TITLE OF THE INVENTION

Piperazinyl and Diazapanyl Benzamides and Benzthioamides

CROSS-REFERENCE TO RELATED APPLICATIONS

Provisional Application No. 60/420495, filed 10/23/02, hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

The research and development of the invention described below was not federally sponsored.

FIELD OF THE INVENTION

The present invention relates to piperazinyl and diazepanyl benzamides and benzthioamides, their synthesis and their use, for example, for the treatment of disorders and conditions mediated by the histamine receptor.

BACKGROUND OF THE INVENTION

Histamine {2-(imidazol-4-yl)ethylamine} is a transmitter substance. Histamine exerts a physiological effect via multiple distinct G-protein coupled receptors. It plays a role in immediate hypersensitivity reactions and is released from mast cells following antigen IgE antibody interaction. The actions of released histamine on the vasculature and smooth muscle system account for the symptoms of the allergic response. These actions occur at the H_1 receptor (Ash, A.S.F. and Schild, H.O., *Br. J. Pharmac. Chemother.* 1966, 27:427–439) and are blocked by the classical antihistamines (e.g. diphenhydramine). Histamine is also an important regulator of gastric acid secretion through its action on parietal cells. These effects of histamine are mediated via the H_2 receptor (Black, J.W. et al., *Nature* 1972, 236:385–390) and are blocked by H_2 receptor antagonists (e.g. cimetidine). The third histamine receptor —H_3— was first described as a presynaptic autoreceptor in the central nervous system (CNS) (Arrang, J.-M. et al., *Nature* 1983, 302:832–837) controlling the synthesis and release of histamine. Recent evidence has

emerged showing that H_3 receptors are also located presynaptically as heteroreceptors on serotonergic, noradrenergic, dopaminergic, cholinergic, and GABAergic (gamma-aminobutyric acid containing) neurons. These H_3 receptors have also recently been identified in peripheral tissues such as vascular smooth muscle. Consequently there are many potential therapeutic applications for histamine H_3 agonists, antagonists, and inverse agonists. (See: "*The Histamine H_3 Receptor-A Target for New Drugs*", Leurs, R., and Timmerman, H., (Eds.), Elsevier, 1998; Morisset, S. et al., *Nature* 2000, 408:860–864.) A fourth histamine receptor —H_4— was recently described by Oda, T. et al. (*J. Biol. Chem.* 2000, 275(47):36781–36786).

The potential use of histamine H_3 agonists in sleep/wake and arousal/vigilance disorders is suggested based on animal studies (Lin, J.-S. et al., *Brain Res.* 1990, 523:325–330; Monti, J.M. et al., *Eur. J. Pharmacol.* 1991, 205:283–287). Their use in the treatment of migraine has also been suggested (McLeod, R.L. et al., *Soc. Neurosci. Abstr.* 1996, 22:2010) based on their ability to inhibit neurogenic inflammation. Other applications could be a protective role in myocardial ischemia and hypertension where blockade of norepinephrine release is beneficial (Imamura, M. et al., *J. Pharmacol. Exp. Ther.* 1994, 271(3):1259–1266). It has been suggested that histamine H_3 agonists may be beneficial in asthma due to their ability to reduce non-adrenergic non-cholinergic (NANC) neurotransmission in airways and to reduce microvascular leakage (Ichinose, M. and Barnes, P.J., *Eur. J. Pharmacol.* 1989, 174:49–55).

Several indications for histamine H_3 antagonists and inverse agonists have similarly been proposed based on animal pharmacology experiments with known histamine H_3 antagonists (e.g. thioperamide). These include dementia, Alzheimer's disease (Panula, P. et al., *Soc. Neurosci. Abstr.* 1995, 21:1977), epilepsy (Yokoyama, H. et al., *Eur. J. Pharmacol.* 1993, 234:129–133), narcolepsy, eating disorders (Machidori, H. et al., *Brain Res.* 1992, 590:180–186), motion sickness, vertigo, attention deficit hyperactivity disorders (ADHD), learning and memory (Barnes, J.C. et al., *Soc. Neurosci. Abstr.* 1993, 19:1813), and schizophrenia (Schlicker, E. and Marr, I., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1996, 353:290–294). (Also see: Stark, H.

