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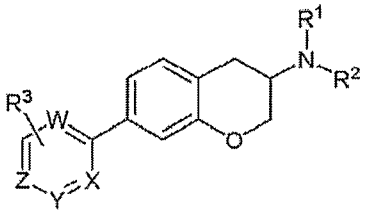
(54) Title: CHROMANE ANTAGONIST OF THE H-3 RECEPTOR



(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 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 above.

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CHROMANE 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. Iinuma, "Histamine and Seizures: Implications for the treatment of epilepsy", CNS Drugs, 5(5); 321-330, (1995)); (K. Hurukami, H. Yokoyama, K. Onodera, K. Iinuma and T. Watanabe, AQ-0 145, "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 cognitive 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, WO 02/12224, and U.S. Patent Publication No. 2005/0171181 A1. 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

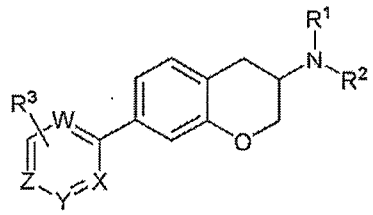
normalization of vestibular reflexes. Accordingly, the receptor is an important target for new therapeutics in Alzheimer disease, mood and attention adjustments, including attention deficit hyperactive disorder (ADHD), cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, 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 WO 96/38142. 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 WO 02/32893 and WO 02/06233.

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 chromane 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

W, X, Y, and Z are independently selected from nitrogen or carbon; wherein the total number of said nitrogens for W, X, Y, and Z does not exceed two;

R^1 and R^2 are independently hydrogen, $(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 4 halogens, or $(C_3\text{-}C_7)$cycloalkyl-$(C_0\text{-}C_4)$alkyl;

or optionally R^1 and R^2, together with the nitrogen to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring, wherein said heterocyclic ring is optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl; and wherein one of the carbons of said heterocyclic ring

that is separated by at least two atoms from said nitrogen in said heterocyclic ring is optionally replaced by O, S, NR^6, or C=O; wherein R^6 is hydrogen, (C_1-C_8)alkyl optionally substituted with 1 to 4 halogens, or (C_3-C_7)cycloalkyl-(C_0-C_4)alkyl, and wherein each (C_0-C_4)alkyl is optionally substituted with 1 to 4
(C_1-C_4)alkyl;

R_3 is hydrogen, (C_1-C_6)alkyl, halo, 5-6 membered aryl optionally fused to a 5 to 6 membered aryl, 5-6 membered heteroaryl, (C_1-C_6)alkoxy, hydroxyl, methylene hydroxyl, -$(C=O)NR_4R_5$, and $S(O)_p(C_1-C_4)$alkyl, where p is 1 or 2;

wherein R^4 and R^5 are each independently selected from the group consisting of
hydrogen;
(C_1-C_8)alkyl optionally substituted with 1 to 4 halogens;
(C_1-C_4)alkyl group optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 (C_1-C_4)alkyl, (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 to 10-membered heteroaryl optionally substituted with a (C_6-C_{10})aryl group and optionally substituted with 1 to 3 (C_1-C_4)alkyl groups;
(C_3-C_7)cycloalkyl;
(C_6-C_{14})aryl;
-(C_0-C_3)alkyl-O-(C_1-C_3)alkyl optionally substituted with (C_1-C_3)alkyl;
-(C_1-C_3)alkyl-C(=O)O-(C_1-C_3)alkyl;
3-8-membered heterocycloalkyl optionally substituted with one or more (C_1-C_4)alkyl-carbonyl groups;
(C_6-C_{10})arylsulfonyl optionally substituted with one or more (C_1-C_2)alkyl;
5-10-membered heteroaryl; 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 4-, 5-, 6-, or 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, (C_1-C_4)alkoxy optionally substituted with one or more (C_1-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_1-C_2)alkoxy;

wherein R^5 is selected from the group consisting of

hydrogen;

(C_1-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, (C_1-C_4)alkyl, (C_1-C_2)alkoxy, (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 (C_1-C_2)alkyl, 1 to 4 (C_1-C_4)alkyl, (C_3-C_7)cycloalkyl, and (C_6-C_{14})aryl;

(C_6-C_{10})aryl optionally substituted with 1 or 2 (C_1-C_2)alkyl;

(C_1-C_4)alkylcarbonyl; 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;

A preferred embodiment includes compounds of claim 1 wherein

W, X, Y, and Z are carbon;

R^1 and R^2, together with the nitrogen to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or two (C_1-C_4)alkyl; and wherein one of the carbons of said heterocyclic ring that is separated by at least two atoms from said nitrogen in said heterocyclic ring is optionally replaced by O, S, NR^6, or C=O, wherein R^6 is hydrogen, (C_1-C_8 alkyl optionally substituted with 1 to 4 halogens, or

(C_3-C_7)cycloalkyl-(C_0-C_4)alkyl, and wherein each (C_0-C_4)alkyl is optionally substituted with one to four (C_1-C_4)alkyl; and

R_3 is (C_1-C_6)alkoxy, -(C=O)NR_4R_5, and SO_2(C_1-C_4)alkyl;

wherein R^4 and R^5 are each independently selected from the group consisting of

hydrogen;

(C_1-C_8)alkyl optionally substituted with 1 to 4 halogens;

(C_1-C_4)alkyl group optionally substituted with a substituent selected from the group consisting of OH, one to four (C_1-C_4)alkyl, (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 one to two halogens, and 5-10-membered heteroaryl optionally substituted with a

(C_6-C_{10})aryl group and optionally substituted with 1 to 3 (C_1-C_4)alkyl groups;

(C_3-C_7)cycloalkyl;

(C_6-C_{14})aryl;

-(C_0-C_3)alkyl-O-(C_1-C_3)alkyl optionally substituted with (C_1-C_3)alkyl;

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

3-8-membered heterocycloalkyl optionally substituted with one or more (C_1-C_4)alkyl-carbonyl groups;

(C_6-C_{10})arylsulfonyl optionally substituted with one or more (C_1-C_2)alkyl;

5-10-membered heteroaryl; 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 4-, 5-, 6-, or 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, (C_1-C_4)alkoxy optionally substituted with one or more (C_1-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_1-C_2)alkoxy.

Another preferred embodiment includes compounds of claim 1 wherein

W, X, Y, and Z are independently selected from nitrogen or carbon; wherein the total number of said nitrogens for W, X, Y, and Z equals one;

R^1 and R^2, together with the nitrogen to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or two (C_1-C_4)alkyl; and wherein one of the carbons of said heterocyclic ring that is separated by at least two atoms from said nitrogen in said heterocyclic ring is optionally replaced by O, S, NR^6, or C=O, wherein R^6 is hydrogen, (C_1-C_8)alkyl optionally substituted with 1 to 4 halogens, or

(C_3-C_7)cycloalkyl-(C_0-C_4)alkyl, and wherein each (C_0-C_4)alkyl is optionally substituted with one to four (C_1-C_4)alkyl; and

R_3 is (C_1-C_6)alkoxy.

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

(3S,4R)-7-(4-Methoxy-phenyl)-3-pyrrolidin-1-yl-chroman-4-ol,

1-[7-(4-Methoxy-phenyl)-chroman-3-yl]-pyrrolidine,

N-Ethyl-3-(3-pyrrolidin-1-yl-chroman-7-yl)-benzamide,

N-Isopropyl-3-(3-pyrrolidin-1-yl-chroman-7-yl)-benzamide,

2-Methoxy-3-(3-pyrrolidin-1-yl-chroman-7-yl)-pyridine,

N-Isopropyl-3-[3-((R)-2-methyl-pyrrolidin-1-yl)-chroman-7-yl]-benzamide,

1-[7-(4-Methanesulfonyl-phenyl)-chroman-3-yl]-pyrrolidine,

N-Ethyl-3-[3-((R)-2-methyl-pyrrolidin-1-yl)-chroman-7-yl]-benzamide, and

N-Isopropyl-4-(3-pyrrolidin-1-yl-chroman-7-yl)-benzamide.

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 and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{16}O, ^{17}O, ^{15}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, ^{123}I respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs 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, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{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. Attention adjustment disorders include, for example, in addition to ADHD, attention-deficit disorders or other 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, 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.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

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, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula I.

As indicated, so-called 'pro-drugs' of the compounds of formula I are also within the scope of the invention. Thus certain derivatives of compounds of formula I which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula I having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E. B Roche, American Pharmaceutical Association).

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 "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.

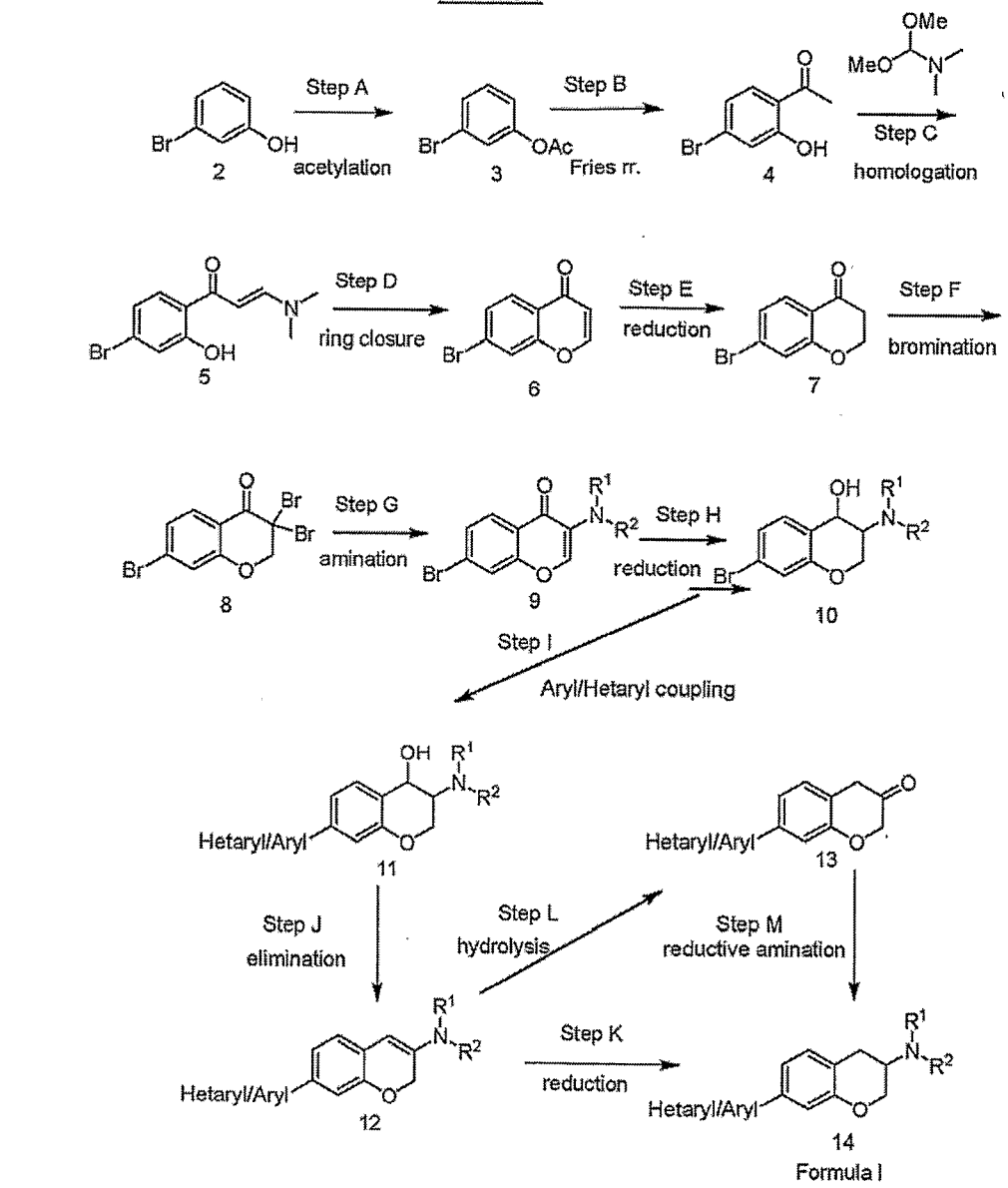
Unless otherwise indicated, the term "heteroaryl" as used herein, includes monocyclic or bicyclic heteroaryl groups having 5 to 9 and 9 to 14 ring members respectively, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur. The heteroaryl group can be unsubstituted, monosubstituted 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.

