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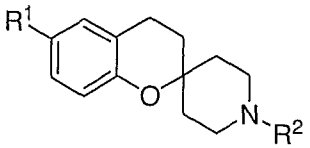
(54) Title: SPIROCHROMANE ANTAGONISTS OF THE H-3 RECEPTOR



(I)

(57) Abstract: This invention is directed to a compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical composition containing a compound of formula I, a process of preparation of a compound of formula I, a method of treatment of a disorder or condition that may be treated by antagonizing histamine H3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula I as described above, and a method of treatment of a disorder or condition selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, Alzheimer's disease, attention-deficit hyperactivity disorder (ADHD), psychotic disorders, cognitive disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy- induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the Gl tract, hyper and hypo motility and acidic secretion of the gastro- intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula I as described above.

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SPIROCHROMANE ANTAGONISTS OF THE H-3 RECEPTOR

Background of the Invention

This invention is directed to compounds of formula I described herein, to a pharmaceutical composition comprising such compounds, and to methods of treatment of disorders or conditions that may be treated by antagonizing histamine-3 (H3) receptors using such compounds.

Histamine is a well-known mediator in hypersensitive reactions (e.g. allergies, hay fever, and asthma) that are commonly treated with antagonists of histamine or "antihistamines." It has also been established that histamine receptors exist in at least two distinct types, referred to as H1 and H2 receptors.

A third histamine receptor (H3 receptor) is believed to play a role in neurotransmission in the central nervous system, where the H3 receptor is thought to be disposed presynaptically on histaminergic nerve endings (Nature, 302, S32- 837 (1983)). The existence of the H3 receptor has been confirmed by the development of selective H3 receptor agonists and antagonists (Nature, 327, 117-123 (1987)) and has subsequently been shown to regulate the release of the neurotransmitters in both the central nervous system and peripheral organs, particularly the lungs, cardiovascular system and gastrointestinal tract.

A number of diseases or conditions may be treated with histamine-3 receptor ligands wherein the H3 ligand may be an antagonist, agonist or partial agonist, see: (Imamura et al., Circ. Res., (1996) 78, 475-481); (Imamura et. al., Circ. Res., (1996) 78, 863-869); (Lin et al., Brain Res. (1990) 523, 325-330); (Monti et al., Neuropsychopharmacology (1996) 15, 31 35); (Sakai, et al., Life Sci. (1991) 48, 2397-2404); (Mazurkiewiez- Kwilecki and Nsonwah, Can. J. Physiol. Pharmacol. (1989) 67, 75-78); (Panula, P. et al., Neuroscience (1998) 44, 465-481); (Wada et al., Trends in Neuroscience (1991) 14,415); (Monti et al., Eur. J. Pharmacol. (1991) 205, 283); (Mazurkiewicz-Kwilecki and Nsonwah, Can. J. Physiol. Pharmacol. (1989) 67, 75-78); (Haas et al., Behav. Brain Res. (1995) 66, 41-44); (De Almeida and Izquierdo, Arch. Int. Pharmacodyn. (1986) 283, 193-198); (Kamei et al., Psychopharmacology (1990) 102, 312-318); (Kamei and Sakata, Japan. J. Pharmacol. (199 1) 57, 437-482); (Schwartz et al., Psychopharmacology; The fourth Generation of Progress, Bloom and Kupfer (eds.), Raven Press, New York, (1995) 3 97); (Shaywitz et al., Psychopharmacology (1984) 82, 73-77); (Dumery and Blozovski, Exp. Brain Res. (1987) 67, 61-69); (Tedford et al., J. Pharmacol. Exp. Ther. (1995) 275, 598-604); (Tedford et al., Soc. Neurosci. Abstr. (1996) 22, 22); (Yokoyama et al., Eur. J. Pharmacol. (1993) 234,129); (Yokoyama and Iinuma, CNS Drugs (1996) 5, 321); (Onodera et al., Prog. Neurobiol. (1994) 42, 685); (Leurs and Timmerman, Prog. Drug Res. (1992) 39,127); (The Histamine H3 Receptor, Leurs and Timmerman (ed.), Elsevier Science, Amsterdam, The Netherlands (1998); (Leurs et al., Trends in Pharm. Sci. (1998) 19, 177-183); (Phillips et al., Annual Reports in Medicinal Chemistry (1998) 33, 31-40);

(Matsubara et al., Eur. J. Pharmacol. (1992) 224, 145); (Rouleau et al., J. Pharmacol. Exp. Ther. (1997) 281 , 1085); (Adam Szelag, "Role of histamine H3-receptors in the proliferation of neoplastic cells in vitro", Med. Sci. Monit., 4(5): 747- 755, (1998)); (Fitzsimons, C , H. Duran, F. Labombarda, B. Molinari and E. Rivera, "Histamine receptors signalling in epidermal tumor cell lines with H-ras gene alterations", Inflammation Res., 47 (Suppl. 1): S50-S51, (1998)); (R. Leurs, R.C. Vollinga and H. Timmerman, "The medicinal chemistry and therapeutic potentials of ligand of the histamine H3 receptor", Progress in Drug Research 45: 170-165, (1995)); (R. Levi and N.C.E. Smith, "Histamine H3-receptors: A new frontier in myocardial ischemia", J. Pharm. Exp. Ther., 292: 825-830, (2000)); (Hatta, E., K Yasuda and R. Levi, "Activation of histamine H3 receptors inhibits carrier-mediated norepinephrine release in a human model of protracted myocardial ischemia", J. Pharm. Exp. Ther., 283: 494-500, (1997); (H. Yokoyama and K. linuma, "Histamine and Seizures: Implications for the treatment of epilepsy", CNS Drugs, 5(5); 321-330, (1995)); (K. Hurukami, H. Yokoyama, K. Onodera, K. linuma and T. Watanabe, AQ-O 145, "A newly developed histamine H3 antagonist, decreased seizure susceptibility of electrically induced convulsions in mice", Meth. Find. Exp. Clin. Pharmacol., 17(C): 70-73, (1995); (Delaunois A., Gustin P., Garbarg M., and Ansay M., "Modulation of acetylcholine, capsaicin and substance P effects by histamine H3 receptors in isolated perfused rabbit lungs", European Journal of Pharmacology 277(2-3):243-50, (1995)); and (Dimitriadou, et al., "Functional relationship between mast cells and C- sensitive nerve fibres evidenced by histamine H3-receptor modulation in rat lung and spleen", Clinical Science 87(2):151-63, (1994). Such diseases or conditions include cardiovascular disorders such as acute myocardial infarction; memory processes, dementia and cognition disorders such as Alzheimer's disease and attention-deficit hyperactivity disorder; neurological disorders such as Parkinson's disease, schizophrenia, depression, epilepsy, and seizures or convulsions; cancer such as cutaneous carcinoma," medullary thyroid carcinoma and melanoma; respiratory disorders such as asthma; sleep disorders such as narcolepsy; vestibular dysfunction such as Meniere's disease; gastrointestinal disorders, inflammation, migraine, motion sickness, obesity, pain, and septic shock.

H3 receptor antagonists have also been previously described in, for example, WO 03/050099, WO 02/0769252, and WO 02/12224. The histamine H3 receptor (H3R) regulates the release of histamine and other neurotransmitters, including serotonin and acetylcholine. H3R is relatively neuron specific and inhibits the release of certain monoamines such as histamine. Selective antagonism of H3R receptors raises brain histamine levels and inhibits such activities as food consumption while minimizing non-specific peripheral consequences. Antagonists of the receptor increase synthesis and release of cerebral histamine and other monoamines. By this mechanism, they induce a prolonged wakefulness, improved cognitive function, reduction in food intake and normalization of vestibular reflexes. Accordingly, the

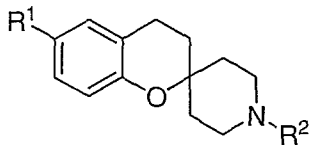
receptor is an important target for new therapeutics in Alzheimer disease, mood and attention adjustments, including attention deficit hyperactive disorder (ADHD), cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, narcolepsy and motion sickness, and various forms of anxiety.

The majority of histamine H3 receptor antagonists to date resemble histamine in possessing an imidazole ring that may be substituted, as described, for example, in WO96/38142. Non-imidazole neuroactive compounds such as beta histamines (Arrang, Eur. J. Pharm. 1985, 111:72-84) demonstrated some histamine H3 receptor activity but with poor potency. EP 978512 and EP 0982300A2 disclose non-imidazole alkyamines as histamine H3 receptor antagonists. WO 02/12224 (Ortho McNeil Pharmaceuticals) describes non-imidazole bicyclic derivatives as histamine H3 receptor ligands. Other receptor antagonists have been described in WO02/32893 and WO02/06233.

This invention is directed to histamine-3 (H3) receptor antagonists of the invention useful for treating the conditions listed in the preceding paragraphs. The compounds of this invention are highly selective for the H3 receptor (vs. other histamine receptors), and possess remarkable drug disposition properties (pharmacokinetics). In particular, the compounds of this invention selectively distinguish H3R from the other receptor subtypes H1R, H2R. In view of the increased level of interest in histamine H3 receptor agonists, inverse agonists and antagonists in the art, novel compounds that interact with the histamine H3 receptor would be a highly desirable contribution to the art. The present invention provides such a contribution to the art being based on the finding that a novel class of spirochromane amines has a high and specific affinity to the histamine H3 receptor.