et al., *Drugs Future* 1996, 21(5):507–520; and Leurs, R. et al., *Prog. Drug Res.* 1995, 45:107–165 and references cited therein.) Histamine H_3 antagonists, alone or in combination with a histamine H_1 antagonist, are reported to be useful for the treatment of upper airway allergic response (U.S. Patent Nos. 5,217,986; 5,352,707 and 5,869,479). Recently, a histamine H_3 antagonist (GT-2331) was identified and is being developed by Gliatech Inc. (Gliatech Inc. Press Release Nov. 5, 1998; *Bioworld Today*, March 2, 1999) for the treatment of CNS disorders.

As noted, the literature related to histamine H_3 ligands has been comprehensively reviewed (*"The Histamine H_3 Receptor-A Target for New Drugs"*, Leurs, R. and Timmerman, H., (Eds.), Elsevier, 1998). Within this reference the medicinal chemistry of histamine H_3 agonists and antagonists was reviewed (see Krause, M. et al., and Phillips, J.G. and Ali, S.M., respectively). The importance of an imidazole moiety containing only a single substitution in the 4-position was noted together with the deleterious effects of additional substitution on activity. Particularly, methylation of the imidazole ring at any of the remaining unsubstituted positions was reported to strongly decrease activity. Additional publications support the hypothesis that an imidazole function is essential for high affinity histamine H_3 receptor ligands (see Ali, S.M. et al., *J. Med. Chem.* 1999, 42:903–909, and Stark, H. et al., and references cited therein). However many imidazole-containing compounds are substrates for histamine methyl transferase, the major histamine metabolizing enzyme in humans, which leads to shortened half-lives and lower bioavailability (see Rouleau, A. et al., *J. Pharmacol. Exp. Ther.* 1997, 281(3):1085–1094). In addition, imidazole-containing drugs, via their interaction with the cytochrome P450 monooxygenase system, can be targets of unfavorable biotransformations due to enzyme induction or enzyme inhibition (see: Kapetanovic, I.M. and Kupferberg, H.J., *Drug Metab. Dispos.* 1984, 12(5):560–564; Sheets, J.J. and Mason, J.I., *Drug Metab. Dispos.* 1984, 12(5):603–606; Back, D.J. and Tjia, J.F., *Br. J. Pharmacol.* 1985, 85:121–126; Lavrijsen, K. et al., *Biochem. Pharmacol.* 1986, 35(11):1867–1878; Albengres, E. et al., *Drug Safety,* 1998, 18(2):83–97). The poor blood brain barrier penetration of earlier histamine H_3 receptor ligands may also be associated with the imidazole

fragment (Ganellin, C.R. et al., *Arch. Pharm. Pharm. Med. Chem. (Weinheim, Ger.)* 1998, 331:395–404).

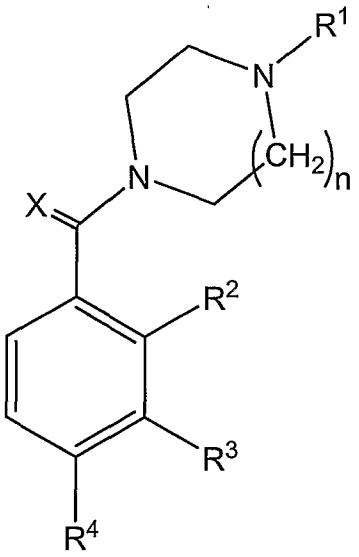
More recently, several publications have described histamine H_3 ligands that do not contain an imidazole moiety, for example: Ganellin, C.R. et al.; Walczynski, K. et al., *Arch. Pharm. Pharm. Med. Chem. (Weinheim, Ger.)* 1999, 332:389–398; Walczynski, K. et al., *Farmaco* 1999, 54:684–694; Linney, I.D. et al., *J. Med. Chem.* 2000, 43:2362–2370; Tozer, M.J. and Kalindjian, S.B., *Exp. Opin. Ther. Patents* 2000, 10:1045–1055; U.S. Patent 5,352,707; PCT Application WO 99/42458, Aug. 26, 1999; PCT Application WO 02/076925; and European Patent Application 0978512, Feb. 9, 2000.