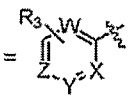
Unless otherwise indicated, the term "heterocyclic ring", as used herein, refers to both heteroaryl and heterocycloalkyl groups, as defined above.

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



Hetaryl/Aryl = 

Step A:

3-Bromophenol (2) is acetylated to give acetate (3) via treatment with acetic anhydride or preferably acetyl chloride in the presence of a non-nucleophilic amine base such as diisopropylethylamine, triethylamine or preferably pyridine in a suitably inert solvent such as chloroform, 1,2-dichloroethane or preferably dichloromethane at temperatures ranging from –10°C to 80°C where room temperature is preferred.

Step B:

Rearrangement of acetate (3) to afford acetophenone (4) is performed in the presence of a strong Lewis acid where aluminum trichoride is preferred, in a solvent such as dichloromethane, carbon disulfide or preferably without solvent at temperatures ranging from 80°-200°C where 120° to 170°C is preferred.

Step C:

Vinylogous amide (5) may be synthesized by treatment of (4) with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) or preferably N,N-dimethylformamide dimethylacetal in xylene, toluene or preferably benzene at temperatures ranging from 50° to 120°C, where 80°-110°C is preferred.

Step D:

Ring closure of intermediate (5) to afford chromenone (6) may be accomplished using a strong inorganic acid such as phosphoric acid, sulfuric acid or preferably concentrated hydrochloric acid in a suitably unreactive solvent such as chloroform, 1,2-dichloroethane or preferably dichloromethane at temperatures ranging from 0° to 100°C where 30-70°C is preferred.

Step E:

Chromanone (7) may be obtained by selective reduction of intermediate (6) with metal hydride reagents where diisobutylaluminum hydride is preferred in suitably inert solvents such as diethyl ether,diisopropyl ether or preferably THF at temperatures ranging from -110°C to 0°C where –80° to –40°C is preferred.

Step F:

Dibromochromanone intermediate (8) may be synthesized by reaction of (7) with brominating agents such as copper (II) bromide or preferably elemental bromine in halogenated solvents such as dichloromethane, chloroform or preferably carbon tetrachloride at temperatures ranging form 10° to 80°C, where ambient temperature is preferred.

Step G:

Conversion of intermediate (8) to aminochromenone (9) may be accomplished by treatment with alkylated amines in polar non-protic solvents such as THF, DMF, NMP or preferably acetonitrile in the presence of an acid scavenging, non-nucleophilic tertiary amine such as diisopropylethylamine or preferably triethylamine, at temperatures ranging from 10° to 80°C where room temperature is preferred.

Step H:

Aminochromanol intermediate (10) may be obtained by in-situ 1,4 and subsequent 1,2 hydride reductions of (9) using metal hydride reagents where sodium borohydride is preferred in suitably inert polar protic solvents such as isopropanol, methanol or preferably ethanol at temperatures ranging from 10°C to 70°C where ambient temperature is preferred.

Step I:

Compounds of the general structure 11 may be formed by coupling the bromo intermediate of the general structure 10 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 toluene or preferably dimethoxyethane and a polar protic solvent such as water, methanol or ethanol, preferably water, at a temperature of from about 10°C to 150°C, preferably about 50°-100°C.

The compounds so formed may be further derivatized using standard reactions familiar to those skilled in the art.

Step J:

Aminochromene intermediate (12) may be formed by acid catalyzed elimination of the alcohol functionality of (10) through treatment with strong organic acids such as trifluoroacetic acid, acetic acid or preferably a mixture of concentrated sulfuric acid and acetic acid in suitably inert solvents such as dichloromethane, 1,2-dichloroethane or preferably chloroform at temperature ranging from 20° to 120°C where 60°-90°C is preferred.

Step K:

Reduction of (12) to afford (14), a compound of formula (I), may be accomplished using hydrogenation catalyzed by reactive metals such as, for example, palladium (0), palladium hydroxide, rhodium or platinum in solvents such as ethanol, methanol or EtOAc or more preferentially through treatment with a metal hydride reagents such as sodium borohydride, sodium cyanoborohydride or preferably sodium triacetoxyborohydride in suitably inert solvents such as dichloromethane, 1,2-dichloroethane or preferably chloroform with 1-5 equivalents of acetic acid at temperatures ranging from –40° to 80°C where –20° to 30°C is preferred.

Step L:

Hydrolysis of intermediate 12 to give isochromanone 13 may be accomplished by treatment with an aqueous solution of a carbonate base such as potassium carbonate, sodium carbonate or preferably sodium bicarbonate with an organic solvent co-solvent such as chloroform, dichloromethane, ether or preferably a mixture of dichloromethane and ether preferably at ambient temperature.

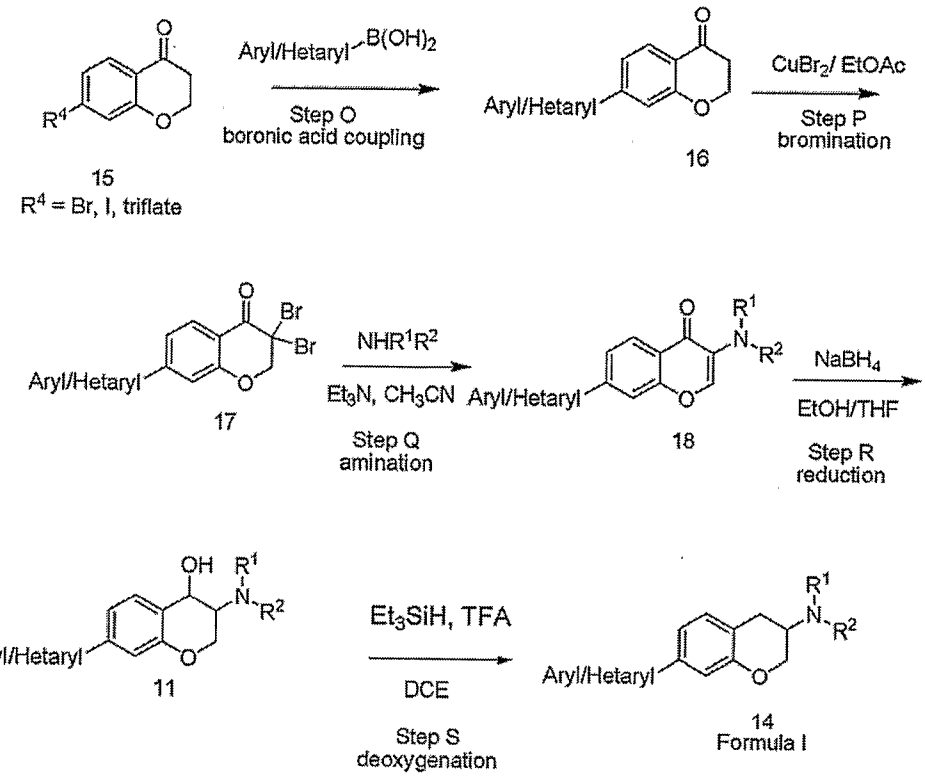
Step M:

Compound 14 of general formula (I) may also be prepared by reductive amination using isochromanone 13 and amine NHR^1R^2 in the presence of a metal hydride such as sodium borohydride, sodium cyanoborohydride or preferably sodium triacetoxyborohydride in suitably inert solvents such as dichloromethane, 1,2-dichloroethane or preferably chloroform with 1-5 equivalents of acetic acid at temperatures ranging from –40° to 80°C where –20° to 30°C is preferred.

The reductive amination may also be performed by first preparing the corresponding imine or iminium species through the agency of reagents such as titanium tetrachloride or titanium (V) isopropoxide in inert solvent such as chloroform, dichloromethane or 1,2 – dichloroethane at temperatures ranging from ~-80° to 0°C, followed by treatment of the so generated imine/iminium species in-situ with metal hydride reagents such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride.

An alternative preparation of compounds of the formula (I) is shown in Scheme 2.

Scheme 2



Step O:

Formation of chromanone intermediate (16) from chromanone (15) may be accomplished following the general conditions described in Scheme 1, step I.

Step P:

Formation of brominated intermediate (17) from intermediate (16) may be done following the bromination conditions describe in Scheme 1, step F.

Step Q:

Intermediate (17) may be converted to aminated intermediate (18) following the general conditions described in Scheme 1, step G.

Step R:

Reduction of intermediate (18) to form intermediate (11) may be accomplished following the general conditions described in Scheme 1, step H.

Step S:

Formation of compound (14) of general formula I may be accomplished by treating intermediate (11) with a strong organic acid such as triflic acid or preferably trifluoroacetic acid in the presence of a hydride source where triethylsilane is preferred in a suitably inert solvent such as chloroform, dichloromethane, 1,2-dichloroethane or no added solvent where 1,2-dichloroethane is preferred at temperature ranging from –40° to 120°C where ~70-110°C is preferred.

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
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 (CAS # 68957-94-8)

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 spectra 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:

Intermediate 1

3-Bromophenyl acetate.

To a cold (ice bath) solution of 3-bromophenol (150 g, 867 mmol) and pyridine (70.0 mL, 867 mmol) in CH_2Cl_2 (1000 mL) acetyl chloride (61.7 mL, 867 mmol) was added in a dropwise manner during 1 h and the mixture was then stirred for 18 h at room temperature. Then to the resulting solution was added water (500 mL), the organic layer was separated and the water one was extracted with CH_2Cl_2 (4 x 150 mL). The combined organic layers were washed with 2.5N $NaHSO_4$ (3 x 150 mL), 3N NaOH (3 x 150 mL), water (2 x 200 mL) and brine (2 x 200 mL), dried over Na_2SO_4 and evaporated to give the title compound as a pink liquid (36.0 g, 96 %). GC/MS data: 214 $(M)^+$ (Calculated for $C_8H_7BrO_2$ 215.04). (calc. monoisotopic mass is $(M)^+$ 213.96). ^1H NMR data (DMSO-d6): 7.44-7.48 (ddd, 1H, J_1 = 1.0 Hz, J_2 = 2.0 Hz, J_3 = 8.1 Hz, Ar-H), 7.43 (t, 1H, J = 2.1 Hz, Ar-H), 7.38 (t, 1H, J = 8.1 Hz, Ar-H), 7.14-7.18 (ddd, 1H, J_1 = 1.0 Hz, J_2 = 2.2 Hz, J_3 = 8.1 Hz, Ar-H), 2.26 (s, 3H, CH_3).

Intermediate 2

1-(2-bromo-6-hydroxyphenyl)ethanone.

The mixture of 3-Bromophenyl acetate (36.0 g, 167 mmol) and unhydrous $AlCl_3$ (33.5 g 251 mmol) was heated to 140 – 150 °C for 2 h. To the resulting black solid was added 100 ml of 5% HCl and the mixture was heated on boiling water bath until the solid material dissolved. After cooling to the room temperature the precipitated brown oil was extracted with CH_2Cl_2 (3 x 150 ml) and to the organic layer was added 300 ml of 5N NaOH. The formed precipitate was dissolved in water, organic layer was separated and the water one was acidified to pH ~ 2 and extracted with EtOAc (5 x 150 mL). Combined extracts were dried over Na_2SO_4 and evaporated to give the title compound as beige crystals (35.8 g, 99%).GC/MS data: 214 $(M)^+$ (Calculated for $C_8H_7BrO_2$ 215.05). (calc. monoisotopic mass is $(M)^+$ 213.96). ^1H NMR data (DMSO-d6): 11.97 (s, 1H, OH), 7.78 (d, 1H, J=8.3 Hz, Ar-H), 7.19 (d, 1H, J=2.0 Hz, Ar-H), 7.13 (dd, 1H, J_1=8.3 Hz, J_2=2.0 Hz, Ar-H), 2.60 (s, 3H, CH_3).