Summary of the Invention

This invention is directed to a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein

R^2 is (Ci-C_4)alkyl;

R^1 is selected from the group consisting of phenyl, naphthyl, 5 to 6-membered heteroaryl, and C(=O)NR^3R^4; wherein said heteroaryl contains 1 to 4 heteroatoms independently selected from N, O, and S; and wherein said phenyl, naphthyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, (CrC_6)alkyl, (C_1-C_6)BIkOXy, carbonyl, carboxyl, cyano, nito, -C(=O)(C_1-C_6)alkyl, -C(=O)NR_3R_4, and -SO_p(C_1-C_4)alkyl, wherein p is 1 or 2;

wherein R^3 and R^4 are each independently selected from the group consisting of

hydrogen;

(CrC $_a$)alkyl optionally substituted with -OH or 1 to 4 halogens;

(Ci-C $_4$)alkyl optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 (CrC $_4$)alkyl groups, bicyclo[2.2.1]hept-2-ene, (C_3-C_7)cycloalkyl, (CrC^dialkylamino, (C_6-Ci $_4$)aryl optionally substituted with a halogen and optionally substituted with (C_6-Ci $_0$)aryloxy optionally substituted with 1 to 2 halogens, and 5-10-membered heteroaryl optionally substituted with (C_6-C_{10})aryl and optionally substituted with 1 to 3 (C-|-C_4)alkyl groups;

(C_3-C_7)cycloalkyl optionally substituted with hydroxy (C_1-C_4JaIRyl;

(C_6-C_{14})aryl;

-(C_2-C_3)alkyl-O-(CrC $_3$)alkyl optionally substituted with (C_r C_3)alkyl;

-(C_2-C_3)alkyl-S-(C_r C_3)alkyl optionally substituted with (C_r C_3)alkyl;

-(C_1-C_3)alkyl-C(=O)O-(C_1-C_3)alkyl;

3 to 8-membered heterocycloalkyl;

(C_6-C_{10})arylsulfonyl optionally substituted with one or more (CrC $_2$)alkyl;

5 to 10-membered heteroaryl; and

(C_6-Ci $_4$)aryl-(Co-C $_4$)alkylene-0-(C_0-C_4)alkyl, wherein each (C_0-C_4)alkyl and each (C_0-C_4)alkylene is optionally substituted with 1 to 4 (CrC $_4$)alkyl;

or optionally R^3 and R^4, together with the nitrogen to which they are attached, form a 3 to 7-membered saturated or unsaturated heterocyclic ring, wherein one of the carbons in said heterocyclic ring is optionally replaced by O, S, NR^5 or CO, and wherein said ring is optionally fused to a (C_6-C_{10})arylene and is optionally substituted at a ring carbon with a substituent selected from the group consisting of

-OH, 5-10-membered heteroaryl optionally substituted with one or more halogens and optionally substituted with one or more (CrC $_2$)alkyl, 5 to 6 membered aryl, (C_1-C_4)alkoxy optionally substituted with one or more (d-C $_2$)alkoxy and optionally substituted with one or more (C_1-C_4)dialkylaminocarbonyl, and 1 to 2 (C_1-C_4)alkyl optionally and independently substituted with one or more (C_r C_2)alkoxy;

wherein R^5 is selected from the group consisting of

hydrogen;

(CrC $_8$)alkyl optionally substituted with 1 to 4 halogens;

5-10-membered heteroaryl optionally substituted with a substituent selected from the group consisting of halogen, (C-|-C_4)alkyl, (C_1-C_2JaIkOXy, (C_6-C_{10})aryl, (C_1-C_4)alkylaminocarbonyl, and cyano;

(C_1-C_4)alkyl group optionally substituted with a substituent selected from the group consisting of (C_1-C_2)alkoxycarbonyl, 5-10-membered heteroaryl optionally

substituted with one or more (Ci-C 2)alkyl, 1 to 4 (C_1-C_4)alkyl, and (C_3-C_7)cycloalkyl;

(C_6-C_{10})aryl optionally substituted with 1 or 2 (C_r C_2)alkyl;

(Ci-C 4)alky)carbonyl; and

(C_6-C_{14})aryl-(Co-C_4)alkylene-0-(Co-C 4)alkyl, wherein each (C_0-C_4)alkyi and each (C_0-C_4)alkylene is optionally substituted with 1 to 4 (CrC 4)alkyl.

A preferred embodiment includes compounds of claims 1 wherein

R^2 is ethyl;

R^1 is C(=O)NR^3R^4;

wherein R^3 and R^4 are each independently (C_r C_4)aIkyl optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 (CrC 4)alkyl groups, bicyclo[2.2.1]hept-2-ene, (C_3-C_7)cycloalkyl, (C_r C_4)dialkylamino, (C_6-C_{14})aryl optionally substituted with a halogen and optionally substituted with (C_6-C_{10})aryloxy optionally substituted with 1 to 2 halogens, and 5-10-membered heteroaryl optionally substituted with (C_6-C_{10})aryl and optionally substituted with 1 to 3 (CrC 4)alkyl groups;

Another preferred embodiment includes compounds of claims 1 wherein

R^2 is ethyl; and

R^1 is phenyl or 5 to 6-membered heteroaryl,

wherein said heteroaryl contains 1 to 4 heteroatoms independently selected from N, O, and S; and wherein said phenyl or heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, (Ci-C βJalkyl, (C_1-C_6)alkoxy, carbonyl, carboxyl, cyano, nito, -C(=O)(CrC 6)alkyl, -C(=O)NR_3R_4, and -SO_p(C_1-C_4)alkyl, wherein p is 1 or 2;

wherein R^3 and R^4 are each independently (C_r C_4)alkyl optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 (CrC 4)alkyl groups, bicyclo[2.2.1]hept-2-ene, (C_3-C_7)cycloalkyl, (CrC 4)dialkylamino, (C_6-C_{14})aryl optionally substituted with a halogen and optionally substituted with (C_6-Cio)aryloxy optionally substituted with 1 to 2 halogens, and 5-10-membered heteroaryl optionally substituted with (C_6-C_{10})aryl and optionally substituted with 1 to 3 (C_1-C_4)alkyl groups.

Preferred and exemplary embodiments of the present invention include the following compounds of formula I:

N-methyl-N-(2-thienylmethyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4 l-piperidine]-6-carboxamide,
N-^^methylthioJethyO-i'-ethyl-S^-dihydrospirofchromene^^'-piperidinel-e-carboxamide,
N-(2-furylmethyl)-N-methyl-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxamide,
N-cyclopenty]-N-methyl-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxannide,
6-[(2-ethylaziridin-1-yl)Garbonyl]-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
e^e-methoxypyridin-S-yO-i'-ethyl-S^-dihydrospirotchromene^^'-piperidine],
6-[4-(methylsulfonyl)phenyl]-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
4-(1 '-ethyl-S,4-dihydrospirotchromene^^'-piperidinl- δ-yObenzoic acid,
N-[(3-methyl-2-thienyl)methyl]-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxamide,
1-[4-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)phenyl]ethanone,
6-(2,5-dihydro-1H-pyrrol-1-ylcarbonyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
3-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)-4-methoxybenzaldehyde,
6-(2,3,4-trimethoxyphenyl)1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
6-(2-methoxypyridin-3-yl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
[3-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)phenyl]methanol,
1-[2-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yi)phenyl]ethanone,
6-[4-(ethylsulfonyl)phenyl]-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
1'-ethyl-6-pyrimidin-5-yl-3,4-dihydrospiro[chromene-2,4'-piperidine],
6-(2-ethoxypyridin-3-yl)-1'-ethyl-3,4-dihydros piro[chromene-2,4'-piperidine],
6-(4-ethoxyphenyl)-1'-ethyl-3,4-dihydrospirotchromene-2,4'-piperidine]
6-(2-ethoxyphenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
1'-ethyl-6-pyridin-3-yl-3,4-dihydrospirotchromene-2,4'-piperidine],
6-(4-methyl-3-nitrophenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
6-(3,4,5-trimethoxyphenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
methyl 4-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)benzoate,
1'-ethyl-6-(4-fluorophenyl)-3,4-dihydrospiro[chromene-2,4'-piperidine],
r-ethyl-6-(4-fluorophenyl)-3,4-dihydrospiro[chromene-2,4'-piperidine],
3-(1 '-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)benzoic acid,
N-^^i'-ethyl-S^-dihydrospirotchromene^^'-piperidinj- δ-yOphenyOacetamide,
6-[3-(1 H-pyrazol-1 -yl)phenyl]1 '-ethyl-3,4-dihydrospiro[chromene-2,4'-pipe πdine], and
6-(2-methoxy-5-methylphenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine].

This invention is also directed to pharmaceutical composition for treating a disorder or condition that may be treated by antagonizing histamine-3 receptors, the composition comprising a compound of formula I and optionally a pharmaceutically acceptable carrier.

This invention is also directed to a method of treatment of a disorder or condition that may be treated by antagonizing histamine-3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula I.

This invention is also directed to a method of treatment of a disorder or condition selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, cognitive disorders, Alzheimer's disease, attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD), psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy- induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro- intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula I.

This invention is also directed to a pharmaceutical composition for treating allergic rhinitis, nasal congestion or allergic congestion comprising: (a) an H3 receptor antagonist compound of formula I or a pharmaceutically acceptable salt thereof; (b) an H1 receptor antagonist or a pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating allergy rhinitis, nasal congestion or allergic congestion.

This invention is also directed to a pharmaceutical composition for treating ADD, ADHD, depression, mood disorders, or cognitive disorders comprising: (a) an H3 receptor antagonist compound of Formula I or a pharmaceutically acceptable salt thereof; (b) a neurotransmitter re-uptake blocker or a pharmaceutically acceptable salt thereof; (c) a pharmaceutically acceptable carrier; wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating depression, mood disorders, and cognitive disorders.

In the general formula I according to the present invention, when a radical is mono- or poly-substituted, said substituent(s) can be located at any desired position(s), unless otherwise stated. Also, when a radical is polysubstituted, said substituents can be identical or different, unless otherwise stated.

The histamine-3 (H3) receptor antagonists of the invention are useful for treating, in particular, ADD, ADHD, obesity, anxiety disorders and respiratory diseases. Respiratory diseases that may be treated by the present invention include adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis.

The pharmaceutical composition and method of this invention may also be used for preventing a relapse in a disorder or condition described in the previous paragraphs. Preventing such relapse is accomplished by administering to a mammal in need of such prevention a compound of formula I as described above.

The disclosed compounds may also be used as part of a combination therapy, including their administration as separate entities or combined in a single delivery system, which employs an effective dose of a histamine H3 antagonist compound of general formula I and an effective dose of a histamine H1 antagonist, such as cetirizine (Zyrtec™), chlorpheniramine (Chlortrimeton™), loratidine (Claritin™), fexofenadine (Allegra™), or desloratadine (Clarinex™) for the treatment of allergic rhinitis, nasal congestion, and allergic congestion.

The disclosed compounds may also be used as part of a combination therapy, including their administration as separate entities or combined in a single delivery system, which employs an effective dose of a histamine H3 antagonist compound of general formula I and an effective dose of a neurotransmitter reuptake blocker. Examples of neurotransmitter reuptake blockers will include the serotonin-selective reuptake inhibitors (SSRI's) like sertraline (Zoloft™), fluoxetine (Prozac™), and paroxetine (Paxil™), or non-selective serotonin, dopamine or norepinephrine reuptake inhibitors for treating ADD, ADHD, depression, mood disorders, or cognitive disorders.

