAMP Kb (nM)
48	A	--
49	A	--
50	A	--
51	D	--
52	B	--
53	B	--

What is claimed is:

1. A compound of formula I



(I)

wherein

X is CO, CH_2 or SO_m;

Y is NR_6, NR_6CO, O or SO_p;

m and p are each individually 0 or an integer of 1 or 2;

R_1 and R_2 are each independently H or an optionally substituted alkyl group or R_1 and R_2 may be taken together with the atom to which they are attached to form an optionally substituted 4- to 7-membered ring optionally containing one or two additional heteroatoms selected from N, O or S

R_3 is NR_7R_8 or an aryl or heteroaryl group each group optionally substituted with the proviso that when Y is NR_6, O or SO_p then R_3 must be an aryl or heteroaryl group each group optionally substituted;

R_4 and R_5 are each independently H, halogen, OR_9 or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_6 and R_9 are each independently H or an optionally substituted alkyl group; and

R_7 and R_8 are taken together with the atom to which they are attached to form an optionally substituted fused bicyclic or tricyclic 9- to 11-membered ring system optionally containing one to three additional heteroatoms selected from N, O or S; or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein wherein X is CO or CH_2.

3. The compound according to claim 1 or claim 2 wherein Y is NR_6, NR_6CO or O.

4. The compound according to any one of claims 1 to 3 wherein R_1 and R_2 are taken together with the atom to which they are attached to form an optionally substituted 5-membered ring.

5. The compound according to any one of claims 1 to 4 wherein Y is O.

6. The compound according to any one of claims 1 to 5 wherein X is CO.

7. The compound according to claim 1 which is one of the following:
(3'S)-1'-(4-phenoxybenzoyl)-1,3'-bipyrrolidine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1-naphthamide;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)quinoline-2-carboxamide;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1-benzothiophene-2-carboxamide;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2-phenylquinazolin-4-amine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-9H-purin-6-amine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)pyridin-2-amine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)thieno[3,2-d]pyrimidin- 4-amine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-7-methylthieno[3,2-d]pyrimidin-4-amine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)isoquinolin-1-amine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-5- (trifluoromethyl)pyridin-2-amine;
N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)pyrimidin-2-amine;
1-[4-(1-benzothien-3-ylamino)benzoyl]-N,N-dimethylpyrrolidin-3-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2,1,3-benzothiadiazol-4-amine;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1H-indol-5-amine;

3-chloro-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)thiophene-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2-naphthamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)isoquinoline-1- carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1-methyl-1H-indole-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-5-methyl-3- phenylisoxazole-4-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-4-methoxyquinoline-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-7-methoxy-1-benzofuran- 2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)biphenyl-4-carboxamide;

5-bromo-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)thiophene-2-carboxamide;

4-cyclohexyl-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)benzamide;

6-chloro-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-2H-chromene-3-carboxamide;

3-chloro-N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-1- benzothiophene-2-carboxamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)-4-phenoxybenzamide;

N-(4-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)quinolin-5-amine;

1-[4-(2,3-dihydro-1,4-benzodioxin-6-ylamino)benzoyl]-N,N-dimethylpyrrolidin-3-amine;

1-[4-(1,3-benzodioxol-5-ylamino)benzoyl]-N,N-dimethylpyrrolidin-3-amine;

(3'S)-1'-(4-phenoxybenzoyl)-1,3'-bipyrrolidine;

(3'S)-1'-[4-(4-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;

(3'S)-1'-[4-(4-fluoro-2-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;

(3'S)-1'-[4-(3-chloro-4-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(3-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(2-chloro-4-fluorophenoxy)benzoyl]-1,3'-bipyrrolidine;
4-{4-[(3'S)-1,3'-bipyrrolidin-1'-ylcarbonyl]phenoxy}quinoline;
(3'S)-1'-{4-[4-(1H-imidazol-1-yl)phenoxy]benzoyl}-1,3'-bipyrrolidine;
4-{4-[(3'S)-1,3'-bipyrrolidin-1'-ylcarbonyl]phenoxy}benzonitrile;
(3'S)-1'-[4-(3-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(3-methoxyphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-chlorophenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-methoxyphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(4-chloro-2-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(2-chloro-4-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-[4-(2-methylphenoxy)benzoyl]-1,3'-bipyrrolidine;
(3'S)-1'-{4-[4-(4-fluorophenoxy)phenoxy]benzoyl}-1,3'-bipyrrolidine;
(3'S)-1'-{4-[3-(3-fluorophenoxy)phenoxy]benzoyl}-1,3'-bipyrrolidine;
(3'S)-1'-{4-[(4-chloro-1-napthyl)oxy]benzoyl}-1,3'-bipyrrolidine;
a stereoisomer thereof; and
a pharmaceutically acceptable salt thereof.

8. A method for the treatment of a central nervous system disorder related to or affected by the Histamine-3 receptor in a patient in need thereof which comprises providing to said patient a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 7 or a stereoisomer or a pharmaceutically acceptable salt thereof.

9. The method according to claim 8 wherein said disorder is a cognitive disorder, a developmental disorder or a sleep disorder.

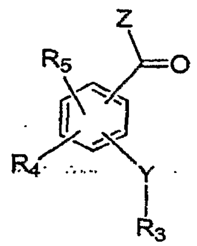
10. The method according to claim 9 wherein said disorder is a cognitive disorder.

11. The method according to claim 10 wherein said disorder is selected from the group consisting of: Alzheimer's disease; a learning disorder; attention deficit disorder; and schizophrenia.

12. A method for the inhibtion of the H3 receptor which comprises contacting said receptor with an effective amount of a compound of formula I as claimed in any one of claims 1 to 7 or a stereoisomer or a pharmaceutically acceptable salt thereof.

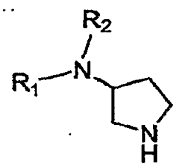
13. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as claimed in any one of claims 1 to 7 or a stereoisomer or a pharmaceutically acceptable salt thereof.

14. A process for the preparation of a compound of formula I as defined in claim 1
which process comprises reacting a compound of formula II



(II)

wherein Z is Cl or OH and Y, R_3, R_4 and R_5 are as described for formula I with an amine of formula III



(III)

wherein R_1 and R_2 are as described for formula I in the presence of a base optionally in the presence of a solvent.