Intermediate 3

(2*E*)-1-(4-bromo-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one.

To a solution of 1-(2-bromo-6-hydroxyphenyl)ethanone (35.8 g, 167 mmol) in dry benzene (800 mL) was added N,N-dimethylformamide dimethylacetal (44 mL, 333 mmol) and

the solution was heated to reflux for 4 h. The reaction mixture was then evaporated to dryness, dissolved in $CHCl_3$ (300 mL) and filtered through SiO_2 (63-100 µm, 200 mL) to give after evaporation the title compound (31.9 g, 71%) as a bright yellow solid. LC/MS data: 270.0 $(M+H)^+$ (Calculated for $C_{11}H_{12}BrNO_2$ 270.13). (calc. monoisotopic mass is 269.01, calc. monoisotopic mass $(M+H)^+$ = 270.01). ^1H NMR data (DMSO-d6): 14.96 (s, 1H, OH), 7.93 (d, 1H, J=12.0 Hz, =CH), 7.87 (d, 1H, J = 9.0 Hz, Ar-H), 7.03 (d, 1H, J = 2.2 Hz, Ar-H), 6.99 (dd, 1H, J_1=9.0 Hz, J_2=2.2 Hz, Ar-H), 5.94 (d, 1H, J=12.0 Hz, =CH), 3.21 (s, 3H, CH_3), 3.00 (s, 3H, CH_3).

Intermediate 4

7-Bromo-4*H*-chromen-4-one.

To a solution of (2*E*)-1-(4-bromo-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one (31.9 g, 118 mmol) in CH_2Cl_2 (900 mL) was added concentrated HCl (100 mL) and the reaction mixture was heated to reflux upon vigorous stirring for 40 minutes. Then the reaction mixture was allowed to cool to room temperature, the organic layer was separated and the water one was extracted with CH_2Cl_2 (100 mL). Combined organic layers were washed with 3M K_2CO_3 (2 x 100mL), dried over Na_2SO_4 and evaporated to give the title compound (26.3 g, 99%) as a pale yellow solid. LC/MS data: 224.9 $(M+H)^+$ (Calculated for $C_9H_5BrO_2$ 225.04) (calc. monoisotopic mass is 223.95, calc. monoisotopic mass $(M+H)^+$ = 224.95). ^1H NMR data (DMSO-d6): 8.29 (d, 1H, J=5.8 Hz, =CH), 7.99 (d, 1H, J=2.0 Hz, Ar-H), 7.94 (d, 1H, J = 8.5 Hz, Ar-H), 7.66 (dd, 1H, J_1=8.5, J_2=1.7 Hz, Ar-H), 6.38 (d, 1H, J=5.8 Hz, =CH).

Intermediate 5

7-Bromo-2,3-dihydro-4*H*-chromen-4-one.

The solution of 7-Bromo-4*H*-chromen-4-one (26.0 g, 116 mmol) in absolute THF (500 mL) was stirred under argon for 1 h and then it was cooled to –80 °C. To a suspension formed a solution of diisobutylaluminum hydride 1M in heptane (173 mL, 173 mmol) was added during 30 minutes and the resulting mixture was stirred at –80 °C for additional 30 minutes. The solution was quenched by mixture of SiO_2 (52 g) and H_2O (52 mL), allowed to warm to 0 °C. Then SiO_2 was filtered, washed with EtOAc and the solution was evaporated to dryness. The residue was dissolved in $CHCl_3$ (400 mL), washed with 1 N NaOH (300 mL), dried over Na_2SO_4 and evaporated. The resulting solid was purified by column chromatography on SiO_2 (63-100 µm, 1200 mL) in $CHCl_3$ (80 - 100%) gradient in hexane to afford 101865-076 (18.1 g, 69%) as a pale yellow solid. LC/MS data: 226.9 $(M+H)^+$ (Calculated for $C_9H_7BrO_2$ 227.06) (calc. monoisotopic mass is 225.96, calc. monoisotopic mass $(M+H)^+$ = 226.96). ^1H NMR data (DMSO-d6): 7.66 (d, 1H, J=8.3 Hz, Ar-H), 7.33 (d, 1H, J=2.0 Hz, Ar-H), 7.25 (dd, 1H, J_1=8.3 Hz, J_2=1.7 Hz, Ar-H), 4.56 (t, 2H, CH_2 , J=6.6 Hz), 2.80 (t, 2H, CH_2 , J=6.6 Hz).

Intermediate 6

3,3,7-tribromo-2,3-dihydro-4*H*-chromen-4-one.

To a vigorously stirring solution of 7-Bromo-2,3-dihydro-4*H*-chromen-4-one (20.0 g, 88.1 mmol) in CCl_4 (400 mL) was added dropwise a solution of bromine (10 mL, 194 mmol) in CCl_4 (100 mL) over 45 minutes. The resulting solution was stirred for 50 minutes and $CHCl_3$ (100 mL) was added to the solution to dissolve the precipitate. The solution was washed with 10% $NaHSO_3$ (75 mL), dried over Na_2SO_4 and evaporated to dryness to give the title compound (32.5 g, 96%) as a yellowish solid. LC/MS data: 302.9 $(M-Br)^+$ (Calculated for $C_9H_5Br_3O_2$ 384.85). (calc. monoisotopic mass is 381.71, calc. monoisotopic mass $(M-Br)^+$= 302.9). ^1H NMR data (DMSO-d6): 7.82 (d, 1H, J = 8.6 Hz, Ar-H), 7.51 (d, 1H, J = 2.0 Hz, Ar-H), 7.42 (dd, 1H, J_1= 8.3, J_2=1.7 Hz, Ar-H), 5.02 (s, 2H, CH_2).

Intermediate 7

7-bromo-3-pyrrolidin-1-yl-2,3-dihydro-4*H*-chromen-4-one.

To a suspension of 3,3,7-tribromo-2,3-dihydro-4*H*-chromen-4-one (32.5 g, 84.4 mmol) in acetonitrile (650 mL) was added pyrrolidine (8.50 mL, 101 mmol), Et_3N (23.5 mL, 169 mmol) and the formed solution was stirred during 16 h at room temperature under argon. The resulting solution was evaporated to dryness, dissolved in EtOAc (500 mL), washed with water (3 x 200 mL), brine (100 mL), dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on SiO_2 (63-100 µm, 800 mL) on EtOAc (0 – 2%) gradient in $CHCl_3$ to afford 101865-118 (12.1 g, 49%) as a yellow solid. LC/MS data: 294.0 $(M+H)^+$ (Calculated for $C_{13}H_{12}BrNO_2$ 294.14). (calc. monoisotopic mass is 293.01, calc. monoisotopic mass $(M+H)^+$ = 294.01). ^1H NMR data (DMSO-d6): 7.99 (d, 1H, J = 8.6 Hz, Ar-H), 7.92 (d, 1H, J = 1.7 Hz, Ar-H), 7.79 (s, 1H, =CH), 7.56 (dd, 1H, J_1= 8.6, J_2=1.7 Hz, Ar-H), 3.16-3.23 (m, 4H, pyrrolidine-CH_2), 1.81-1.88 (m, 4H, pyrrolidine-CH_2).

Intermediate 8

7-bromo-3-pyrrolidin-1-ylchroman-4-ol.

To a solution of 7-bromo-3-pyrrolidin-1-yl-2,3-dihydro-4*H*-chromen-4-one (12.1 g, 41.2 mmol) in EtOH (1200 mL) was portionally added $NaBH_4$ (15.7 g, 412 mmol) and the suspension was vigorously stirred for 14 h. To the solution formed was added water (100 mL) and the solution was evaporated to driness. The residue was dissolved in $CHCl_3$ (300 mL), washed with water (3 x 100 mL), dried over Na_2SO_4 and evaporated to dryness to afford 101865-122 (11.1 g, 92%) as a white solid. LC/MS data: 298.1 $(M+H)^+$, (Calculated for $C_{13}H_{16}BrNO_2$ 298.18). (calc. monoisotopic mass is 297.04, monoisotopic mass $(M+H)^+$= 298.04). ^1H NMR data (DMSO-d6): 7.19 (d, 1H, J = 8.1 Hz, Ar-H), 7.06 (dd, 1H, J_1= 8.1, J_2=2.0 Hz, Ar-H), 7.00 (d, 1H, J = 2.0 Hz, Ar-H), 5.01 (br d, 1H, J=4.2 Hz, OH), 4.59 (m, 1H,

CH), 4.24 (ddd, 1H, J_1=10.6 Hz, J_2=3.7 Hz, J_3=1.5 Hz, CH), 4.05 (t, 1H, J = 10.6 Hz, CH), 2.68-2.72 (m, 2H, pyrrolidine-CH_2), 2.57-2.62 (m, 2H, pyrrolidine-CH_2), 2.44 (dt, 1H, J_d=10.6 Hz, J_t=3.2 Hz, CH), 1.73-1.66 (m, 4H, pyrrolidine-CH_2). The HCl salt was made as followed. 7-bromo-3-pyrrolidin-1-ylchroman-4-ol hydrochloride. To a suspension of 7-bromo-3-pyrrolidin-1-ylchroman-4-ol (11.1 g, 37.2 mmol) in *i*PrOH (250mL) was added concentrated HCl (3.4 mL, 37.2 mmol) and the solution was stirred at room temperatire for 3h. Then the suspension was evaporated to dryness and the residue was recrystallized from *i*PrOH (300 mL) and ether (200 mL) in fridge to afford 101865-123 (9.3 g, 75%) as a white crystals. LC/MS data: 298.1 $(M+H)^+$, (Calculated for $C_{13}H_{16}BrNO_2$ 298.18). (calc. monoisotopic mass is 297.04, monoisotopic mass $(M+H)^+$= 298.04). ^{1}H NMR data (DMSO-d6): 9.85 (br s, 1H, NH^+), 7.31 (d, 1H, J = 8.3 Hz, Ar-H), 7.20 (dd, 1H, J_1= 8.3, J_2=2.0 Hz, Ar-H), 7.13 (d, 1H, J = 2.0 Hz, Ar-H), 6.72 (br d, 1H, J=5.1 Hz, OH), 4-89-4.94 (m, 1H, CH), 4.54 (ddd, 1H, J_1=10.8 Hz, J_2=3.7 Hz, J_3=1.0 Hz, CH), 4.16 (t, 1H, J = 10.8 Hz, CH), 2.69-2.81 (m, 2H, pyrrolidine-CH_2), 2.52-2.64 (m, 1H, CH), 3.17-3.38 (m, 2H, pyrrolidine-CH_2+H_2O), 1.83-2.09 (m+m, 4H, pyrrolidine-CH_2).

Intermediate 9

3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)benzoic acid.

To a stirring solution of 7-bromo-3-pyrrolidin-1-ylchroman-4-ol (5 g, 17 mmol) in DME (50 mL) in the atmosphere of argon were added successively $Pd(PPh_3)_4$ (0.80 g, 0.68 mmol) and 3-carboxyphenylboronic acid (5.08 g, 30 mmol). After 15 minutes of stirring 3M Na_2CO_3 (34 mL, 102 mmol) was added dropwise. The mixture was heated to reflux for 48 h. Then it was cooled, acidified to pH ~ 4 by HCl (conc.), evaporated to dryness and co-evaporated with dioxane and with DMF. The title compound was used in the next step without purification.

Intermediate 10

3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-isopropylbenzamide.