The compounds of the present invention may have optical centers and therefore may occur in different enantiomeric configurations. Formula I, as depicted above, includes all enantiomers, diastereomers, and other stereoisomers of the compounds depicted in structural formula I, as well as racemic and other mixtures thereof. Individual isomers can be obtained by known methods, such as optical resolution, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate.

The present invention also includes isotopically labeled compounds, which are identical to those recited in formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, $^{18}0$, ^{17}O, ^{15}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, ^{123}I, respectively. Compounds of the present invention and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or- other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, Le$_1$, ^{3}H, and carbon-14, Le., ^{14}C, isotopes are particularly

preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Anxiety disorders include, for example, generalized anxiety disorder, panic disorder, PTSD, and social anxiety disorder. Mood adjustment disorders include, for example, depressed mood, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and depressed mood. Cognitive disorders include, for example, ADHD, attention-deficit disorder (ADD) or other attention adjustment or cognitive disorders due to general medical conditions. Psychotic disorders include, for example, schizoaffective disorders and schizophrenia; sleep disorders include, for example, narcolepsy and enuresis.

Examples of the disorders or conditions which may be treated by the compound, composition and method of this invention are also as follows: depression, including, for example, depression in cancer patients, depression in Parkinson's patients, post-myocardial infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression, neuropathic pain, manic depressive illness, including manic depressive illness with mixed episodes and manic depressive illness with depressive episodes, seasonal affective disorder, bipolar depression BP I_1 bipolar depression BP II, or major depression with dysthymia; dysthymia; phobias, including, for example, agoraphobia, social phobia or simple phobias; eating disorders, including, for example, anorexia nervosa or bulimia nervosa; chemical dependencies, including, for example, addictions to alcohol, cocaine, amphetamine and other psychostimulants, morphine, heroin and other opioid agonists, phenobarbital and other barbiturates, nicotine, diazepam, benzodiazepines and other psychoactive substances; Parkinson's diseases, including, for example, dementia in Parkinson's disease, neuroleptic-induced parkinsonism or tardive dyskinesias; headache, including, for example, headache associated with vascular disorders; withdrawal syndrome; age-associated learning and mental disorders; apathy; bipolar disorder; chronic fatigue syndrome; chronic or acute stress; conduct disorder; cyclothymic disorder; somatoform disorders such as somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated disorder, and somatoform NOS; incontinence; inhalation disorders;

intoxication disorders; mania; oppositional defiant disorder; peripheral neuropathy; post-traumatic stress disorder; late luteal phase dysphoric disorder; specific developmental disorders; SSRI "poop out" syndrome, or a patient's failure to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response; and tic disorders including Tourette's disease.

As an example, the mammal in need of the treatment or prevention may be a human. As another example, the mammal in need of the treatment or prevention may be a mammal other than a human.

Pharmaceutically acceptable salts of the compounds of formula I include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids that form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases that form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components, which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be

ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula I include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula I.

Compounds of formula I containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula I, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-arginine.

Unless otherwise indicated, the term "halo", as used herein includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein includes includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and t-butyl.

Unless otherwise indicated, the term "alkoxy", as used herein, includes straight-chain and branched alkoxy groups and includes for example methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy.

Unless otherwise indicated, the term "alkylene", as used herein, includes a divalent radical derived from straight-chain or branched alkane. Examples of alkylene radicals are methylene, ethylene (1,2-ethylene or 1,1-ethylene), trimethylene (1,3-propylene), tetramethylene (1,4-butylene), pentamethylene and hexamethylene.

Unless otherwise indicated, the term "cycloalkyl", as used herein, unless otherwise indicated, includes non-aromatic saturated cyclic alkyl moieties wherein alkyl is as defined above. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Unless otherwise indicated, the term "heterocycloalkyl", as used herein, refer to non-aromatic cyclic groups containing one or more heteroatoms, prefereably from one to four

heteroatoms, each preferably selected from oxygen, sulfur and nitrogen. The heterocycloalkyl groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of non-aromatic heterocycloalkyl groups are aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholino, thiomorpholino, thioxanyl, pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1 .0]heptanyl, quinolizinyl, quinuclidinyl, 1,4-dioxaspiro[4.5]decyl, 1,4-dioxaspiro[4.4]nonyl, 1,4-dioxaspiro[4.3]octyl, and 1,4-dioxaspiro[4.2]heptyl.

Unless otherwise indicated, the term "saturated heterocycle", as used herein, includes a saturated monocyclic groups having 4 to 7 ring members, which contains 1 nitrogen atom. Examples of saturated heterocycles are azetidinyl, pyrrolidinyl and piperidinyl.

Unless otherwise indicated, the term "aryl", as used herein, includes and organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl, napthyl, indenyl, and fluroenyl. "Aryl" encompases fused ring groups wherein at least one ring is aromatic.

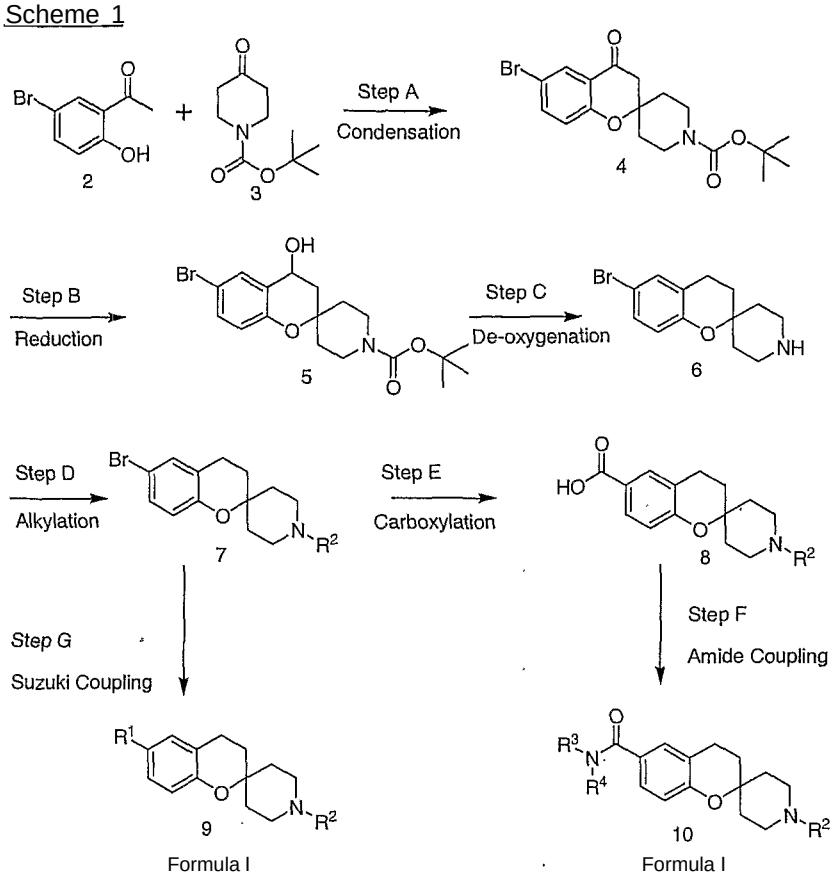
Unless otherwise indicated, the term "heteroaryl" as used herein, includes monocyclic or bicyclic heteroaryl groups having 5 to 9 and 9 to 14 ring members respectively, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur. The heteroaryl group can be unsubstituted, monosubstituted or disubstituted. Examples of heteroaryl groups include, but are not limited to thiophenyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiadiazinyl, isobenzofuranyl, benzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolinyl, isoquinolyl, cinnolinyl, phthalazinyl, naphthyridinyl, quinazolinyl, quinoxalinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, pyrrolopyrazinyl, pyrrolopyridinyl, and imidazopyridinyl.

Unless otherwise indicated, the term "heterocyclic ring", as used herein, refers to both heteroaryl and heterocycloalkyl groups, as defined above.

Detailed Description of the Invention

The compound of formula I according to the invention may be prepared by the general procedure shown in Scheme 1.

Scheme 1



In Scheme 1, compounds of the formula (I) are prepared as follows.

Step A:

Following the general procedure described by M. Yamato.etal. (Chem.Pharm. Bull. (1981), 29(12), 3494-8), hydroxyacetophenone 2, N-t-butoxycarbonyl-4-piperidone 3 are condensed in the presence of a secondary amine base such as morpholine, piperidine or preferably pyrrolidine, in an alcohol solvent such as isopropanol, ethanol or preferably methanol with heating between 50°C and 110°C, where refluxing temperature is preferred to afford the spirochromanone amine 4.

Step B:

Intermediate of the general structure 4 may be converted to the spirochromanol amine intermediate of the general structure 5 via treatment with metal hydride reducing agents such as sodium cyanoborohydride, sodium triacetoxyborohydride, lithium borohydride or preferably sodium borohydride in suitably inert solvents such as THF, methanol or preferably ethanol at temperatures ranging from -10 °C to 80°C where 10°C to 40°C is preferable.

Step C:

Deoxygenation and removal of the BOC protecting group of intermediate of general structure 5 to afford spirochromane amine intermediate of general structure 6 may be

accomplished by treatment with a strong organic acid, where trifluoroacetic acid is preferred, in the presence of a hydride source such as preferably triethylsilyl hydride in a suitably inert solvent such as methylene chloride, carbon tetrachloride, 1,2-dichloroethane or preferably with no added solvent at temperatures ranging from 50-130°C where 90-120°C is preferred.

Step D:

Intermediate of general structure 6 may be alkylated with C_r C_4alkyl chlorides or preferably bromides or iodides in the presence of an organic amine base such as triethylamine or diisopropyl-ethyl amine or an inorganic carbonate base such as cesium carbonate, sodium carbonate or preferably potassium carbonate in a suitably non-reactive solvent such as THF or preferably acetone at temperatures ranging from 0 -80°C where ambient temperature is preferred to afford intermediate of general structure 7.

Step E:

Carboxylation of intermediate of general structure 7 may be achieved first by lithium-halogen exchange using a lithium base such as tert-butyl lithium, sec-butyl lithium or preferably n-butyl lithium in an inert solvent such as diethyl ether or preferably THF at temperatures ranging from - 110--30°C where -80 ~50°C is preferred, and subsequent treatment with dry ice or preferably gaseous carbon dioxide to afford intermediate of general structure 8.