The compounds of the present invention do not contain the imidazole moiety, and its inherent liabilities, and yet maintain potency at the human H_3 receptor as determined by receptor binding to the human histamine H_3 receptor (see Lovenberg, T.W. et al., *Mol. Pharmacol.* 1999, 55:1101–1107). Screening using the human receptor is particularly important for the identification of new therapies for the treatment of human disease. Conventional binding assays are determined using rat synaptosomes (Garbarg, M. et al., *J. Pharmacol. Exp. Ther.* 1992, 263(1):304–310), rat cortical membranes (West, R.E. et al., *Mol. Pharmacol.* 1990, 38:610–613), and guinea pig brain (Korte, A. et al., *Biochem. Biophys. Res. Commun.* 1990, 168(3):979–986). Only limited studies have been performed previously using human tissue but these allude to significant differences in the pharmacology of rodent and primate receptors (West, R.E. et al., *Eur. J. Pharmacol.* 1999, 377:233–239).

We now describe a series of piperazinyl and diazepanyl benzamides and benzthioamides with the ability to modulate the activity of the histamine receptor, specifically the H_3 receptor, without the inherent problems associated with the presence of an imidazolyl moiety.

SUMMARY OF THE INVENTION

The present invention is directed to pharmaceutically active piperazinyl and diazepanyl benzamides and benzthioamides, methods of making them, and methods of using them. The invention features compounds of formula **(I)**:



(I)

wherein

R^1 is C_{1-10} alkyl, C_{3-8} alkenyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{3-8} alkenyl, or (C_{1-8} alkylcarbonyl)C_{1-8} alkyl;

n is 1 or 2;

X is O or S;

one of R^2, R^3 and R^4 is G and the other two independently are hydrogen, fluoro, chloro, bromo, nitro, trifluoromethyl, methyl, or C_{1-3}alkoxy;

G is LQ;

L is unbranched $-(CH_2)_m-$ wherein m is an integer from 1 to 7 (preferably m is 1 to 4, more preferably m is 1);

Q is NR^8R^9 wherein R^8 is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, 3-9 membered carbocyclyl, 3-12 membered heterocyclyl (preferably 5-9 or 5-8-membered heterocyclyl), phenyl, (6-9-membered heterocyclyl)C_{1-6} alkylene, and (phenyl)C_{1-6} alkylene; and R^9 is independently selected from C_{1-6} alkyl, C_{3-6} alkenyl, 6-9 membered carbocyclyl, 3-12 membered heterocyclyl (preferably 5-9 or 5-8-membered heterocyclyl), phenyl, (6-9-membered heterocyclyl)C_{1-6} alkylene, and (phenyl)C_{1-6} alkylene; or

Q is a saturated 3-12 membered N-linked heterocyclyl, wherein, in addition to the N-linking nitrogen, the 3-12 membered heterocyclyl may optionally contain between 1 and 3 additional heteroatoms independently selected from O, S, and NH;

wherein Q is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxy, halo, carboxamide, C_{1-6} alkyl, 5-9 membered or 6-9 membered heterocyclyl, -N(C_{1-6} alkyl)(5-9 membered or 6-9 membered heterocyclyl), -NH(5-9 membered or 6-9 membered heterocyclyl), -O(5-9 or 6-9 membered heterocyclyl), (5-9 membered or 6-9 membered heterocyclyl)C_{1-3} alkylene, C_{1-6} alkoxy, (C_{3-6} cycloalkyl)-O-, phenyl, (phenyl)C_{1-3} alkylene, and (phenyl)C_{1-3} alkylene-O-, where each of above heterocyclyl, phenyl, and alkyl groups may be optionally substituted with from 1 to 3 substituents independently selected from trifluoromethyl, methoxy, halo, nitro, cyano, hydroxy, and C_{1-3} alkyl;