To a cold (ice bath) solution of 3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)benzoic acid (11.53 g, 34 mmol) in DMF (120 mL) was added $iPrNH_2$ (14.6 mL, 170 mmol) and Et_3N (18.6 mL) (to reach pH ~ 9). Then BOP (21 g, 48 mmol) was added and the mixture was stirred at room temperature for 48 h. The reaction mixture was evaporated to dryness, dissolved in water (100 mL) and saturated K_2CO_3 (50 mL) was added. The resulting suspension was extracted with ether (400 mL). Etherial layer was washed with 0.1N K_2CO_3 (2 x 100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated. The column chromatography of the residue on SiO_2 (600 mL, 63-100 µm) in $CHCl_3$ → *i*PrOH (8%) gradient gave after evaporation the title compound (3.76 g, 29%) as a pale yellow solid. LC/MS data: 381.1 $(M+H)^+$ (Calculated for $C_{23}H_{28}N_2O_3$ 380.48). (calc. monoisotopic mass is 380.21, calc.

monoisotopic mass $(M+H)^+$ = 381.21). ^1H NMR data (DMSO-d6): 8.30 (d, 1H, J = 7.8 Hz, NH), 8.06 (s, 1H, Ar-H), 7.82 (d, 1H, J = 7.8 Hz, Ar-H), 7.76 (d, 1H, J = 8.1 Hz, Ar-H), 7.51 (t, 1H, J = 7.7 Hz, Ar-H), 7.36 (d, 1H, J = 8.1 Hz, Ar-H), 7.25 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.8 Hz, Ar-H), 7.15 (d, 1H, J = 1.5 Hz, Ar-H), 4.88-5.04 (br s, 1H, OH), 4.66 (br s, 1H, CH), 4.27 (dd, 1H, J_1 = 2.7 Hz, J_2 = 10.5 Hz, CH), 4.03-4.17 (m, 2H, CH), 2.69-2.79 (m, 2H, pyrrolidine-CH_2), 2.56-2.68 (m, 2H, pyrrolidine-CH_2), 2.45-2.53 (m, 1H, CH+DMSO), 1.67-1.76 (m, 4H, pyrrolidine-CH_2), 1.18 (d, 6H, J = 6.6 Hz, CH_3).

Example 1

3-(3,4-Dihydro-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-isopropylbenzamide.

A solution of 3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-isopropylbenzamide (0.5 g, 1.32 mmol) in a mixture of DCE (20 mL) and TFA (17 mL) was refluxed for 24 h. After this time LC/MS showed no SM by ELSD. The reaction mixture was evaporated to dryness, dissolved in DCE (10 mL) and added dropwise to a cold (ice bath) solution of STAB (0.56 g, 2.64 mmol) and acetic acid (0.4 mL, 6.60 mmol) in DCE (10 mL). The formed solution was vigorously stirred for 21 h. Then water (20 mL) and 10N NaOH (to reach pH ~ 12) were added and organic layer was separated. The water one was extracted with chloroform (2 x 10 mL). Organic layers were combined, dried over Na_2SO_4 with SiO_2 (1 mL, 63-100 μm), evaporated and co-evaporated with CCl_4 to give the title compound (270 mg, 56%) as a yellow solid. LC/MS data: 365.1 $(M+H)^+$ (Calculated for $C_{23}H_{28}N_2O_2$ 364.49). (calc. monoisotopic mass is 364.22, calc. monoisotopic mass $(M+H)^+$ = 365.22). ^1H NMR data (DMSO-d6): 8.29 (d, 1H, J = 7.8 Hz, NH), 8.05 (s, 1H, Ar-H), 7.80 (d, 1H, J = 7.5 Hz, Ar-H), 7.74 (d, 1H, J = 7.7 Hz, Ar-H), 7.49 (t, 1H, J = 7.7 Hz, Ar-H), 7.15-7.21 (m, 2H, Ar-H), 7.11 (s, 1H, Ar-H), 4.30-4.34 (m, 1H, CH), 4.07-4.17 (m, 1H, CH), 3.92 (dd, 1H, J_1 = 7.7 Hz, J_2 = 10.7 Hz, CH), 3.01 (dd, 1H, J_1 = 3.9 Hz, J_2 = 15.4 Hz, CH), 2.78 (dd, 1H, J_1 = 8.0 Hz, J_2 = 16.3 Hz, CH), 2.55-2.68 (m, 5H, CH+pyrrolidine-CH_2), 1.65-1.74 (m, 4H, pyrrolidine-CH_2), 1.18 (d, 6H, J = 6.6 Hz, CH_3). The HCl salt of the title compound was prepared as followed. 3-(3,4-Dihydro-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-isopropylbenzamide hydrochloride. To a solution of 3-(3,4-Dihydro-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-isopropylbenzamide (647 mg, 1.78 mmol) in dioxane (8 mL) was added dropwise 0.4M solution of HCl in dioxane (4.45 mL) and the resulting mixture was vigorously stirred for 5 minutes. Then the mixture was evaporated to dryness and the residue was crystallized from MeOH/Et_2O to afford 101865-155 (592 mg, 83%) as a beige crystals. LC/MS data: 365.2 $(M+H)^+$ (Calculated for $C_{23}H_{28}N_2O_2$ 364.49). (calc. monoisotopic mass is 364.22, calc. monoisotopic mass $(M+H)^+$ = 365.22). ^1H NMR data (DMSO-d6): 11.08 (m, 1H, NH^+), 8.34 (d, 1H, J = 8.1 Hz, NH), 8.07 (s, 1H, Ar-H), 7.83 (d, 1H, J = 7.8 Hz, Ar-H), 7.77 (d, 1H, J = 7.8 Hz, Ar-H), 7.51 (dd, 1H, J_1=J_2 = 7.8 Hz, Ar-H), 7.33 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.8 Hz, Ar-H), 7.27 (d, 1H, J = 8.1 Hz, Ar-H), 7.25 (d, 1H, J = 1.7 Hz, Ar-H), 4.51 (br d, 1H, J=10.5 Hz, CH), 4.34 (dd, 1H, J_1 = 7.3 Hz, J_2 =

11.0 Hz, CH), 4.08-4.17 (m, 1H, CH), 3.81-3.90 (m, 1H, CH), 3.55-3.65 (m, 2H, pyrrolidine-CH_2), 3.18-3.37 (m, 4H, CH+pyrrolidine-CH_2+H_2O), 1.97-2.10 (m, 2H, pyrrolidine-CH_2), 1.84-1.96 (m, 2H, pyrrolidine-CH_2), 1.19 (d, 6H, J = 6.6 Hz, CH_3).

Intermediate 11

N-ethyl-3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)benzamide.

To a cold (ice bath) solution of 3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)benzoic acid (~34 mmol) in DMF (120 mL) was added $EtNH_2$·HCl (13.86 g, 170 mmol) and Et_3N (5 mL) (to reach pH ~ 9). Then BOP (22.54 g, 51 mmol) was added ant the mixture was stirred at room temperature for 24 h. The reaction was monitored by LC/MS (the peak with $(M+H)^+$=340.0 attributed to 101918-056 should disappear).The reaction mixture was evaporated to dryness, dissolved in water (100 mL) and saturated K_2CO_3 was added. The resulting suspension was extracted with ether (300 mL) and EtOAc (3 x 200 mL). Combined organic layers were washed with 0.1N K_2CO_3 (2 x 205 mL) and brine (100 mL), dried over Na_2SO_4+SiO_2 (5 mL, 63-100 μm) and evaporated. The resulting residue was washed with EtOAc (50 mL) and dried in the vacuum of an oil pump to give the title compound (3.86 g, 31%) as a pale yellow solid. LC/MS data: 367.2 $(M+H)^+$ (Calculated for $C_{22}H_{26}N_2O_3$ 366.45). (calc. monoisotopic mass is 366.19, calc. monoisotopic mass $(M+H)^+$ = 367.19). ^1H NMR data (DMSO-d6): 8.56 (t, 1H, J = 5.2 Hz, NH), 8.07 (s, 1H, Ar-H), 7.81 (d, 1H, J = 7.8 Hz, Ar-H), 7.77 (d, 1H, J = 8.4 Hz, Ar-H), 7.52 (dd, 1H, J_1 = J_2 = 6.8 Hz, Ar-H), 7.36 (d, 1H, J = 6.8 Hz, Ar-H), 7.26 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.8 Hz, Ar-H), 7.11 (d, 1H, J = 1.7 Hz, Ar-H), 4.91-5.07 (br s, 1H, OH), 4.67 (br s, 1H, CH), 4.28 (dd, 1H, J_1 = 2.7 Hz, J_2 = 10.3 Hz, CH), 4.10 (t, 1H, J = 10.5 Hz, CH), 3.27-3.35 (m, 2H, CH_2+H_2O), 2.71-2.80 (m, 2H, pyrrolidine-CH_2), 2.60-2.70 (m, 2H, pyrrolidine-CH_2), 2.47-2.58 (m, 1H, CH+DMSO), 1.68-1.77 (m, 4H, pyrrolidine-CH_2), 1.14 (t, 3H, J = 7.2 Hz, CH_3).

Example 2

3-(3,4-Dihydro-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-ethylbenzamide.

A solution of N-ethyl-3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)benzamide (0.50 g, 1.4 mmol) in a mixture of DCE (20 mL) and TFA (18 mL) was refluxed for 24 h. After this time LC/MS showed no SM by ELSD. The reaction mixture was evaporated to dryness, dissolved in DCE (10 mL) and added dropwise to a cold (ice bath) solution of STAB (0.58 g, 2.74 mmol) and acetic acid (0.4 mL, 6.85 mmol) in DCE (10 mL). The formed solution was vigorously stirred for 21 h. Then water (20 mL) and 10N NaOH (to reach pH ~ 12) were added and organic layer was separated. The water one was extracted with chloroform (2 x 10 mL). Organic layers were combined, dried over Na_2SO_4 with SiO_2 (1 mL, 63-100 μm), evaporated and co-evaporated with CCl_4 to give 101865-152 (374 mg, 78%) as a

yellow solid. LC/MS data: 351.2 $(M+H)^+$ (Calculated for $C_{22}H_{26}N_2O_2$ 350.46). (calc. monoisotopic mass is 350.20, calc. monoisotopic mass $(M+H)^+$ = 351.20). ^1H NMR data (DMSO-d6): 8.54 (t, 1H, J = 5.2 Hz, NH), 8.06 (s, 1H, Ar-H), 7.79 (d, 1H, J = 7.8 Hz, Ar-H), 7.75 (d, 1H, J = 8.3 Hz, Ar-H), 7.50 (dd, 1H, $J_1 = J_2 = 7.8$ Hz, Ar-H), 7.16-7.21 (m, 2H, Ar-H), 7.11 (s, 1H, Ar-H), 4.07-4.17 (m, 1H, CH), 3.92 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 10.5$ Hz, CH), 3.27-3.34 (m, 2H, CH_2+H_2O), 3.01 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 16.1$ Hz, CH), 2.78 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 15.9$ Hz, CH), 2.56-2.68 (m, 5H, CH+pyrrolidine-CH_2), 1.65-1.74 (m, 4H, pyrrolidine-CH_2), 1.14 (t, 3H, J = 7.1 Hz, CH_3). The HCl salt of the title compound was made as followed. 3-(3,4-Dihydro-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-ethylbenzamide hydrochloride. To a solution of 3-(3,4-Dihydro-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-ethylbenzamide (808 mg, 2.31 mmol) in dioxane (30 mL) was added dropwise 0.4M solution of HCl in dioxane (5.77 mL) and the resulting mixture was vigorously stirred for 5 minutes. Then the mixture was evaporated to dryness and the residue was crystallized from MeOH/Et_2O to afford 101865-156 (625 mg, 70%) as a beige crystals. LC/MS data: 351.1 $(M+H)^+$ (Calculated for $C_{22}H_{26}N_2O_2$ 350.46). (calc. monoisotopic mass is 350.20, calc. monoisotopic mass $(M+H)^+$ = 351.20). ^1H NMR data (DMSO-d6): 10.98 (m, 1H, NH^+), 8.59 (t, 1H, J = 5.4 Hz, NH), 8.09 (s, 1H, Ar-H), 7.82 (d, 1H, J = 7.6 Hz, Ar-H), 7.78 (d, 1H, J = 8.3 Hz, Ar-H), 7.52 (dd, 1H, $J_1 = J_2$ = 7.6 Hz, Ar-H), 7.34 (dd, 1H, $J_1 = 1.7$ Hz, $J_2 = 7.7$ Hz, Ar-H), 7.27 (d, 1H, J = 8.1 Hz, Ar-H), 7.24 (d, 1H, J = 1.7 Hz, Ar-H), 4.51 (br d, 1H, J=10.5 Hz, CH), 4.35 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 =$ 11.5 Hz, CH), 3.81-3.91 (m, 1H, CH), 3.55-3.65 (m, 2H, pyrrolidine-CH_2), 3.18-3.36 (m, 6H, CH+CH_2+ pyrrolidine-CH_2+H_2O), 1.97-2.10 (m, 2H, pyrrolidine-CH_2), 1.84-1.95 (m, 2H, pyrrolidine-CH_2), 1.14 (t, 3H, J = 7.2 Hz, CH_3).