Step F:

Acid intermediate of the general structure 8 may be reacted with a primary or secondary amines of general formula HNR^3R^4 , where R^3 and R^4 are as defined in the specification amine, in the presence of a coupling reagent such as dicyclohexyl carbodiimide, carbonyl diimidazole, tripropylphosphonic anhydride, alkyl chloroformate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, O(benzotriazol-1 -yl)-N,N,N',N'-tetramethyluranium hexafluorophosphate or any other such standard literature reagents in the presence of a trialkyl amine base, such as triethyl amine or diisopropylethyl amine, wherein O(benzotriazol-1-yl)-N,N,N',N'-tetramethyluranium hexafluorophosphate and diisopropylethyl amine are a preferred combination in a reaction inert solvent, where ethyl acetate, from -78 °C to 40 °C, where room temperature is preferred to afford the *N*-acylated compounds of the general structure 10, a compound of Formula I.

Step G:

Compounds of the general structure 9, a compound of Formula I may be formed by coupling the bromo intermediate of the general structure 7 with aryl or heteroaryl boronic acids with an organopalladium catalyst such as tetrakis(triphenylphosphine)palladium (0), dichloropalladium bistriphenylphosphine or tris(dibenzylidine-acetone)dipalladium, preferably tetrakis(triphenylphosphine)palladium (0) and an alkali metal base, such as sodium

carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, sodium hydroxide or potassium hydroxide, preferably sodium carbonate, in a solvent system containing dimethoxyethane or preferably toluene and a polar protic solvent such as water, methanol or ethanol, preferably a mixture of water and ethanol, at a temperature of from about 10°C to 150°C, preferably about 50°-100°C.

Rotomers are possible for an embodiment of the inventive compound of formula I and are within the scope of the invention.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula I contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel (Wiley, New York, 1994).

In the examples below the following terms are intended to have the following, general meaning:

DIPEA: diisopropylethylamine

DMF: dimethyformamide

$MgSO_4$: magnesium sulfate

DMA: dimethyl acetamide

LRMS: low resolution mass spectrometry

°C: degrees Celsius

calcd: calculated

d: day(s); doublet (spectral)

DCE: 1,2-dichloroethane

EtOAc: ethyl acetate
g: grams
HBTU: O-(benzotriazol-1 -yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
hr: hours
Hz: hertz
J: coupling constant (in NMR)
L: liter(s)
LAH: lithium aluminum hydride
MHz: megahertz
Min: minute(s)
m/z : mass to charge ratio (in mass spectrometry)
obsd: observed
PPTs: pyridinium p-toluenesulfonate
TsO: p-toluenesulfonate
Rf: retention factor (in chromatography)
Rt: retention time (in chromatography)
rt: room temperature
s: singlet (NMR); second(s)
STAB: sodium triacetoxyborohydride
t: triplet
TFA: trifluoroacetic acid
TFAA: trifluoroacetic anhydride
THF: tetrahydrofuran
TLC: thin layer chromatography
Ts: tosyl, p-toluenesulfonyl
TsOH: p-toluenesulfonic acid
T_3P: 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide

Solvents were purchased and used without purification. Yields were calculated for material judged homogenous by thin layer chromatography and NMR. Thin layer chromatography was performed on plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with either an aqueous $KMnO_4$ solution or an ethanolic solution of 12-molybdophosphoric acid. Flash column chromatography unless otherwise stated, was performed with using either pre-packed Biotage™ or ISCO™ columns using the size indicated. Nuclear magnetic resonance (NMR) spectra were acquired on a Unity 400 or 500 at 400 MHz or 500 MHz for ^1H, respectively, and 100 MHz or 125 MHz for ^{13}C NMR, respectively. Chemical shifts for proton ^1H NMR speGtra are reported in parts per million

relative to the singlet of $CDCl_3$ at 7.24 ppm. Chemical shifts for ^{13}C NMR spectra are reported in parts per million downfield relative to the centerline of the triplet of $CDCl_3$ at 77.0 ppm. Mass spectra analyses were performed on a APCI Gilson 215, micromass ZMD (50% Acetonitrile / 50% water) spectrometer.

The following intermediates may be prepared by the procedures shown:

Step 1:

Intermediate 1

Spiro[2H-1 -benzopyran-2,4'-piperidine]-1 '-carboxylic acid, 6-bromo-3,4-dihydro-4-oxo-, 1,1-dimethylethyl ester.

A mixture of 5'-bromo-2'-hydroxyacetophenone (50.0 g, 232.5 mmol), t-butyl 4-oxo-1-piperidinecaboxylate (46.3 g, 232.4 mmol) and pyrrolidine (50 ml_, 599.0 mmol) in methanol (500 mL) was refluxed for 17h, then cooled and concentrated. The red colored residue was dissolved in EtOAc (600 mL) and washed with water (2 x 200 mL), aqueous ~3M citric acid (2x 150 mL), water and brine. The organics were dried ($MgSO_4$) and concentrated to a thick, light orange foamy tar. Hexanes (~ 100 mL) was added and the vessel walls were scratched to induce crystallization. Another 150 mL hexanes was added and the mixture was stirred for 66 hrs, then filtered, rinsed with hexanes and air dried to afford 73.2 g (79%) of the title compound as a dull yellow solid: NMR ($CDCl_3$) δ 7.94 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 8.7, 2.5 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 3.85 (br s, 2H), **3.16** (br t, J = 11.6 Hz, 2H), 2.69 (s, 2H), 1.**98** (br d, J= 13.3 Hz, 2H), 1.62-1 .54 (m, 2H), 1.43 (s, 9H).

Step 2

Intermediate 2

teit-Butyl 6-bromo-4-hydroxy-3,4-dihydro-1'W-spiro[chromene-2,4'-piperidine]-**1'-carboxylate.**

Spiro[2H-1-benzopyran-2,4'-piperidine]-1 '-carboxylic acid, 6-bromo-3,4-dihydro-4-OXO-, 1,1-dimethylethyl ester (73.2 g, 184.7 mmol) was slurried in EtOH (1500 mL), stirred for 30 min and then sodium borohydride (7.Og, 185.0 mmol) was added. Over 15 min all solids dissolved to give an orange solution. The mixture was carefully quenched with water and then concentrated. The residue was partitioned between EtOAc (750 mL) and water (200 mL). The organics were washed again with water and then brine, dried ($MgSO_4$) and concentrated to a thick orange oil. Re-concentration from diethyl ether and then hexanes following by evacuation under high vacuum afforded 73.8g (100%) of the title compound as a light yellow-orange foam: NMR ($CDCl_3$) δ 7.55 (dd, J = 2.5, 0.8 Hz, 1H), 7.26 (dd, J = 8.7, 2.5 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 4.82 (dd, J = 13.3, 6.6 Hz, 1H), 3.83 (br s, 2H), 3.27-3.00 (m, 2H), 2.11 (dd, J = 13.7, 6.2 Hz, 1H), 1.99-1 .73 (m, 4H), 1.68-1 .40 (m, 11H).

Step 3

Intermediate 3

6-Bromo-3,4-dihydrospiro[chrornene-2,4'-piperidine].

Triethylsilane (100 mL, 626.1 mmol) was added to a solution te/t-butyl 6-bromo-4-hydroxy-3,4-dihydro-1 H-spiro[chromene-2,4'-piperidine]-1 '-carboxylate (63.8g, 160.2 mmol) in trifluoroacetic acid (600 mL) and the resulting mixture was refluxed for 7.5 hrs. After cooling, the reaction was concentrated. Diethyl ether (400 mL) was added and the mixture was stirred to break up the solids then filtered and air dried to afford 57.44g (90%) of the trifluoroacetate salt of the title compound as a yellow solid: NMR (DMSOd $_6$) δ 8.79 (br s, 1H), 8.61 (br s, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.21 (dd, J = 8.7, 2.5 Hz, 1H), 3.20-3.10 (m, 2H), 3.10-2.95 (m, 2H), 2.72 (t, J = 6.6 Hz, 2H), 1.85-1 .69 (m, 6H).

Step 4

Intermediate 4

β-Bromo-i'-ethyl-S^-dihydrospirotchromene^^'-piperidine].

6-Bromo-3,4-dihydrospiro[chromene-2,4'-piperidine].) (15.Og, 37.86 mmol), potassium carbonate (21.Og, 151.9 mmol) and ethyl iodide (3.3 mL, 41.3 mmol) were stirred in acetone (300 mL) for 16h. The reaction was filtered through Celite and concentrated. The residue was partitioned between CH_2Cl_2 and 1N NaOH. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated to give an orange oil with yellow solid. This material was redissolved in -200 mL of 2:1 EtOAc/ ethyl ether and filtered to remove insoluble impurities. Concentration yielded 11.46 g (98%) of the title compound as a slightly cloudy, light orange oil: NMR ($CDCl_3$) δ 7.17-7.13 (m, 2H), 6.69 (d, J = 9.5 Hz, 1H), 2.74-2.65 (m, 4H), 2.44 (q, J = 7.2 Hz, 2H), 2.34 (dt, J = 11.6, 2.5 Hz, 2H), 1.83-1 .73 (m, 4H), 1.65 (dt, J = 11.4, 4.5 Hz, 2H), **1**.09 (t, J = 7.3 Hz. 3H).

Step 5

Intermediate 5

Preparation of 1'-ethyl-S^-dihydrospirofchromene^^'-piperidinel- 6-carboxylic acid.

nBuLi (2.5 M/hexanes, 12.9 mL, 32.25 mmol) was added over 2min to a -78 ªC solution of 6-bromo-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine] (10.Og, 32.23 mmol) in THF (10OmL). After stirring at -78 ºC for 2h, carbon dioxide gas was bubbled into the mixture for 30 min. After warming to rt, the reaction was concentrated. 1N aq. HCl (33 mL) was added and the mixture was stirred well to break up the solids, then this was extracted with EtOAc (2x75 mL). The aqueous phase was then concentrated to dryness to afford a hygroscopic, light yellow solid. This was stirred for 2h with THF (50 mL) to help remove residual lithium bromide, filtered and dried under nitrogen to yield 8.2 g of the title compound as a hygroscopic, light yellow powder: NMR (DMSO-d $_B$) δ 7.64 (d, J = 2.1 Hz, 1H), 7.60 (dd, J

= 8.7, 2.1 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 2.73-2.64 (m,4H), 2.53-2.36 (m, 4H)$_1$ 1.76-1.62 (m, 6H), 1.01 (t, J = 7.3 Hz, 3H); LCMS m/z calcd. for $C_{16}H_{21}NO_3$, 275.2, found, 276.2 (M+1).