provided however that when R^1 is methyl, G is not piperidin-1-ylmethyl; and

wherein each of the above alkyl, alkylene, alkenyl, heterocyclyl, cycloalkyl, carbocyclyl, and aryl groups may each be independently and optionally substituted with between 1 and 3 substituents independently selected from trifluoromethyl, methoxy, halo, amino, nitro, hydroxy, and C_{1-3} alkyl;

or a pharmaceutically acceptable salt, ester, tautomer, solvate or amide thereof.

The invention also features a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier; and methods of preparing or formulating such compositions. A composition of the invention may further include more than one compound of the invention, or a combination therapy (combination formulation or combination of differently formulated active agents).

The invention also provides methods of treating certain conditions and diseases, each of which methods includes administering a therapeutically effective (or jointly effective) amount of a compound or composition of the invention to a subject in need of such treatment. The disclosed compounds are useful in methods for treating or preventing neurologic disorders including sleep/wake and arousal/vigilance disorders (e.g. insomnia and jet lag), attention deficit hyperactivity disorders (ADHD), learning and memory disorders, cognitive dysfunction, migraine, neurogenic inflammation, dementia, mild cognitive impairment (pre-dementia), Alzheimer's disease, epilepsy, narcolepsy, eating disorders, obesity, motion sickness, vertigo, schizophrenia,

substance abuse, bipolar disorders, manic disorders and depression, as well as other histamine H_3 receptor mediated disorders such as upper airway allergic response, asthma, itch, nasal congestion and allergic rhinitis in a subject in need thereof. For example, the invention features methods for preventing, inhibiting the progression of, or treating upper airway allergic response, asthma, itch, nasal congestion and allergic rhinitis.

In yet another embodiment, the disclosed compounds may be used in a combination therapy method including administering a jointly effective dose of an H_3 antagonist and administering a jointly effective dose of a histamine H_1 antagonist, such as loratidine (CLARITIN™), desloratidine (CLARINEX™), fexofenadine (ALLEGRA™) and cetirizine (ZYRTEC™), for the treatment of allergic rhinitis, nasal congestion, and allergic congestion.

In yet another embodiment, the disclosed compounds may be used in a combination therapy method, including administering a jointly effective dose of an H_3 antagonist and administering a jointly effective dose of a neurotransmitter re-uptake blocker, such as a selective serotonin re-uptake inhibitor (SSRI) or a non-selective serotonin, dopamine or norepinephrine re-uptake inhibitor, including fluoxetine (PROZAC™), sertraline (ZOLOFT™), paroxetine (PAXIL™) and amitryptyline, for the treatment of depression, mood disorders or schizophrenia.

Additional features and advantages of the invention will become apparent from the detailed description and examples below, and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides phenylpiperidine compounds useful for the treatment of disorders and conditions modulated by a histamine receptor.

A. Terms

Certain terms are defined below and by their usage throughout this disclosure.

As used herein, "C_{a-b}" (where *a* and *b* are integers) refers to a radical containing from *a* to *b* carbon atoms inclusive. For example, C_{1-3} denotes a radical containing 1, 2 or 3 carbon atoms.

As used herein, "halo" or "halogen" shall mean monovalent radicals of chlorine, bromine, fluorine and iodine.

As used herein, the term "alkyl", whether used alone or as part of a substituent group, shall include straight and branched saturated carbon chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and the like. Unless otherwise noted, "lower" when used with alkyl means a carbon chain composition of 1-4 carbon atoms. "Alkylene" refers to a bivalent hydrocarbyl group, such as methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$) or propylene ($-CH_2CH_2CH_2-$), and so on.