Intermediate 12

4-(4-Hydroxy-3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)benzoic Acid.

7-bromo-3-pyrrolidin-1-ylchroman-4-ol (10.0 g, 0.034 mol) was dissolved in DME (6 mL). $(PPh_3)_4Pd$ (0.78 g, 0.68 mmol) and 4-carboxybenzene boronic acid (6.8 g, 0.041 mol) were added in a flow of argon. The reaction mixture was stirred in a flow of argon for 20 min. Then a 3 M solution of Na_2CO_3 (68 mL, 0.2 mol) was added. The mixture was refluxed for 48 h and acidified with HCl to pH 4. The reaction mass was evaporated to dryness, and then coevaporated sequentially with dioxane and with DMF. The dry title compound was used for the next stage without purification.

Intermediate 13

4-(4-Hydroxy-3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)-*N*-isopropylbenzamide.

4-(4-Hydroxy-3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)benzoic Acid (~0.034 mol) was dissolved in DMF (120 mL), and the solution was cooled in an ice bath. Isopropylamine (14.5 mL, 0.170 mol) and BOP (22.5 g, 0.051 mol) were added. The mixture

was stirred for 15 min under cooling with ice, then for 24 h at room temperature. The reaction was monitored by LC/MS . When complete, the reaction was evaporated to dryness. Water (100 mL), ethyl acetate (300 mL), and a saturated solution of K_2CO_3 (50 mL) were added. The mixture was vigorously stirred, and the liquid phase was decanted. H_2O (50 mL) was added to the residual mass, and the product was extracted with ethyl acetate. The organic layer was washed with 0.1N K_2CO_3 (2 × 250 mL), brine (100 mL), dried with Na_2SO_4 + SiO_2 (5 mL), and evaporated. The residue was purified by chromatography (silica gel 63–100 μm, 800 mL; chloroform/isopropanol 100:0 → 92:8). The solvent was evaporated to give the title compound as beige crystals. Yield: 3.1 g (0.008 mol, 24%). LC/MS data: 381.2 $(M+H)^+$ (calculated for $C_{23}H_{28}N_2O_3$ 380.49). (Calc. monoisotopic mass is 380.21. Calc. monoisotopic mass $(M+H)^+$ is 381.21). ^1H NMR data (DMSO-d6): 8.22 (d, 1H, NH, J = 7.6 Hz), 7.91 (d, 2H, ArH, J = 8.3 Hz), 7.71 (d, 2H, ArH, J=8.3 Hz), 7.35 (d, 1H, ArH, J = 8.1 Hz), 7.25 (dd, 1H, ArH, J_1 = 7.6. Hz J_2 = 1.7 Hz), 7.11 (d, 1H, ArH, J = 1.5 Hz), 5.96 (d, 1H, J = 3.9 Hz), 4.66 (s, 1H), 4.27 (dd, 1H, J_1 = 10.8. Hz J_2 = 2.9 Hz), 4.05-4.16 (m, 2H), 3.24-3.27 (m, 1H, CH_3), 2.58-2.78 (m, 4H α, $2CH_2$), 1.71 (s, 4H β, $2CH_2$), 1.18 (d, 6H, 2Me, J = 6.6 Hz).

Intermediate 14

***N*-Isopropyl-4-(3-pyrrolidin-1-yl-2*H*-chromen-7-yl)benzamide.**

Compound 4-(4-Hydroxy-3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)-*N*-isopropylbenzamide (2.78 g, 7.31 mmol) was dissolved in dichloroethane (96 mL). TFA (96 mL, 1.24 mol) was added in a flow of argon, and the mixture was refluxed for 48 h. The reaction was monitored by TLC (ethyl acetate/methanol 80:20): the spot of the starting compound should disappear. The reaction mass was evaporated to dryness, and the crude title compound was used for the next stage without purification.

Example 3

***N*-Isopropyl-4-(3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)benzamide.**

N-Isopropyl-4-(3-pyrrolidin-1-yl-2*H*-chromen-7-yl)benzamide (2.65 g, 7.31 mmol) was dissolved in dichloroethane (90 mL). This solution was added dropwise to a mixture of STAB (3.10 g, 14.62 mmol) and AcOH (2.1 mL, 36.55 mmol) in dichloroethane (10 mL) cooled to 0 °C in a flow of argon. The reaction mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC (ethyl acetate/methanol 80:20; R_f of the title compound is 0.3). Water (100 mL) was added. The reaction mixture was alkalized to pH 11 with 3N NaOH and stirred for 5 min. The organic layer was separated, and the aqueous one was subjected to extraction with dichloromethane (3 × 100 mL). The combined extracts were dried with Na_2SO_4 and evaporated to give analytically pure title compound as a cream-colored powder. Yield: 2.58 g (7.07 mmol, 97%). LC/MS data: 365.2 $(M+H)^+$ (calculated for $C_{23}H_{28}N_2O_2$ 364.5) (Calc. monoisotopic mass is 364.22. Calc. monoisotopic mass $(M+H)^+$ is 365.22). ^1H NMR data (DMSO-d6): 8.20 (d, 1H, NH, J = 7.8 Hz), 7.89 (d, 2H, ArH, J = 8.6 Hz), 7.69 (d, 2H, ArH,

J=8.6 Hz), 7.18 (d, 2H, ArH, J = 1.5 Hz), 7.07 (s, 1H, ArH), 4.28-4.36 (m, 1H), 4.05-4.15 (m, 1H), 3.89-3.96 (m, 1H), 3.01 (dd, 1H, J_1 = 16.4. Hz J_2 = 5.1 Hz), 2.73-2.82 (m, 1H), 2.55-2.67 (m, 5H α, $2CH_2$+CH), 1.69 (s, 4H β, $2CH_2$), 1.17 (d, 6H, 2Me, J = 6.6 Hz). The HCl salt of the title compound was made as followed: *N*-Isopropyl-4-(3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)benzamide Hydrochloride. A 0.4 M solution of HCl in dioxane (17.5 mL, 7.0 mmol) was added to a solution of free base title compound (2.55 g, 7.0 mmol) in absolute dioxane (25 mL). The reaction mixture was evaporated to dryness, and the residue was crystallized from MeOH/Et_2O (1:3). Yielding the HCl salt of the title compound: 2.29 g (5.57 mmol, 81%) as white crystals. LC/MS data: 365.2 $(M+H)^+$ (calculated for $C_{23}H_{28}N_2O_2$ 364.5) (Calc. monoisotopic mass is 364.22. Calc. monoisotopic mass $(M+H)^+$ is 365.22). ^{1}H NMR data (DMSO-d6): 10.78 (s, 1H, NH), 8.23 (d, 1H, NH, J = 7.8 Hz), 7.92 (d, 2H, ArH, J = 8.3 Hz), 7.72 (d, 2H, ArH, J=8.3 Hz), 7.33 (dd, 1H, ArH, J_1 = 8.1Hz, J_2 = 1.7 Hz), 7.27 (d, 1H, ArH, J = 8.1 Hz), 7.21 (d, 1H, ArH, J = 1.48 Hz), 4.49 (d, 1H, J = 10.5 Hz), 4.32-4.40 (m, 1H), 4.06-4.16 (m, 1H), 3.81-3.91 (m, 1H), 3.56-3.66 (m, 2H), 3.15-3.28 (m, 3H α, $2CH_2$), 1.64-2.11 (m, 4H β, $2CH_2$), 1.18 (d, 6H, 2Me, J = 6.6 Hz).

Intermediate 15

7-[4-(Methylsulfonyl)phenyl]-3-pyrrolidin-1-ylchroman-4-ol.

To a stirred solution of 7-bromo-3-pyrrolidin-1-ylchroman-4-ol (3.13 g, 9.36 mmol) in DME (60 mL) in the atmosphere of argon were added successively $Pd(PPh_3)_4$ (0.86 g, 0.75 mmol) and 4-(methanesulfonyl)phenylboronic acid CAS # 149104-88-1 (2.8 g, 14 mmol). After 5 minutes of stirring, 3M Na_2CO_3 (19 mL, 56.2 mmol) was added dropwise. The mixture was refluxed for 20 h and cooled. The organic layer was separated, and the water one was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4+silica gel (1 mL, 63–100 μm), and evaporated. The column chromatography on silica gel (100 mL, 63–100 μm) first in EtOAc (0, 20, 50, 100%) gradient in $CHCl_3$ then in MeOH (0 → 8%) gradient in EtOAc gave 101865-127 (1.64 g, 47%) as an orange solid. LC/MS data: 374.1 $(M+H)^+$ (calculated for $C_{20}H_{23}NO_4S$ 373.47). (Calc. monoisotopic mass is 373.13, calc. monoisotopic mass $(M+H)^+$ is 374.13). ^{1}H NMR data (DMSO-d6): 7.97 (d, 2H, J = 8.6 Hz, Ar-H), 7.90 (d, 2H, J = 8.6 Hz, Ar-H), 7.39 (d, 1H, J = 7.8 Hz, Ar-H), 7.28 (d, 1H, J = 8.1 Hz, Ar-H), 7.16 (br s, 1H, Ar-H), 4.93-5.08 (m, 1H, OH), 4.68 (br s, 1H, CH), 4.25-4.34 (m, 1H, CH), 4.11 (t, 1H, J = 10.5 Hz, CH), 3.24 (s, 3H, SCH_3), 2.70-2.81 (m, 2H, pyrrolidine-CH_2), 2.58-2.69 (m, 2H, pyrrolidine-CH_2), 2.47-2.53 (m, 1H, CH+DMSO), 1.67-1.77 (m, 4H, pyrrolidine-CH_2).

Intermediate 16

1-{7-[4-(methylsulfonyl)phenyl]-2*H*-chromen-3-yl}pyrrolidine.

7-[4-(Methylsulfonyl)phenyl]-3-pyrrolidin-1-ylchroman-4-ol (673 mg, 1.80 mmol) was dissolved in dichloroethane (24 mL) in a flow of argon. TFA (24 mL, 306 mol) was added, and the reaction mixture was refluxed for 4 days. The reaction was monitored by LC/MS: the peak with $(M+H)^+$=374.1. The reaction mass was evaporated to dryness and used for the next stage without purification.

Example 3

1-{7-[4-(Methylsulfonyl)phenyl]-3,4-dihydro-2*H*-chromen-3-yl}pyrrolidine.