Example 1

6^Pyrrolidin-i-ylcarbonylJ-i'-ethyl-S^-dihydrospirofchromene^^'-piperidine].

To a solution **of 1'-ethyl-S^-dihydrospirofchromene^^'-piperidinel-e-carboxylic acid** (Step 5) (0.2Og, 0.726 mmol) in Λ, Λ-dimethylacetamide (3 ml_) was added diisopropyl-ethylamine (0.13 mL, 0.728 mmol), pyrrolidine (0.065 mL, 0.779 mmol) and a solution of *O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluranium hexafluorophosphate (0.275g, 0.725 mmol) in DMF (4 mL). This mixture was stirred at rt for 16h, concentrated, re-dissolved in EtOAc and washed with 1N aq. LiCI, water and brine. After drying ($MgSO_4$), the organics were concentrated to afford an orange-yellow oil (0.161g). An additional portion of material was obtained by concentrating the aqueous washes and rinsing the resulting salts with MeOH. This rinse was combined with the previous portion of crude product. This was purified by flash chromatography, flushing first with 20% MeOH/EtOAc and then eluting with 20% MeOH/EtOAc +1% NH_4OH to yield 0.164g, (69%) of the title compound as a hygroscopic orange solid, the HCI salt of which had: NMR (MeOH-d_4) δ 7.38-7.34 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 3.65-3.48 (m, 6H), 3.34-3.21 (m overlapping MeOH signal, 4H), 2.88 (t, J = 6.8 Hz, 2H), 2.12-1.89 (m, 10H), 1.38 (t, J = 7.3 Hz, 3H); LCMS m/z calcd. for $C_{20}H_{28}N_2O_2$, 328.2, found, 329.3 (M+1).

Examples 2-26

The following examples (2-26) were prepared using this general protocol:

Portions of boronic acid solutions (0.5M in EtOH , 0.5 mL) and 1.0 mL of 0.1 M EtOH solution of 6-bromo-3,4-dihydrospiro[chrornene-2,4'-piperidine] were added to reaction vials. To these, as bulk, were manually added 0.200 mL of 1.5 M Na_2CO_3 solution in water and 0.2 mL of 0.025 M tetrakis(triphenylphosphine) palladium (O)solution in toluene. Vials were capped and shaken at 85ªC for 18 hours. Added 2.5 mL EtOAc and 1.5mL 1N NaOH to reaction vials. The vials were capped, shaken well, and vortexed if needed. The top layers were transferred to MCX cartridges (pre-conditioned with 2 x 3.0 mL MeOH). The loaded columns were rinsed with 5.0 mL EtOAc and 5.0 mL MeOH (discarded). The columns were placed over tared collection tubes and eluted with 5.0 mL 1N NH3/MeOH. The eluted material was then evaporated to dryness and purified by HPLC using the following conditions:

Column: 21.2 x 50 mm Phenomenex Synergy Max-RP C12, 4um

Flow rate: 25 mL/min; Injection volume: 900 uL in DMSO (10-30 mg)

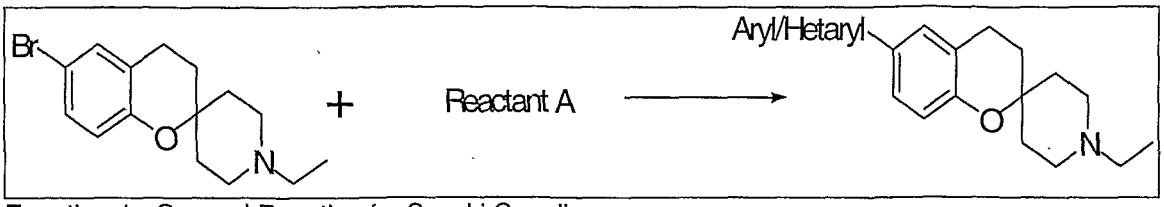
Solvents: A: Water; B: Acetonitrile; C: 1% aq. TFA

Gradients: Determined based on retention time in pre-purification analyses. Range from Focused Gradient 1 (5% B to 10% B over first 2.0 minutes, to 90% B over next 2.0

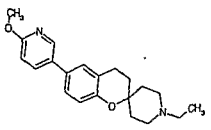
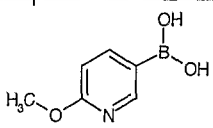
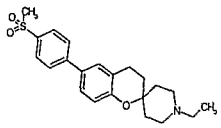
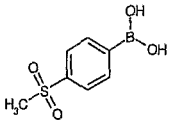
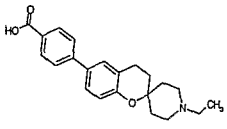
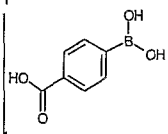
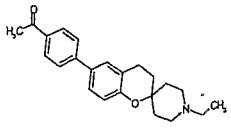
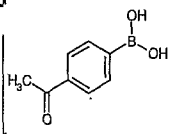
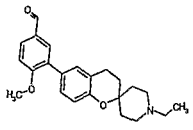
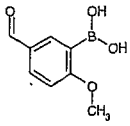
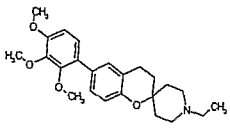
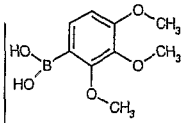
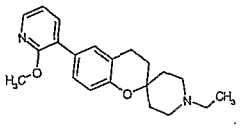
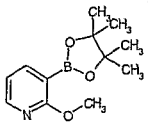
minutes, C held at 5% all 4.0 minutes); to Focused Gradient 6 (55% B to 85% B over first 2.0 minutes, to 90% B over next 2.0 minutes, C held at 5% all 4.0 minutes).

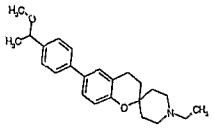
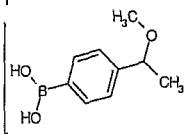
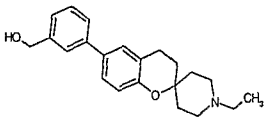
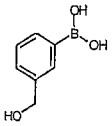
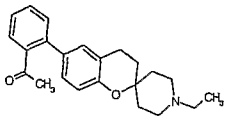
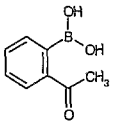
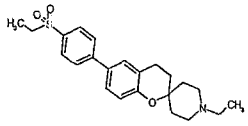
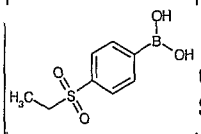
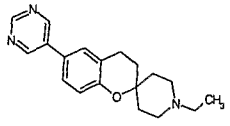
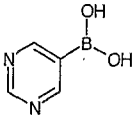
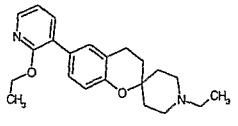
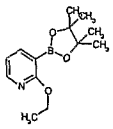
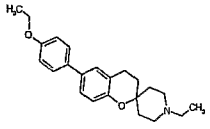
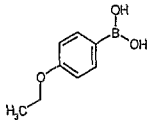
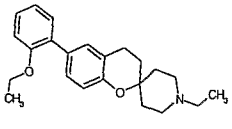
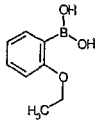
Detectors: DAD, MS: ES (+) mode.

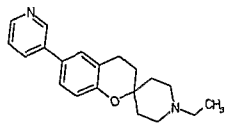
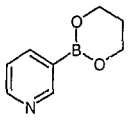
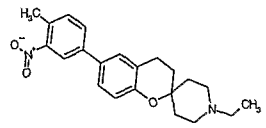
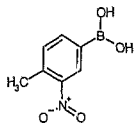
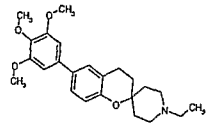
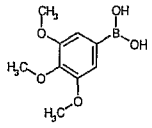
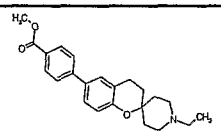
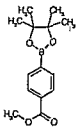
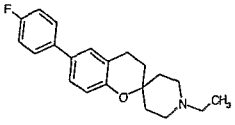
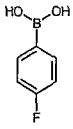
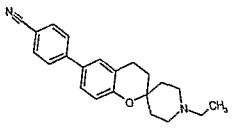
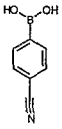
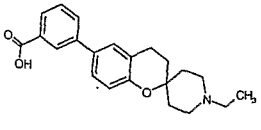
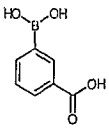
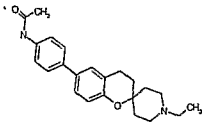
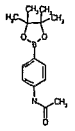
Fraction Collection: Triggered by selected ion recording MS; one tube per injection.