As used herein, unless otherwise noted, "alkenyl" shall mean an alkylene group with at least two hydrogen atoms replaced with a pi bond to form a carbon-carbon double bond, such as propenyl, butenyl, pentenyl, and so on. Where the alkenyl group is R^8 or R^9, the open radical (point of attachment to the rest of the molecule) is on sp^3 carbon, as illustrated by allyl, and the double bond or bonds is therefore at least alpha (if not beta, gamma, etc.) to the open radical.

As used herein, "alkylidene" refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon radical derived by removal of two hydrogen atoms from the same carbon atom of a parent alkane, alkene or alkyne. The divalent radical center forms a double bond with a single atom on the rest of the molecule. Typical alkylidene radicals include, but are not limited to, ethanylidene; propylidenes such as propan-1-ylidene, propan-2-ylidene, cyclopropan-1-ylidene; butylidenes such as butan-1-ylidene, butan-2-ylidene, 2-methyl-propan-1-ylidene, cyclobutan-1-ylidene; and the like.

As used herein, unless otherwise noted, "alkoxy" shall denote an oxygen ether radical of the above-described straight or branched chain alkyl groups. For example, methoxy, ethoxy, n-propoxy, sec-butoxy, t-butoxy, n-hexyloxy and the like.

As used herein, unless otherwise noted, "cycloalkyl" shall denote a three- to eight-membered, saturated monocyclic carbocyclic ring structure. Suitable

examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein, unless otherwise noted, "cycloalkenyl" shall denote a three- to eight-membered, partially unsaturated, monocyclic, carbocyclic ring structure, wherein the ring structure contains at least one double bond. Suitable examples include cyclohexenyl, cyclopentenyl, cycloheptenyl, cyclooctenyl, cyclohex-1,3-dienyl and the like.

As used herein, unless otherwise noted, "aryl" shall refer to carbocyclic aromatic groups such as phenyl, naphthyl, and the like. Divalent radicals include phenylene ($-C_6H_4-$) which is preferably phen-1,4-diyl, but may also be phen-1,3-diyl.

As used herein, unless otherwise noted, "aralkyl" shall mean any alkyl group substituted with an aryl group such as phenyl, naphthyl, and the like. Examples of aralkyls include benzyl, phenethyl, and phenylpropyl.

As used herein, unless otherwise noted, "carbocyclyl" shall mean any cyclic group consisting of 3-12 carbon atoms, and preferably 6-9 carbon atoms, in the skeleton ring or rings, if the carbocycle is a fused or spiro bicyclic or tricyclic group. A carbocycle may be saturated, unsaturated, partially unsaturated, or aromatic. Examples include cycloalkyl, cycloalkenyl, cycloalkynyl; specific examples include phenyl, benzyl, indanyl, and biphenyl. A carbocycle may have substituents that are not carbon or hydrogen, such as hydroxy, halo, halomethyl, and so on as provided elsewhere herein.

As used herein, unless otherwise noted, the terms "heterocycle", "heterocyclyl" and "heterocyclo" shall denote any three-, four-, five-, six-, seven-, or eight-membered monocyclic, nine- or ten-membered bicyclic, or thirteen- or fourteen-membered tricyclic ring structure containing at least one heteroatom moiety selected from the group consisting of NH, O, SO, SO_2, (C=O), and S, and preferably NH, O, or S, optionally containing one to four additional heteroatoms in each ring. In some embodiments, the heterocyclyl contains between 1 and 3 or between 1 and 2 additional heteroatoms. Unless otherwise specified, a heterocyclyl may be saturated, partially unsaturated, aromatic or partially aromatic. The heterocyclyl group may be attached at any heteroatom or carbon atom that results in the creation of a stable structure.

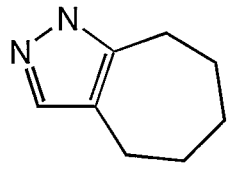
Exemplary monocyclic heterocyclic groups can include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazaolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, hexahydroazepinyl, 4-piperidinyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dixolane and tetrahydro-1,1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, triazolyl, tetrazolyl, azetidinyl and the like.