A solution of 1-{7-[4-(methylsulfonyl)phenyl]-2*H*-chromen-3-yl}pyrrolidine (639 g, 1.80 mmol) in dichloroethane (15 mL) was added dropwise to a mixture of STAB (763 mg, 3.60 mmol) and AcOH (0.5 mL, 9.0 mmol) in dichloroethane (10 mL) cooled to 0 °C in a flow of argon. The reaction mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC (ethyl acetate/methanol 80:20; R_f of product is 0.23). Water (20 mL) was added to the reaction mixture. The latter was alkalized to pH 11 with 3N NaOH and stirred for 5 min. The organic layer was separated, and the aqueous one was subjected to extraction with dichloromethane (3 × 20 mL). The combined extracts were dried with Na_2SO_4 and evaporated to give analytically pure compound title compound as a brown powder. Yield: 497 mg (1.39 mmol, 77%). LC/MS data: 358.1 $(M+H)^+$ (calculated for $C_{20}H_{23}NO_2S$ 357.47). (Calc. monoisotopic mass is 357.14, calc. monoisotopic mass $(M+H)^+$ is 358.1). ^1H NMR data (DMSO-d6): 7.96 (d, 2H, NH, J = 8.6 Hz), 7.89 (d, 2H, ArH, J = 8.6 Hz), 7.22 (s, 2H, ArH,), 7.12 (s, 1H, ArH), 4.33 (d, 1H, J = 10.2 Hz), 3.91-3.98 (m, 1H), 3.24 (s, 3H, Me), 2.97-3.08 (m, 1H), 2.76-2.84 (m, 1H), 2.55-2.68 (m, 5H α, $2CH_2$+CH), 1.65-1.75 (m, 4H β, $2CH_2$). The HCl salt of the title compound was generated as followed: 1-{7-[4-(Methylsulfonyl)phenyl]-3,4-dihydro-2*H*-chromen-3-yl}pyrrolidine Hydrochloride. 0.4 M HCl/dioxane (4.33 ml, 1.73 mmol) was added to a solution of free base title compound (618 mg, 1.73 mmol) in absolute dioxane (10.0 mL). The reaction mixture was evaporated to dryness and crystallized from MeOH/Et_2O (1:3). Yield of the titile compound as the HCl salt, 515 mg (1.3 mmol, 75.6%,) as yellow crystals. LC/MS data: 358.1 $(M+H)^+$ (calculated for $C_{20}H_{23}NO_2S$ 357.47). (Calc. monoisotopic mass is 357.14, calc. monoisotopic mass $(M+H)^+$ is 358.1). ^1H NMR data (DMSO-d6): 10.73 (s, 1H, NH), 7.98 (d, 2H, NH, J = 8.6 Hz), 7.98 (d, 2H, ArH, J = 8.6 Hz), 7.36 (dd, 1H, ArH, J1 = 8.1 Hz, J2 = 1.7 Hz), 7.31 (d, 1H, ArH, J = 1.7 Hz), 4.49 (d, 1H, J = 11.2 Hz), 4.34-4.40 (m, 1H), 3.82-3.92 (m, 1H), 3.56-3.66 (m, 2H), 3.17-3.28 (m, 6H), 1.83-2.09 (m, 4H β, $2CH_2$).

Intermediate 17

7-(2-Methoxypyridin-3-yl)-3-pyrrolidin-1-ylchroman-4-ol.

To a stirred solution of 7-bromo-3-pyrrolidin-1-ylchroman-4-ol (2.0 g, 6.71 mmol) in DME (40 mL) in the atmosphere of argon were added successively $Pd(PPh_3)_4$ (0.39 g, 0.34 mmol) and 2-methoxypyridine-3-boronic acid (1.55 g, 10.1 mmol). After 5 minutes of stirring

2M Na_2CO_3 (17 mL, 33.6 mmol) was added dropwise. The mixture was refluxed for 7 h and cooled. The organic layer was separated, and the water one was subjected to extraction with ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 + silica gel (1 mL, 63-100 μm) and evaporated. The column chromatography on SiO_2 (100 mL, 63-100 μm) first in EtOAc (0, 50, 100%) gradient in $CHCl_3$, then in MeOH (0 → 8%) gradient in EtOAc gave 2.2 g of a solidifying yellow oil that appeared to contain Ph_3PO (12% by LC/MS (ELSD)). The substance was dissolved in Et_2O (25 mL). Water (25 mL) was added, and the mixture was acidified with $NaHSO_4$ to pH ~ 2. The ethereal layer was separated, and the water one was subjected to extraction with ether (25 mL). The water layer was then alkalized to pH ~ 12 with K_2CO_3 (sat.), and the product was extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were dried over Na_2SO_4+SiO_2 (2 mL, 63-100 μm) and evaporated to give the title compound (1.2 g, 36%) as a yellow solid. LC/MS data: 327.1 $(M+H)^+$ (calculated for $C_{19}H_{22}N_2O_3$ 326.39). (Calc. monoisotopic mass is 326.16, calc. monoisotopic mass $(M+H)^+$ is 327.16). ^1H NMR data (DMSO-d6): 8.15 (dd, 1H, J_1 = 1.7 Hz, J_2 = 4.9 Hz, Ar-H), 7.70 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.3 Hz, Ar-H), 7.29 (d, 1H, J = 8.1 Hz, Ar-H), 7.04-7.08 (m, 2H, Ar-H), 6.95 (d, 1H, J = 1.5 Hz, Ar-H), 4.88-5.03 (m, 1H, OH), 4.64 (br s, 1H, CH), 4.25 (dd, 1H, J_1 = 2.4 Hz, J_2 = 10.3 Hz, CH), 4.08 (t, 1H, J = 11.7 Hz, CH), 3.86 (s, 3H, OCH_3), 2.69-2.80 (m, 2H, pyrrolidine-CH_2), 2.57-2.68 (m, 2H, pyrrolidine-CH_2), 2.43-2.55 (m, 1H, CH+DMSO), 1.66-1.78 (m, 4H, pyrrolidine-CH_2).

Intermediate 18

7-(2-Methoxypyridin-3-yl)-2*H*-chromen-3(4*H*)-one.

7-(2-Methoxypyridin-3-yl)-3-pyrrolidin-1-ylchroman-4-ol (0.80 g, 2.46 mmol) was dissolved in AcOH (9.3 mL, 162.6 mmol). Concentrated H_2SO_4 (3.2 mL, 59.04 mmol) was added, and the mixture was refluxed at 80 °C for 6 h. The reaction was monitored by TLC (ethyl acetate/methanol 80:20): the spot of the starting alcohol should disappear. Water (20 mL) and ether/dichloromethane mixture (2:1) (20 mL) were added. The mixture was neutralized with a saturated solution of $NaHCO_3$ to pH 8. The organic layer was separated, and the aqueous one was subjected to extraction with ether/dichloromethane mixture (2:1) (3 × 20 mL). The combined extracts were dried with Na_2SO_4 and evaporated to dryness. The residue was dried by coevaporation with chloroform. The dry residue was used for the next stage without additional .

Example 4

2-Methoxy-3-(3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)pyridine.

A solution of 7-(2-Methoxypyridin-3-yl)-2*H*-chromen-3(4*H*)-one. (0.63 g, 2.46 mmol) in chloroform (10 mL) was added dropwise to a mixture of STAB (1.04 g, 4.92 mmol), pyrrolidine (0.31 mL, 3.69 mmol), and AcOH (0.70 mL, 12.30 mmol) in chloroform (10 mL) cooled to – 20 °C in a flow of argon. The reaction mixture was stirred at room temperature for 24 h. The

reaction was monitored by TLC (ethyl acetate/methanol 80:20; R_f of product 101918-071 is 0.3). Water H_2O (20 mL) was added. The mixture was alkalized to pH 11 with 3N NaOH and stirred for 5 min. The organic layer was separated, and the aqueous one was subjected to extraction with chloroform (3 × 20 mL). The combined extracts were dried with Na_2SO_4 + silica gel and evaporated. The residue was recrystallized from ethyl acetate to afford the title compound as yellow crystals. Yield: 0.26 g (0.85 mmol, 34.8%). LC/MS data: 311.2 $(M+H)^+$ (calculated for $C_{19}H_{22}N_2O_2$ 310.4). (Calc. monoisotopic mass is 310.17, calc. monoisotopic mass $(M+H)^+$ is 311.17). ^1H NMR data (DMSO-d6): 8.14 (dd, 1H, ArH, J_1 = 4.9 Hz, J_2 = 1.9 Hz), 7.69 (dd, 1H, ArH, J_1 = 7.1 Hz, J_2 = 2.0 Hz), 7.12 (d, 1H, ArH, J = 7.8 Hz), 7.06 (dd, 1H, ArH, J_1 = 7.3 Hz, J_2 = 4.9 Hz), 6.99 (dd, 1H, ArH, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 6.92 (d, 1H, J = 1.5 Hz), 4.26-4.33 (m, 1H), 3.89-3.94 (m, 1H), 3.87 (s, 3H, Me), 2.95-3.04 (m, 1H), 2.71-2.82 (m, 1H), 2.54-2.69 (m, 5H α, $2CH_2$, CH), 1.64-1.75 (m, 4H β, $2CH_2$). The HCl salt of the title compound was made as followed: 2-Methoxy-3-(3-pyrrolidin-1-yl-3,4-dihydro-2*H*-chromen-7-yl)pyridine Dihydrochloride. 4 M HCl/dioxane (0.66 mL, 2.66 mmol) was added to a solution of compound 101918-071 (0.41g, 1.33 mmol) in absolute dioxane (5.0 mL). The reaction mixture was evaporated to dryness and crystallized from MeOH/Et_2O (1:3). Yield of HCl salt 0.29 g (0.83 mmol, 62.4%,) as white crystals. LC/MS data: 311.1 $(M+H)^+$ (calculated for $C_{19}H_{22}N_2O_2$ 310.4). (Calc. monoisotopic mass is 310.17, calc. monoisotopic mass $(M+H)^+$ is 311.17). ^1H NMR data (DMSO-d6): 10.96 (s, 1H, NH), 8.17 (dd, 1H, ArH, J_1 = 4.9 Hz, J_2 = 1.9 Hz), 7.72 (dd, 1H, ArH, J_1 = 7.3 Hz, J_2 = 2.0 Hz), 7.22 (d, 1H, ArH, J = 7.8 Hz), 7.13 (dd, 1H, ArH, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 7.10-7.03 (m, 2H, ArH), 4.24-4.49 (m, ?H), 3.57 (s, 3H, Me), 3.79-3.86 (m, 1H), 3.56-3.66 (m, 2H), 3.16-3.36 (m, 4H α, $2CH_2$), 1.83-2.11 (m, 4H β, $2CH_2$).

Intermediate 19

N-ethyl-3-(3,4-dihydro-3-oxo-2H-chromen-7-yl)benzamide.

A solution of N-ethyl-3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)benzamide (1.95 g, 5.33 mmol) in a mixture of DCE (80 mL) and TFA (70 mL) was refluxed for 23 h. After this time LC/MS showed no SM by ELSD. The reaction mixture was evaporated to dryness, dissolved in EtOAc (100 mL) and washed with saturated $NaHCO_3$ (150 mL). Water layer was extracted with EtOAc (2 x 50 mL). Organic layers were combined, dried over Na_2SO_4+SiO_2 (2 mL, 63-100 μm), evaporated to dryness and co-evaporated with $CHCl_3$. The substance was immediately used in the next step as a solution in $CHCl_3$ (50 mL) without further purification because of its instability.

Example 5

N-ethyl-3-(3,4-dihydro-3-((R)-2-methylpyrrolidin-1-yl)-2H-chromen-7-yl)benzamide.