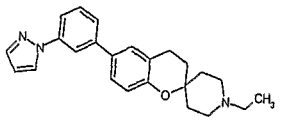
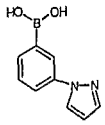
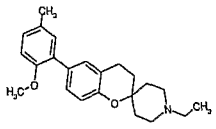
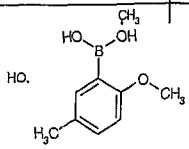


Equation 1. General Reaction for Suzuki Coupling

Example#	MOLSTRUCTURE	REACTANT A	MOLFORMULA	MW	OBSERVED MH+
2			C21 H26 N2 O2	338.4484	339.14
3			C22 H27 N O3 S	385.5253	386.11
4			C22 H25 N O3	351.4435	352.13
5			C23 H27 N O2	349.4713	350.14
6			C23 H27 N O3	365.4703	366.13
7			C24 H31 N O4	397.5119	398.15
8			C21 H26 N2 O2	338.4484	339.15

Example#	MOLSTRUCTURE	REACTANT A	MOLFORMULA	MW	OBSERVED MH+
9			C24 H31 N O2	365.5139	366.17
10			C22 H27 N O2	337.4603	338.15
11			C23 H27 N O2	349.4713	350.14
12			C23 H29 N O3 S	399.5521	400.12
13			C19 H23 N3 O	309.4107	310.13
14			C22 H28 N2 O2	352.4752	353.16
15			C23 H29 N O2	351.4871	352.14
16			C23 H29 N O2	351.4871	352.15

Example#	MOLSTRUCTURE	REACTANT A	MOLFORMULA	MW	OBSERVED MH+
17			C20 H24 N2 O	308.4226	309.15
18			C22 H26 N2 O3	366.4584	367.13
19			C24 H31 N O4	397.5119	398.16
20			C23 H27 N O3	365.4703	366.14
21			C21 H24 F N O	325.4246	326.12
22			C22 H24 N2 O	332.4446	333.13
23			C22 H25 N O3	351.4435	352.13
24			C23 H28 N2 O2	364.4862	365.16

Example#	MOLSTRUCTURE	REACTANT A	MOLFORMULA	MW	OBSERVED MH+
25			C24 H27 N3 O	373.4973	374.16
26			23 H29 N O2	351.4871	352.15

Examples 27-46

The following example (27-46) were prepared using this general protocol:

Portions of amine solutions (0.25M in 0.5M DIPEA/DMA , 0.200 mL) and 0.200 mL of 1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxylic acid solution (0.25M in 0.5M DIPEA/DMA) were added to reaction vials. To these, as bulk, were manually added 0.200 mL of 0.25 M HBTU solution in dry DMF. The vials were capped and shaken at RT for 24 hours. 2.0 mL DCE and 2.0 mL 1M NaOH were added, and the mixtures were shake well, vortexed (if needed). The bottom phase was aspirated to hydromatrix cartridges situated over tared collection tubes. DCE (2.0 mL) was added to the material remaining in the reaction vials, then this bottom layer was also aspirated to the hydromatrix cartridges. The hydromatrix cartridges were then eluted with 4.5 mL DCE. The resulting filtrates were evaporated to dryness and purified by HPLC using the following conditions:

Column: 21.2 x 50 mm Phenomenex Synergy Max-RP C12, 4um

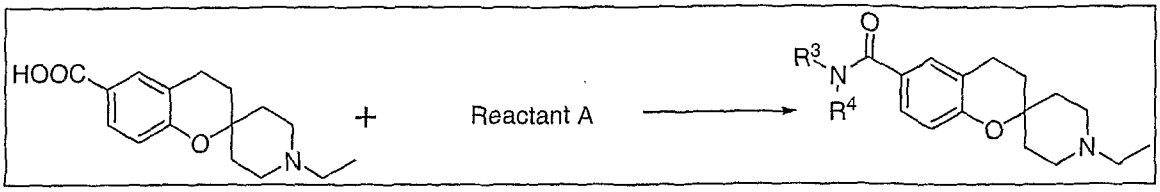
Flow rate: 25 mL/min; Injection volume: 900 uL in DMSO (10-30 mg)

Solvents: A: Water; B: Acetonitrile; C: 1% aq. TFA

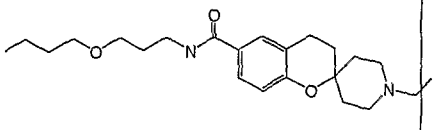
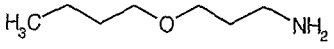
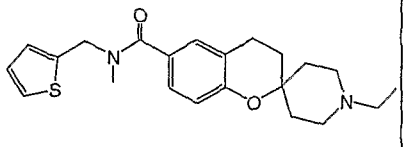
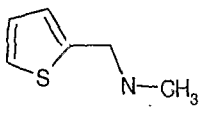
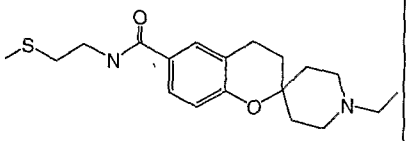
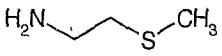
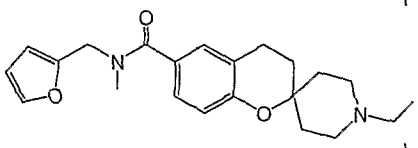
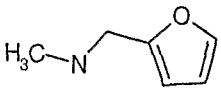
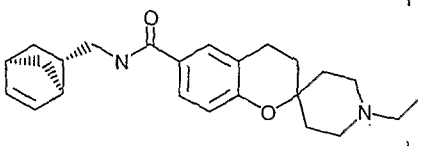
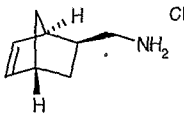
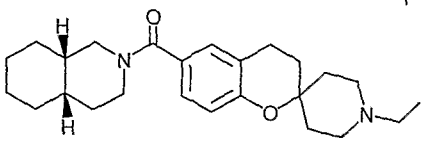
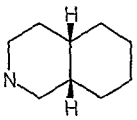
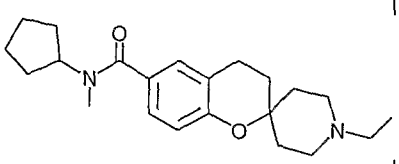
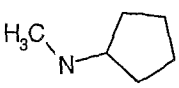
Gradients: Determined based on retention time in pre-purification analyses. Range from Focused Gradient 1 (5% B to 10% B over first 2.0 minutes, to 90% B over next 2.0 minutes, C held at 5% all 4.0 minutes); to Focused Gradient 6 (55% B to 85% B over first 2.0 minutes, to 90% B over next 2.0 minutes, C held at 5% all 4.0 minutes).

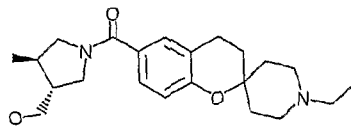
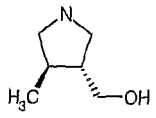
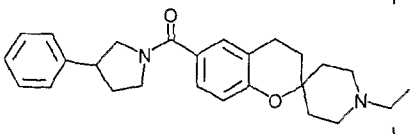
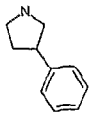
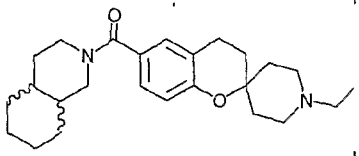
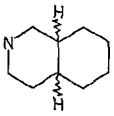
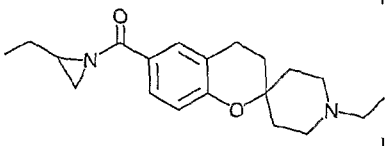
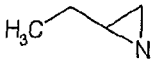
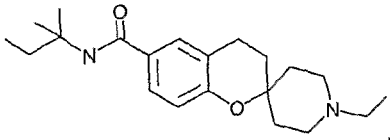
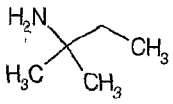
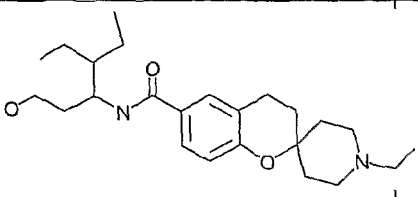
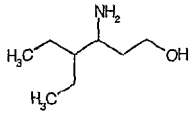
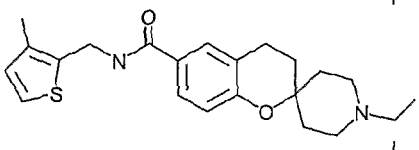
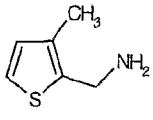
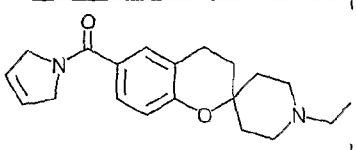
Detectors: DAD, MS: ES (+) mode.

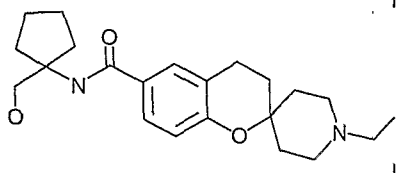
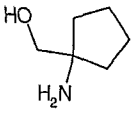
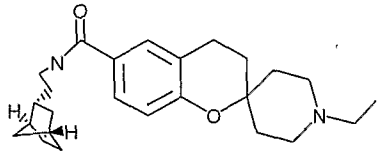
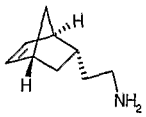
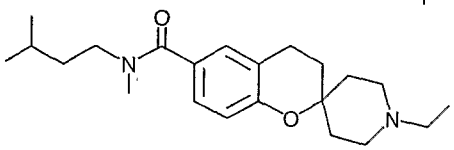
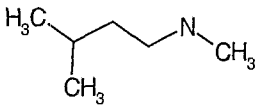
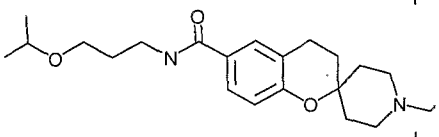
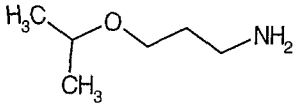
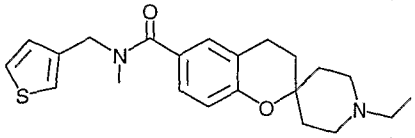
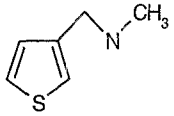
Fraction Collection: Triggered by selected ion recording MS; one tube per injection.



Equation 2. General Reaction for Amide Formation

Example #	MOLSTRUCTURE	REACTANT A	MOL FORMULA	MW	OBSERVE MH+
27			C23 H36 N2 O3	388.548	389.16
28			C22 H28 N2 O2 S	384.541	385.07
29			C19 H28 N2 O2 S	348.508	349.17
30			C22 H28 N2 O3	368.474	369.19
31		 Chiral	C24 H32 N2 O2	380.529	381.13
32			C25 H36 N2 O2	396.571	397.24
33			C22 H32 N2 O2	356.507	357.14

Example #	MOLSTRUCTURE	REACTANT A	MOL FORMULA	MW	OBSERVE MH+
34			C22 H32 N2 O3	372.506	373.19
35			C26 H32 N2 O2	404.551	405.2
36			C25 H36 N2 O2	396.571	397.24
37			C20 H28 N2 O2	328.453	397.24
38			C21 H32 N2 O2	344.496	345.23
39			C24 H38 N2 O3	402.575	403.19
40			C22 H28 N2 O2 S	384.541	385.14
41			C20 H26 N2 O2	326.437	327.12

Example #	MOLSTRUCTURE	REACTANT A	MOL FORMULA	MW	OBSERVE MH+
42			C22 H32 N2 O3	372.506	373.14
43			C25 H34 N2 O2	394.556	395.21
44			C22 H34 N2 O2	358.523	359.24
45			C22 H34 N2 O3	374.522	375.23
46			C22 H28 N2 O2 S	384.541	385.16

The composition of the present invention may be a composition comprising a compound of formula I and optionally a pharmaceutically acceptable carrier. The composition of the present invention may also be a composition comprising a compound of formula I, a histamine H_1 antagonist and optionally a pharmaceutically acceptable carrier. The composition of the present invention may also be a composition comprising a compound of formula I, a neurotransmitter re-uptake blocker and optionally a pharmaceutically acceptable carrier.