To a cold (ice bath) vigorously stirring solution of (R)-2-methylpyrrolidine (0.68 g, 8.0 mmol, prepared as a solution in 10 mL of $CHCl_3$ after washing of the solution of (R)-2-

methylpyrrolidine hydrobromide (1.32 g, 8.0 mmol) with 10N NaOH (10 mL)), STAB (2.26 g, 10.7 mmol) and AcOH (1.53 mL, 26.7 mmol) in $CHCl_3$ (30 mL) was added dropwise a solution of N-ethyl-3-(3,4-dihydro-3-oxo-2H-chromen-7-yl)benzamide in $CHCl_3$ (50 mL). After 5 min the cold bath was removed and the mixture was stirred during 15 h at room temperature. Then water (100 mL) and 10N NaOH (to reach pH ~ 12) were added, organic layer was separated and the water one was extracted with $CHCl_3$ (3 x 25 mL). The combined organic layers were dried over Na_2SO_4+SiO_2 (2 mL, 63-100 μm), evaporated to dryness and co-evaporated with CCl_4. The resulting brown oil (1.65 g) was chromatographed on SiO_2 (100 mL, 63-100 μm) in $CHCl_3$ → EtOAc → MeOH (5%) gradient to give 101865-159 (0.319 g, 16 % per 2 steps). LC/MS data: 365.2 $(M+H)^+$ (Calculated for $C_{23}H_{28}N_2O_2$ 364.48). (calc. monoisotopic mass is 364.22, calc. monoisotopic mass $(M+H)^+$ = 365.22). ^1H NMR data (DMSO-d6): 8.55 (t, 1H, J = 5.2 Hz, NH), 8.06 (br s, 1H, Ar-H), 7.79 (d, 1H, J = 7.8 Hz, Ar-H), 7.75 (d, 1H, J = 7.8 Hz, Ar-H), 7.50 (dd, 1H, J_1 = J_2 = 7.8 Hz, Ar-H), 7.17-7.22 (m, 2H, Ar-H), 7.11 (d, 1H, J = 5.6 Hz, Ar-H), 4.29 (br t, 1H, J = 11.0 Hz, CH), 3.85-3.98 (m, 1H, CH), 3.25-3.34 (m, 3H, CH+CH_2), 2.56-3.20 (m, 5H, CH+pyrrolidine-CH_2), 1.28-2.07 (m, 4H, CH+ pyrrolidine-CH_2), 1.14 (t, 3H, J = 7.4 Hz, CH_3), 1.00 (dd, 3H, J_1 = 7.1 Hz, J_2 = 9.6 Hz, pyrrolidine-CH_3). The HCl salt of the title compound was prepared as followed: N-ethyl-3-(3,4-dihydro-3-((R)-2-methylpyrrolidin-1-yl)-2H-chromen-7-yl)benzamide hydrochloride. To a solution of free base of the title compound (0.318 g, 0.87 mmol) in dioxane (12 mL) was added dropwise 0.4M solution of HCl in dioxane (2.2 mL, 0.88 mmol) and the resulting mixture was vigorously stirred for 5 minutes. Then the mixture was evaporated to dryness and the residue was crystallized from MeOH/Et_2O to afford 101865-161 (0.306 g, 88%) as an orange crystals. LC/MS data: 365.2 $(M+H)^+$ (Calculated for $C_{23}H_{28}N_2O_2$ 364.48). (calc. monoisotopic mass is 364.22, calc. monoisotopic mass $(M+H)^+$ = 365.22). ^1H NMR data (DMSO-d6): 10.34-10.96 (m, 1H, NH^+), 8.54-8.63 (m, 1H, NH), 8.09 (br s, 1H, Ar-H), 7.82 (d, 1H, J = 8.1 Hz, Ar-H), 7.78 (d, 1H, J = 7.8 Hz, Ar-H), 7.52 (dd, 1H, J_1 = J_2 = 7.8 Hz, Ar-H), 7.24-7.35 (m, 3H, Ar-H), 3.71-4.61 (m, 4H, CH), 3.12-3.66 (m, 5H, pyrrolidine-CH_2+CH_2+H_2O), 1.21-2.27 (m, 8H, CH+pyrrolidine-CH_2+CH_3), 1.15 (t, 3H, J = 7.3 Hz, CH_3).

Intermediate 20

3-(3,4-dihydro-3-oxo-2H-chromen-7-yl)-N-isopropylbenzamide.

A solution of 3-(3,4-dihydro-4-hydroxy-3-(pyrrolidin-1-yl)-2H-chromen-7-yl)-N-isopropylbenzamide (2.54 g, 6.68 mmol) in a mixture of DCE (100 mL) and TFA (90 mL) was refluxed for 23 h. After this time LC/MS showed no SM by ELSD. The reaction mixture was evaporated to dryness, dissolved in EtOAc (120 mL) and washed with saturated $NaHCO_3$ (200 mL). Water layer was extracted with EtOAc (2 x 75 mL). Organic layers were combined, dried over Na_2SO_4+SiO_2 (2 mL, 63-100 μm), evaporated to dryness and co-evaporated with

$CHCl_3$. The title compound was immediately used in the next step as a solution in $CHCl_3$ (70 mL) without further purification because of its instability.

Example 6

3-(3,4-dihydro-3-((R)-2-methylpyrrolidin-1-yl)-2H-chromen-7-yl)-N-isopropylbenzamide.

To a cold (ice bath) vigorously stirring solution of (R)-2-methylpyrrolidine (0.85 g, 10 mmol, prepared as a solution in 10 mL of $CHCl_3$ after washing of the solution of (R)-2-methylpyrrolidine hydrobromide (1.66 g, 10 mmol) with 10N NaOH (10 mL)), STAB (2.84 g, 13.4 mmol) and AcOH (1.9 mL, 33.4 mmol) in $CHCl_3$ (40 mL) was added dropwise a solution of 3-(3,4-dihydro-3-oxo-2H-chromen-7-yl)-N-isopropylbenzamide in $CHCl_3$ (70 mL). After 5 min the cold bath was removed and the mixture was stirred during 15 h at room temperature. Then water (100 mL) and 10N NaOH (to reach pH ~ 12) were added, organic layer was separated and the water one was extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were dried over Na_2SO_4+SiO_2 (2 mL, 63-100 μm), evaporated to dryness and co-evaporated with CCl_4. The resulting brown oil (3.3 g) was chromatographed on SiO_2 (150 mL, 63-100 μm) in $CHCl_3$ → EtOAc → MeOH (4%) gradient to give the title compound (0.746 g, 29 % per 2 steps). LC/MS data: 379.2 $(M+H)^+$ (Calculated for $C_{24}H_{30}N_2O_2$ 378.51). (calc. monoisotopic mass is 378.23, calc. monoisotopic mass $(M+H)^+$ = 379.23). ^1H NMR data (DMSO-d6): 8.29 (d, 1H, J = 7.6 Hz, NH), 8.05 (br s, 1H, Ar-H), 7.80 (d, 1H, J = 7.7 Hz, Ar-H), 7.74 (d, 1H, J = 7.9 Hz, Ar-H), 7.49 (dd, 1H, J_1 = J_2 = 7.6 Hz, Ar-H), 7.17-7.22 (m, 2H, Ar-H), 7.11 (d, 1H, J = 5.9 Hz, Ar-H), 4.29 (br t, 1H, J = 12.0 Hz, CH), 4.07-4.18 (m, 1H, CH), 3.85-3.98 (m, 1H, CH), 2.56-3.20 (m, 6H, CH+pyrrolidine-CH_2), 1.27-2.07 (m, 4H, CH+ pyrrolidine-CH_2), 1.18 (d, 6H, J = 6.6 Hz, CH_3), 1.00 (dd, 3H, J_1 = 6.1 Hz, J_2 = 9.3 Hz, pyrrolidine-CH_3). The HCl salt of the title compound was prepared as followed: N-ethyl-3-(3,4-dihydro-3-((R)-2-methylpyrrolidin-1-yl)-2H-chromen-7-yl)benzamide hydrochloride.

To a solution of free base (0.74 g, 1.96 mmol) in dioxane (10 mL) was added dropwise 0.4M solution of HCl in dioxane (4.9 mL, 1.96 mmol) and the resulting mixture was vigorously stirred for 5 minutes. Then the mixture was evaporated to dryness and the residue was crystallized from MeOH/Et_2O to afford 101865-162 (0.399 g, 49%) as an orange crystals. LC/MS data: 379.2 $(M+H)^+$ (Calculated for $C_{24}H_{30}N_2O_2$ 378.51). (calc. monoisotopic mass is 378.23, calc. monoisotopic mass $(M+H)^+$ = 379.23). ^1H NMR data (DMSO-d6): 11.10-10.47 (m, 1H, NH^+), 8.31 (d, 1H, J = 7.8 Hz, NH), 8.07 (br s, 1H, Ar-H), 7.82 (d, 1H, J = 7.8 Hz, Ar-H), 7.77 (d, 1H, J = 7.3 Hz, Ar-H), 7.51 (dd, 1H, J_1 = J_2 = 7.6 Hz, Ar-H), 7.24-7.35 (m, 3H, Ar-H), 3.72-4.59 (m, 5H, CH), 3.14-3.67 (m, 4H, CH+pyrrolidine-CH_2+H_2O), 1.22-2.29 (m, 7H, pyrrolidine-CH_2+CH_3), 1.19 (d, 6H, J = 6.6 Hz, CH_3).

Intermediate 21

7-(4-methoxyphenyl)-2,3-dihydrochromen-4-one.

4-Oxo-3,4-dihydro-2H-chromen-7-yl trifluoromethanesulfonate (Koch, Biggers, JOC, 1994, 59, 1216) (2.50 g, 8.44 mmol), 4-methoxyphenylboronic acid (1.92g, 12.63 mmol), potassium carbonate (1.0g, 8.4 mmol), potassium phosphate tribasic (2.7 g, 12.72 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.49g, 0.42 mmol) in dioxane (25 mL) were refluxed for 20 h, cooled, filtered through diatomaceous earth and concentrated. The residue was dissolved in EtOAc and washed with water and brine, dried ($MgSO_4$) and concentrated to afford an orange solid (3.32g). Chromatography on silica gel using 50% to 75% CH_2Cl_2/hexanes yielded 1.43g (67%) of the title compound as a flaky white solid: NMR ($CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.21 (dd, J = 7.9, 1.9 Hz, 1H), 7.12 (d, J = 1.7 Hz, 1H), 4.55 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 2.81 (t, J = 6.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 191.7, 162.4, 160.4, 148.7, 132.1, 128.6, 127.8, 120.2, 119.8, 115.4, 114.6, 67.4, 55.6, 38.0.

Intermediate 22

3,3-Dibromo-7-(4-methoxyphenyl)-2,3-dihydrochromen-4-one

7-(4-Methoxyphenyl)-2,3-dihydrochromen-4-one (1.43g, 5.62 mmol) and copper(II)bromide (2.64g, 11.82 mmol) slurried in EtOAc (60 mL) were refluxed. Two additional portions of copper(II)bromide (1.3g, 5.82 mmol - each) were added at 20h and 40h and after ~64h total reaction time, the mixture was cooled, filtered and washed with water and brine.After drying ($MgSO_4$), the organics were concentrated to afford 2.33g (100%) of the title compound as a yellow solid: NMR ($CDCl_3$) δ 8.02 (d, J =8.3 Hz, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.34 (dd, J = 8.3, 1.7 Hz, 1H), 7.20 (d, J = 1.7 Hz, 1H), 6.98 (d, J = 9.1 Hz, 2H), 4.74 (s, 2H), 3.85 (s, 3H).

Intermediate 23

7-(4-Methoxyphenyl)-3-(pyrrolidin-1-yl)-4H-chromen-4-one

3,3-Dibromo-7-(4-methoxyphenyl)-2,3-dihydrochromen-4-one (2.24g, 5.44 mmol), pyrrolidine (0.91 mL, 10.90 mmol) and triethylamine (1.55 mL, 11.1 mmol) in CH_3CN (70 mL) were stirred at room temperature for 70h. The yellow precipitate that formed was collected, rinsed with water and ether and air dried to afford 0.96 g (55%) of the title compound: NMR ($CDCl_3$) δ 8.23 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.51-7.49 (m, 2H), 7.40 (s, 1H), 6.97 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H), 3.26-3.21 (m, 4H), 1.97-1.90 (m, 4H).

Intermediate 24

7-(4-methoxyphenyl)-3-(pyrrolidin-1-yl)-3,4-dihydro-2H-chromen-4-ol

A slurry of 7-(4-methoxyphenyl)-3-(pyrrolidin-1-yl)-4H-chromen-4-one (0.90g, 2.80 mmol) in THF/EtOH (23 mL/14 mL) was treated with sodium borohydride (1.1g, 29.1 mmol) and stirred for 18h at room temperature. The resulting orange solution was quenched with 20 mL water and concentrated at 40°C. The residue was partitioned between EtOAc and water, the separated organics were washed with water and brine, dried ($MgSO_4$) and concentrated to yield a ~9:1 mixture of cis/trans isomers as a yellow solid (0.88g). Flash chromatography using EtOAc as eluent afforded first 37 mg of ~5:1 trans:cis material. Later column fractions were concentrated, triturated with ether and recrystallized from EtOAc to yield 411 mg of the cis isomer as a flaky, light orange tinged solid.

Trans isomer data: NMR ($CDCl_3$) δ 7.47 (d, J = 9.1 Hz, 2H), 7.36 (d, J = 7.9 Hz, 1H), 7.12 (dd, J = 8.3, 1.9 Hz, 1H), 7.01 (d, J = 1.7 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 4.77 (d, J = 4.6 Hz, 1H), 4.33-4.23 (m, 2H), 3.82 (s, 3H), 2.90-2.58 (m, 5H), 1.77-1.73 (m, 4H); R_f = 0.36 (20% MeOH/EtOAc).

Cis isomer data: NMR ($CDCl_3$) δ 7.49 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 7.9 Hz, 1H), 7.15 (dd, J = 8.3, 1.9 Hz, 1H), 7.04 (d, J = 1.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 5.30 (br s, 1H), 4.32-4.27 (m, 1H), 4.22 (br t, J = 10.6 Hz, 1H), 3.84 (s, 3H), 2.99 (br s, 2H), 2.90-2.68 (m, 3H), 1.91 (br s, 4H); R_f = 0.22 (20% MeOH/EtOAc).

Example 7

1-(7-(4-Methoxyphenyl)-3,4-dihydro-2H-chromen-3-yl)pyrrolidine

Trifluoroacetic acid (2 mL) was added to a solution of cis-7-(4-methoxyphenyl)-3-(pyrrolidin-1-yl)-3,4-dihydro-2H-chromen-4-ol (0.05 g, 0.154 mmol) and triethylsilane (0.1 mL, 0.626 mmol) in 1,2-dichloroethane (2 mL). This mixture was refluxed for 16h, cooled and concentrated. The residue was dissolved in EtOAc and washed with aq. K_2CO_3 and brine, dried ($MgSO_4$) and concentrated to give a 45 mg of a tan colored solid. Flash chromatography using EtOAc and 10% MeOH/EtOAc for elution yielded 37 mg (78%) of the title compound as a light yellow solid: R_f = 0.35 (20% MeOH/EtOAc); NMR ($CDCl_3$) δ 7.50 (d, J = 8.7 Hz, 2H), 7.12-7.06 (m, 2H), 7.02 (d, J = 1.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 4.43 (sym mult, 1H), 3.90 (t, J = 9.8 Hz, 1H), 3.84 (s, 3H), 3.05-2.99 (m, 1H), 2.89-2.83 (m, 1H), 2.80-2.64 (m, 5H), 1.92-1.65 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 159.3, 154.8, 140.5, 133.5, 130.5, 128.2, 119.3, 114.5, 114.4, 69.4, 57.8, 55.6, 52.1, 31.9, 23.5; MS(APCI) m/z calcd. for $C_{20}H_{23}NO_2$, 309.2, found, 310.3 (M+1).

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 H_1 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_1 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_1 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 I 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 I to 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

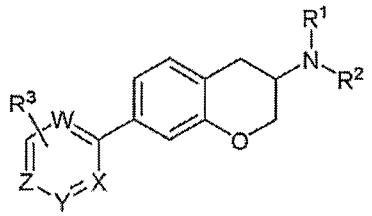
The *in vitro* affinity of the compounds in the present invention at the rat or human histamine H3 receptors can be determined according to the following procedure. Frozen rat frontal brain or frozen human post-mortem frontal brain is homogenized in 20 volumes of cold 50 mM Tris HCl containing 2 mM $MgCl_2$ (pH to 7.4 at 4 °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 °C) and centrifuged again. The final pellet is resuspended in 50 mM Tris HCl containing 2 mM MgCl2 (pH to 7.4 at 25 °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:



or a pharmaceutically acceptable salt thereof, wherein

W, X, Y, and Z are independently selected from nitrogen or carbon; wherein the total number of said nitrogens for W, X, Y, and Z does not exceed two;

R^1 and R^2 are independently hydrogen, $(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 4 halogens, or $(C_3\text{-}C_7)$cycloalkyl-$(C_0\text{-}C_4)$alkyl;

or optionally R^1 and R^2, together with the nitrogen to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring, wherein said heterocyclic ring is optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl; and wherein one of the carbons of said heterocyclic ring that is separated by at least two atoms from said nitrogen in said heterocyclic ring is optionally replaced by O, S, NR^6, or C=O; wherein R^6 is hydrogen, $(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 4 halogens, or $(C_3\text{-}C_7)$cycloalkyl-$(C_0\text{-}C_4)$alkyl, and wherein each $(C_0\text{-}C_4)$alkyl is optionally substituted with 1 to 4
$(C_1\text{-}C_4)$alkyl;

R_3 is hydrogen, $(C_1\text{-}C_8)$alkyl, halo, 5-6 membered aryl optionally fused to a 5 to 6 membered aryl, 5-6 membered heteroaryl, $(C_1\text{-}C_8)$alkoxy, hydroxyl, methylene hydroxyl, $-(C=O)NR_4R_5$, and $S(O)_p(C_1\text{-}C_4)$alkyl, where p is 1 or 2;

wherein R^4 and R^5 are each independently selected from the group consisting of
hydrogen;
$(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 4 halogens;
$(C_1\text{-}C_4)$alkyl group optionally substituted with a substituent selected from the group consisting of OH, 1 to 4 $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_4)$dialkylamino, $(C_6\text{-}C_{14})$aryl optionally substituted with a halogen and optionally substituted with $(C_6\text{-}C_{10})$aryloxy optionally substituted with 1 to 2 halogens, and 5 to 10-membered heteroaryl optionally substituted with a $(C_6\text{-}C_{10})$aryl group and optionally substituted with 1 to 3
$(C_1\text{-}C_4)$alkyl groups;
$(C_3\text{-}C_7)$cycloalkyl;
$(C_6\text{-}C_{14})$aryl;
$-(C_0\text{-}C_3)$alkyl-O-$(C_1\text{-}C_3)$alkyl optionally substituted with $(C_1\text{-}C_3)$alkyl;
$-(C_1\text{-}C_3)$alkyl-C(=O)O-$(C_1\text{-}C_3)$alkyl;

3-8-membered heterocycloalkyl optionally substituted with one or more $(C_1$-$C_4)$alkyl-carbonyl groups;

$(C_6$-$C_{10})$arylsulfonyl optionally substituted with one or more $(C_1$-$C_2)$alkyl;

5-10-membered heteroaryl; 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 4-, 5-, 6-, or 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, $(C_1$-$C_4)$alkoxy optionally substituted with one or more $(C_1$-$C_2)$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 $(C_1$-$C_2)$alkoxy;

wherein R^5 is selected from the group consisting of

hydrogen;

$(C_1$-$C_8)$alkyl optionally substituted with 1 to 4 halogens;

5-10-membered heteroaryl optionally substituted with a substituent selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_2)$alkoxy, $(C_6$-$C_{10})$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 $(C_1$-$C_2)$alkyl, 1 to 4 $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, and $(C_6$-$C_{14})$aryl;

$(C_6$-$C_{10})$aryl optionally substituted with 1 or 2 $(C_1$-$C_2)$alkyl;

$(C_1$-$C_4)$alkylcarbonyl; 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;

2. A compound of claim 1 wherein

W, X, Y, and Z are carbon;

R^1 and R^2, together with the nitrogen to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or two $(C_1$-$C_4)$alkyl; and wherein one of the carbons of said heterocyclic ring that is separated by at least two atoms from said nitrogen in said heterocyclic ring is

optionally replaced by O, S, NR^6, or C=O, wherein R^6 is hydrogen, (C_1-C_8 alkyl optionally substituted with 1 to 4 halogens, or

(C_3-C_7)cycloalkyl-(C_0-C_4)alkyl, and wherein each (C_0-C_4)alkyl is optionally substituted with one to four (C_1-C_4)alkyl; and

R_3 is (C_1-C_6)alkoxy, -(C=O)NR_4R_5, and SO_2(C_1-C_4)alkyl;

wherein R^4 and R^5 are each independently selected from the group consisting of

hydrogen;

(C_1-C_8)alkyl optionally substituted with 1 to 4 halogens;

(C_1-C_4)alkyl group optionally substituted with a substituent selected from the group consisting of OH, one to four (C_1-C_4)alkyl, (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 one to two halogens, and 5-10-membered heteroaryl optionally substituted with a (C_6-C_{10})aryl group and optionally substituted with 1 to 3 (C_1-C_4)alkyl groups;

(C_3-C_7)cycloalkyl;

(C_6-C_{14})aryl;

-(C_0-C_3)alkyl-O-(C_1-C_3)alkyl optionally substituted with (C_1-C_3)alkyl;

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

3-8-membered heterocycloalkyl optionally substituted with one or more (C_1-C_4)alkyl-carbonyl groups;

(C_6-C_{10})arylsulfonyl optionally substituted with one or more (C_1-C_2)alkyl;

5-10-membered heteroaryl; 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 4-, 5-, 6-, or 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, (C_1-C_4)alkoxy optionally substituted with one or more (C_1-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_1-C_2)alkoxy.

3. The compound of claim 1 wherein

W, X, Y, and Z are independently selected from nitrogen or carbon; wherein the total number of said nitrogens for W, X, Y, and Z equals one;

R^1 and R^2, together with the nitrogen to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or two (C_1-C_4)alkyl; and wherein one of the carbons of said heterocyclic ring that is separated by at least two atoms from said nitrogen in said heterocyclic ring is optionally replaced by O, S, NR^6, or C=O, wherein R^6 is hydrogen, (C_1-C_8)alkyl optionally substituted with 1 to 4 halogens, or (C_3-C_7)cycloalkyl-(C_0-C_4)alkyl, and wherein each (C_0-C_4)alkyl is optionally substituted with one to four (C_1-C_4)alkyl; and

R_3 is (C_1-C_6)alkoxy.

4. A compound of claim 1 selected from the group consisting of
(3S,4R)-7-(4-Methoxy-phenyl)-3-pyrrolidin-1-yl-chroman-4-ol,
1-[7-(4-Methoxy-phenyl)-chroman-3-yl]-pyrrolidine,
N-Ethyl-3-(3-pyrrolidin-1-yl-chroman-7-yl)-benzamide,
N-Isopropyl-3-(3-pyrrolidin-1-yl-chroman-7-yl)-benzamide,
2-Methoxy-3-(3-pyrrolidin-1-yl-chroman-7-yl)-pyridine,
N-Isopropyl-3-[3-((R)-2-methyl-pyrrolidin-1-yl)-chroman-7-yl]-benzamide,
1-[7-(4-Methanesulfonyl-phenyl)-chroman-3-yl]-pyrrolidine,
N-Ethyl-3-[3-((R)-2-methyl-pyrrolidin-1-yl)-chroman-7-yl]-benzamide,
N-Isopropyl-4-(3-pyrrolidin-1-yl-chroman-7-yl)-benzamide,
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.