The composition of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. The composition may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular, intraperitoneal, or subcutaneous or through an implant) nasal, vaginal, sublingual, rectal or topical administration or in a form suitable for administration by inhalation or insufflation.

Pharmaceutically acceptable salts of compounds of formula I may be prepared by one or more of three methods: (i) by reacting the compound of formula I with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or (iii) by converting one salt of the compound of formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

Also included within the scope of the invention are metabolites of compounds of formula I, that is, compounds formed in vivo upon administration of the drug. Some examples of metabolites in accordance with the invention include: (i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3 \rightarrow -CH_2OH$); (ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof ($-OR \rightarrow -OH$); (iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^aR^b \rightarrow -NHR^a$ or $-NHR^b$); (iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof ($-NHR^a \rightarrow -NH_2$); (v) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof ($-CONR^cR^d \rightarrow COOH$).

Isotopically labeled compounds of formula I of this invention can generally be prepared by carrying out the procedures disclosed in the preceeding Schemes and/or in the Examples and Preparations, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents such as pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose; fillers such as lactose, microcrystalline cellulose or calcium phosphate; lubricants such as magnesium stearate, talc or silica; disintegrants such as potato starch or sodium starch glycolate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents such as sorbitol syrup,

methyl cellulose or hydrogenated edible fats; emulsifying agents such as lecithin or acacia, non-aqueous vehicles such as almond oil, oily esters or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid.

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative. The composition may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient or ingredients in a composition may be in powder form for reconstitution with a suitable vehicle, for example, sterile pyrogen-free water, before use. The term "active ingredient" as used herein refers to a compound of the formula I, a histamine H_1 antagonist, or a neurotransmitter re-uptake blocker.

The composition of the invention may also be formulated in a rectal composition such as suppositories or retention enemas, for example, containing conventional suppository bases such as cocoa butter or other glycerides. A composition for vaginal administration is preferably a suppository that may contain, in addition to the active ingredient or ingredients, excipients such as cocoa butter or a suppository wax. A composition for nasal or sublingual administration is also prepared with standard excipients well known in the art.

For intranasal administration or administration by inhalation, the composition may be conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active ingredient or ingredients. Capsules and cartridges, made, for example, from gelatin, for use in an inhaler or insufflator may be formulated containing a powder mix of an active ingredient or ingredients and a suitable powder base such as lactose or starch. The active ingredient or ingredients in the composition may range in size from nanoparticles to microparticles.

An exemplary dose of the composition of the invention comprising a compound of formula I for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is about 0.01 to about 1000 mg of the compound of formula I per unit dose which could be administered, for example, 1 to 3 times per day.

An exemplary dose of the composition of the invention comprising a compound of formula I and a histamine Hi antagonist or a neurotransmitter re-uptake blocker for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is about 0.01 to about 500 mg of the compound of formula I and of about 0.01 mg to about 500 mg of the histamine H_1 antagonist or the neurotransmitter re¬ uptake blocker per unit dose which could be administered, for example, 1 to 3 times per day.

Aerosol formulations for treatment of the conditions referred to herein in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains about 20 µg to about 1000 µg of the compound of formula I. The overall daily dose with an aerosol will be within the range about 100 µg to about 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time. Aerosol formulations containing a compound of formula I and a histamine H_1 antagonist or a neurotransmitter re-uptake blocker are preferably arranged so that each metered dose or "puff" of aerosol contains about 100 µg to about 10,000 µg of the compound of formula I and about 100 µg to about 30,000 µg of the histamine H_1 antagonist or the neurotransmitter re¬ uptake blocker. Administration may be several times daily, for example 1, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time. The composition of the invention comprising a compound of formula I and a histamine H-i antagonist or a neurotransmitter re-uptake blocker may optionally contain a pharmaceutically acceptable carrier and may be administered in both single and multiple dosages as a variety of different dosage forms, such as tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. The pharmaceutically acceptable carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compound of formula I is present in such dosage forms at concentration levels ranging from about 0.1% to about 99.9% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage, and the histamine H_1 antagonist or the neurotransmitter re-uptake blocker is present in such dosage forms at concentration levels ranging from about 0.1% to about 99.9% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage.

The compound of formula I and the histamine H-, antagonist may be administered together or separately/ When administered separately, the compound of formula I and the histamine H_1 antagonist may be administered in either order, provided that after administration of the first of the two active ingredients, the second active ingredient is administered within 24 hours or less, preferably 12 hours or less.

The compound of formula I and the neurotransmitter re-uptake blocker may be administered together or separately. When administered separately, the compound of formula 1 and the neurotransmitter re-uptake blocker may be administered in either order, provided that after administration of the first of the two active ingredients, the second active ingredient is administered within 24 hours or less, preferably 12 hours or less.

A preferred dose ratio of compound of formula 1to the histamine H_1 antagonist or to the neurotransmitter re-uptake blocker for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is from about 0.001 to about 1000, preferably from about 0.01 to about 100.

The composition may be homogeneous, wherein by homogeneous it is meant that the active ingredient or ingredients are 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 composition is then subdivided into unit dosage forms of the type described herein containing from about 0.1 to about 1000 mg of the active ingredient or ingredients. Typical unit dosage forms contain from about 1 to about 300 mg, for example about 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient or,ingredients. 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 dosage of the active ingredient or ingredients in the composition and methods of this invention may be varied; however, it is necessary that the amount of the active ingredient or ingredients in such a composition be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, the particular compounds administered, the duration of the treatment, and other factors. All dosage ranges and dosage levels mentioned herein refer to each active ingredient present in the pharmaceutical composition of the present invention, as well as those used in the methods of the present invention. Generally, dosage levels of between about 0.01 and about 100 mg/kg of body weight daily are administered to humans and other mammals. A preferred dosage range in humans is about 0.1 to about 50 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A preferred dosage range in mammals other than humans is about 0.01 to about 10.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A more preferred dosage

range in mammals other than humans is about 0.1 to about 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

The pharmaceutical composition comprising the compound of formula I and the histamine H_1 antagonist or the neurotransmitter re-uptake blocker may be administered at dosages of a therapeutically effective amount of the compound of formula I and of the second active ingredient in single or divided doses.

The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The dosage amounts set forth in this description and in the appended claims may be used, for example, for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine any variation in the dosage amount that may be required for a subject whose weight falls outside the about 65 kg to about 70 kg range, based upon the medical history of the subject. The pharmaceutical combinations may be administered on a regimen of up to 6 times per day, preferably 1 to 3 times per day, such as 2 times per day or once daily.

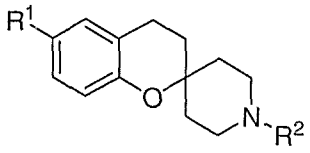
Determination of Biological Activity

The *in vitro* affinity of the compounds in the present invention at the rat or human histamine H3 receptors can be determined according to the following procedure. Frozen rat frontal brain or frozen human post-mortem frontal brain is homogenized in 20 volumes of cold 50 mM Tris HCl containing 2 mM $MgCl_2$ (pH to 7.4 at 4 ^{0}C). The homogenate is then centrifuged at 45,000 G for 10 minutes. The supernatant is decanted and the membrane pellet resuspended by Polytron in cold 50 mM Tris HCl containing 2 mM MgCl2 (pH to 7.4 at 4 ^{0}C) and centrifuged again. The final pellet is resuspended in 50 mM Tris HCl containing 2 mM MgCl2 (pH to 7.4 at 25 ^{0}C) at a concentration of 12 mg/mL Dilutions of compounds are made in 10% DMSO / 50 mM Tris buffer (pH 7.4) (at 10 x final concentration, so that the final DMSO concentration is 1%). Incubations are initiated by the addition of membranes (200 microliters) to 96 well V-bottom polypropylene plates containing 25 microliters of drug dilutions and 25 microliters of radioligand (1 nM final concentration 3H-N-methyl-histamine). After a 1 hour incubation, assay samples are rapidly filtered through Whatman GF/B filters and rinsed with ice-cold 50 mM Tris buffer (pH 7.4) using a Skatron cell harvester. Radioactivity is quantified using a BetaPlate scintillation counter. The percent inhibition of specific binding can then be calculated.

A person of ordinary skill in the art could adapt the above procedure to other assays.

CLAIMS:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

R^2 is (C_r C_4)alkyl;

R^1 is selected from the group consisting of phenyl, naphthyl, 5 to 6-membered heteroaryi, and C(=O)NR^3R^4; wherein said heteroaryi contains 1 to 4 heteroatoms independently selected from N, O, and S; and wherein said phenyl, naphthyl, and heteroaryi are optionally substituted with 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, (Gi-C_6)alkyl,

(CrC $_B$)a!koxy, carbonyl, carboxyl, cyano, nito, -C(=O)(CrC $_6$)alkyl, -C(=O)NR_3R_4, and -SO_p(Ci-C_4)alkyl, wherein p is 1 or 2;

wherein R^3 and R^4 are each independently selected from the group consisting of

hydrogen;

(CrC $_8$)alkyl optionally substituted with -OH or 1 to 4 halogens;

(CrC $_4$)alkyl optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 (C_r C_4)alkyl groups, bicyclo[2.2.1]hept-2-ene, (C_3-C_7)cycloalkyl, (C_r C_4)dialkylamino, (C_6-C_{14})aryl optionally substituted with a halogen and optionally substituted with (C_6-Ci $_0$)aryloxy optionally substituted with 1 to 2 halogens, and 5-10-membered heteroaryi optionally substituted with (C_6-C_{10})aryl and optionally substituted with 1 to 3 (CrC $_4$)alkyl groups;

(C_3-C_7)cycloalkyl optionally substituted with hydroxy (C_r C_4)alkyl;

(C_6-C_{14})aryl;

-(C_2-C_3)alkyl-O-(C_r C_3)alkyl optionally substituted with (d-C $_3$)alkyl;

-(C_2-C_3)alkyl-S-(CrC $_3$)alkyl optionally substituted with (CrC $_3$)alkyl;

-(CrC $_3$)alkyl-C(=O)O-(CrC $_3$)alkyl;

3 to 8-membered heterocycloalkyl;

(C_6-C_{10})arylsulfonyl optionally substituted with one or more (CrC $_2$)alkyl;

5 to 10-membered heteroaryi; and

(C_6-C_{14})aryl-(C_0-C_4)alkylene-O-(C_0-C_4)alkyl, wherein each (C_0-C_4)alkyl and each (C_0-C_4)alkylene is optionally substituted with 1 to 4 (C_1-C_4)alkyl;

or optionally R^3 and R^4, together with the nitrogen to which they are attached, form a 3 to 7-membered saturated or unsaturated heterocyclic ring, wherein one of the carbons in said heterocyclic ring is optionally replaced by O, S, NR^5 or CO, and wherein said ring is optionally

fused to a (C_6-C_{10})arylene and is optionally substituted at a ring carbon with a substituent selected from the group consisting of

-OH, 5-10-membered heteroaryl optionally substituted with one or more halogens and optionally substituted with one or more (C_1-C_2)alkyl, 5 to 6 membered aryl, (C_r C_4)alkoxy optionally substituted with one or more (Ci-C_2)alkoxy and optionally substituted with one or more (C_r C_4)dialkylaminocarbonyl, and 1 to 2 (CrC $_4$)alkyl optionally and independently substituted with one or more (CrC $_2$)alkoxy;

wherein R^5 is selected from the group consisting of

hydrogen;

(C_r C_8)alkyl optionally substituted with 1 to 4 halogens;

5-10-membered heteroaryl optionally substituted with a substituent selected from the group consisting of halogen, (CrC $_4$)alkyl, (Ci-C_2)alkoxy, (C_6-C_{10})aryl, (C_1-C_4)alkylaminocarbonyl, and cyano;

(GrC^alkyl group optionally substituted with a substituent selected from the group consisting of (C_1-C_2)alkoxycarbonyl, 5-10-membered heteroaryl optionally substituted with one or more (C_1-G_2)alkyl, 1 to 4 (CrC^alkyl, and (C_3-C_7)cycloalkyl;

(C_6-C_{10})aryl optionally substituted with 1 or 2 (C_r C_2)alkyl;

(C_r C_4)alkylcarbonyl; and

(C_6-C_{14})aryl-(Co-C_4)alkylene-0-(Co-C_4)alkyl, wherein each (C_0-C_4)alkyl and each (C_0-C_4)alkylene is optionally substituted with 1 to 4 (CrC $_4$)alkyl.

2. A compound of claim 1 wherein

R^2 is ethyl;

R^1 is C(=O)NR^3R^4;

wherein R^3 and R^4 are each independently (CrC $_4$)alkyl optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 (C_r C_4)alkyl groups, bicyclo[2.2.1]hept-2-ene, (C_3-C_7)cycloalkyl, (CrC $_4$)dialkylamino, (C_6-C_{14})aryl optionally substituted with a halogen and optionally substituted with

(C_6-Cio)aryloxy optionally substituted with 1 to 2 halogens, and 5-10-membered heteroaryl optionally substituted with (C_6-C_{10})aryl and optionally substituted with 1 to 3 (CrC $_4$)alkyl groups;

3. A compound of claim 1 wherein

R^2 is ethyl; and

R^1 is phenyl or 5 to 6-membered heteroaryl,

wherei π said heteroaryl contains 1 to 4 heteroatoms independently selected from N, O, and S; and wherein said phenyl or heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, (CrC βJalkyl, (C_1-C_6)alkoxy, carbonyl, carboxyl, cyano, nito, -C(=O) (C_1-C_6)alkyl, -C(=O)NR_3R_4, and -SO_p(C_1-C_4)alkyl, wherein p is 1 or 2;

wherein R^3 and R^4 are each independently (C_r C_4)alkyl optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 (C_r C_4)alkyl groups, bicyclo[2.2.1]hept-2-ene, (C_3-C_7)cycloalkyl, (C_1-C_4)dialkylamino, (C_6-C_{14})aryl optionally substituted with a halogen and optionally substituted with (C_6-C_{10})aryloxy optionally substituted with 1 to 2 halogens, and 5-10-membered heteroaryl optionally substituted with (C_6-C_{10})aryl and optionally substituted with 1 to 3 (C-|-C_4)alkyl groups.

4. A compound of claim 1 selected from the group consisting of

N-methyl-N-(2-thienylmethyl)-1 '-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxamide,

N-^^methylthiojethylJ-i'-ethyl-S^-dihydrospirofchromene^^'-piperidineJ- 6-carboxamide,

N-(2-furylmethyl)-N-methyl-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxamide,

N-cyclopentyl-N-methyJ-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxamide,

6-[(2-ethylaziridin-1-yl)carbonyl]-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],

6-(6-methoxypyridin-3-yl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],

6-[4-(methylsulfonyl)phenyl]-1'-ethyl-3,4-dihydrospirotchromene-2,4'-piperidine],

4-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)benzoic acid,

N-[(3-methyl-2-thienyl)methyl]-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine]-6-carboxamide,

1-[4-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)phenyl]ethanone,

6-(2,5-dihydro-1 H-pyrrol-1 -ylcarbonyl)-1 '-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],

3-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)-4-methoxybenzaldehyde,

6-(2,3,4-trimethoxyphenyl)1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],

6-(2-methoxypyridin-3-yl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],

[3-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)phenyl]methanol,

'(-^-(I'-ethyl-S^-dihydrospirotchromene^^'-piperidinl- 6-yOphenyOethanone,

B-^^ethylsulfonyOphenyO-i'-ethyl-S^-dihydrospirotchromene^^'-piperidine],

1'-ethyl-6-pyrimidin-5-yl-3,4-dihydrospiro[chromene-2,4'-piperidine],

6-(2-ethoxypyridin-3-yl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],

6-(4-ethoxyphenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],

6-(2-ethoxyphenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
1'-ethyl-6-pyridin-3-yl-3,4-dihydrospiro[chromene-2,4'-piperidine],
6-(4-methyl-3-nitrophenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2 ,4'-piperidine],
6-(3,4,5-trimethoxyphenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
methyl 4-(1 '-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)benzoate,
1'-ethyl-6-(4-fluorophenyl)-3,4-dihydrospiro[chromene-2,4'-piperidine],
1'-ethyl-6-(4-fluorophenyl)-3,4-dihydrospiro[chromene-2,4'-piperidine],
3-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)benzoic acid,
N-[4-(1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-6-yl)phenyl]acetannide,
6-[3-(1 H-pyrazol-1 -yl)phenyl]1 '-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
6-(2-methoxy-5-methylphenyl)-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine],
and pharmaceutically acceptable salts thereof.

5. A pharmaceutical composition for treating a disorder or condition that may be treated by antagonizing histamine-3 receptors, the composition comprising a compound of formula I as described in claim 1, and optionally a pharmaceutically acceptable carrier.

6. A method of treatment of a disorder or condition that may be treated by antagonizing histamine-3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula I as described in claim 1.

7. The method of claim 6 selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, cognitive disorders, Alzheimer's disease, attention-deficit disorder, attention-deficit hyperactivity disorder, psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy-induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro- intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula I as described in claim 1.

8. The method of claim 7, wherein the disorder or condition is selected from the group consisting of anxiety disorders, attention-deficit hyperactivity disorder, attention-deficit disorder, respiratory diseases, obesity, cognitive disorders, and psychotic disorders.

9. The method of claim 7, wherein the disorder or condition is a respiratory disease selected from the group consisting of adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis.

10. A pharmaceutical composition for treating allergic rhinitis, nasal congestion or allergic congestion comprising:

(a) an H3 receptor antagonist compound of formula I; or a pharmaceutically acceptable salt thereof;

(b) an H1 receptor antagonist or a pharmaceutically acceptable salt thereof; and

(c) a pharmaceutically acceptable carrier;

wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating allergy rhinitis, nasal congestion or allergic congestion.

11. The pharmaceutical composition according to claim 10, wherein said H1 receptor antagonist is selected from the group consisting of cetirizine chlorpheniramine, loratidine, fexofenadine, and desloradine.

12. A pharmaceutical composition for treating attention-deficit disorder, attention-deficit hyperactivity disorder, depression, mood disorders, or cognitive disorders comprising:

a) an H3 receptor antagonist compound of Formula I or a pharmaceutically acceptable salt thereof;

b) a neurotransmitter re-uptake blocker or a pharmaceutically acceptable salt thereof;

c) a pharmaceutically acceptable carrier;

wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating depression, mood disorders, and cognitive disorders.

13. The pharmaceutical composition according to claim 12, wherein the neurotransmitter re-uptake blocker is selected from the group consisting of sertraline, fluoxetine and paroxetine.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/000235

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/10 A61K31/438 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No
A	EP 0 564 358 A1 (ADIR [FR]) 6 October 1993 (1993-10-06) claims 1,18	1-13
A	WO 97/37630 A (RICHTER GEDEON VEGYESZET [HU]; HARSANYI KALMAN [HU]; SZABADKAI ISTVAN) 16 October 1997 (1997-10-16) claims 1,5,6	1-13
A	WO 94/18204 A (MERCK & CO INC [US]; BALDWIN JOHN J [US]; CLAREMON DAVID A [US]; ELLIO) 18 August 1994 (1994-08-18) From the examples it is apparent that the formula in claim 1 is incorrect in that a ring oxygen is missing page 1, line 26 - line 27; claim 1	1-13

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[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on prionty claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or pnority date and not in conflict with the application but cited to understand the principle ortheory underlying the invention

"X" document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu¬ments, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2007	16/05/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office P B 5818 Patentlaan 2 NL- 2280 HV RiJSWIJk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Gettins, Marc

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/000235

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 2002/183309 A1 (COWART MARLON D [US] ET AL) 5 December 2002 (2002-12-05) paragraphs [0002], [0091], [0104]; claims 66,71	1-13
A	US 5 633 247 A (BALDWIN JOHN J [US] ET AL) 27 May 1997 (1997-05-27) claims 1,8; table II	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2007/000235

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) tor the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/compos ition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2007/000235

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