For example, where Q is a saturated 3-12 membered N-linked heterocyclyl, Q necessarily contains at least one nitrogen, and the carbon atoms are sp^3 hybridized. Where Q is a fused bicyclic heterocyclyl, the carbon atoms of the ring linked to L is sp^3 hybridized, provided the adjacent ring (and the common carbon atoms) may be sp^2, such as an indanyl where one of the carbon atoms has been replaced with nitrogen.

In general, exemplary bicyclic heterocyclyls include benzthiazolyl, benzoxazolyl, benzoxazinyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopridyl, furopyridinyl (such as furo{2,3-c}pyridinyl, furo{3,1-b}pyridinyl), or furo{2,3-b}pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl (such as 1,2,3,4-tetrahydroquinolinyl), tetrahydroisoquinolinyl(such as 1,2,3,4-tetrahydroisoquiunolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isoindolyl, tetrahydroindoazolyl (such as 4,5,6,7-tetrahydroindazolyl), isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl,

quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl,

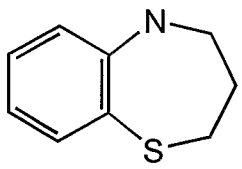


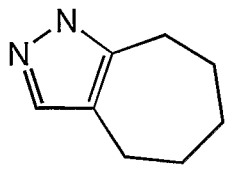
,


, and the like.

Exemplary tricyclic heterocylclic groups include acridinyl, phenoxazinyl, phenazinyl, phenothiazinyl, carbozolyl, perminidinyl, phenanthrolinyl, carbolinyl, naphthothienyl, thianthrenyl, and the like.

Preferred heterocyclyl groups include morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, pyrimidinyl, pyridyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, acridinyl, azepinyl, hexahydroazepinyl, azetidinyl, indolyl, isoindolyl, thiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 1,3,4-trihydroisoquinolinyl, 4,5,6,7-tetrahydroindadolyl, benzoxazinyl, benzoaxzolyl, benzthiazolyl, benzimidazolyl, tetrazolyl, oxadiazolyl,



and


.

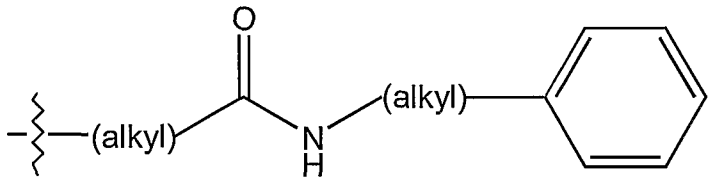
As used herein, unless otherwise noted, the term "heterocyclyl-alkyl" or "heterocyclyl-alkylene" shall denote any alkyl group substituted with a heterocyclyl group, wherein the heterocycly-alkyl group is bound through the alkyl portion to the central part of the molecule. Suitable examples of heterocyclyl-alkyl groups include, but are not limited to piperidinylmethyl, pyrrolidinylmethyl, piperidinylethyl, piperazinylmethyl, pyrrolylbutyl, piperidinylisobutyl, pyridylmethyl, pyrimidylethyl, and the like.

When a particular group is "substituted" (e.g., alkyl, alkylene, cycloalkyl, aryl, heterocyclyl, heteroaryl), that group may have one or more substituents, preferably from one to five substituents, more preferably from one to three substituents, most preferably from one to two substituents, independently selected from the list of substituents.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the

art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenyl(alkyl)amido(alkyl)" substituent refers to a group of the formula



The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes prevention, inhibition of onset, or alleviation of the symptoms of the disease or disorder being treated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

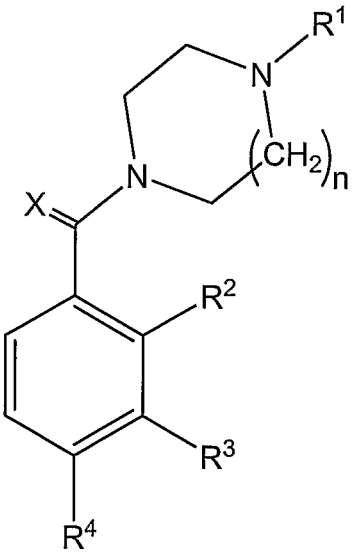
Abbreviations used in the specification, particularly in the Schemes and Examples, are as follows:

DBAD	=	Di-*tert*-butyl azodicarboxylate
DCE	=	1,2-dichloroethane
DCM	=	Dichloromethane
DEAD	=	Diethyl azodicarboxylate

DMA	=	*N,N*-dimethylacetamide
DMAP	=	4-*N,N*-dimethylamino-pyridine
DME	=	1,2-dimethoxyethane
DMF	=	Dimethylformamide
DMSO	=	Dimethylsulfoxide
RT	=	Room temperature
TEA	=	Triethylamine
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran

B. Compounds

The invention features compounds of formula **(I)**:



(I)

wherein

R^1 is C_{1-10} alkyl, C_{3-8} alkenyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{3-8} alkenyl, or (C_{1-8} alkylcarbonyl)C_{1-8} alkyl;

n is 1 or 2;

X is O or S;

one of R^2, R^3 and R^4 is G and the other two independently are hydrogen, fluoro, chloro, bromo, nitro, trifluoromethyl, methyl, or C_{1-3}alkoxy;

G is LQ;

L is unbranched $-(CH_2)_m-$ wherein m is an integer from 1 to 7;

Q is NR^8R^9 wherein R^8 is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, 3-9 membered carbocyclyl, 3-12 membered heterocyclyl (preferably 5-9 or 5-8-membered heterocyclyl), phenyl, (6-9-membered heterocyclyl)C_{1-6} alkylene, and (phenyl)C_{1-6} alkylene; and R^9 is independently selected from C_{1-6} alkyl, C_{3-6} alkenyl, 6-9 membered carbocyclyl, 3-12 membered heterocyclyl (preferably 5-9 or 5-8-membered heterocyclyl), phenyl, (6-9-membered heterocyclyl)C_{1-6} alkylene, and (phenyl)C_{1-6} alkylene; or

Q is a saturated 3-12 membered N-linked heterocyclyl, wherein, in addition to the N-linking nitrogen, the 3-12 membered heterocyclyl may optionally contain between 1 and 3 additional heteroatoms independently selected from O, S, and NH;

wherein Q is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxy, halo, carboxamide, C_{1-6} alkyl, 5-9 membered or 6-9 membered heterocyclyl, -N(C_{1-6} alkyl)(5-9 membered or 6-9 membered heterocyclyl), -NH(5-9 membered or 6-9 membered heterocyclyl), -O(5-9 or 6-9 membered heterocyclyl), (5-9 membered or 6-9 membered heterocyclyl)C_{1-3} alkylene, C_{1-6} alkoxy, (C_{3-6} cycloalkyl)-O-, phenyl, (phenyl)C_{1-3} alkylene, and (phenyl)C_{1-3} alkylene-O-, where each of above heterocyclyl, phenyl, and alkyl groups may be optionally substituted with from 1 to 3 substituents independently selected from trifluoromethyl, methoxy, halo, nitro, cyano, hydroxy, and C_{1-3} alkyl;

provided however that when R^1 is methyl, G is not piperidin-1-ylmethyl; and

wherein each of the above alkyl, alkylene, alkenyl, heterocyclyl, cycloalkyl, carbocyclyl, and aryl groups may each be independently and optionally substituted with between 1 and 3 substituents independently selected from trifluoromethyl, methoxy, halo, amino, nitro, hydroxyl, and C_{1-3} alkyl;

or a pharmaceutically acceptable salt, ester, tautomer, solvate or amide thereof.

Preferred compounds of formula (I) include those wherein:

(a) n is 1;

(b) R^1 is C_{1-10} alkyl (preferably branched);

(c) R^1 is branched C_{3-5} alkyl;

(d) one of R^2, R^3 and R^4 is G; (preferably one of R^3 and R^4 is G)

(e) R^4 is G;

(f) L is unbranched $-(CH_2)_m-$, wherein m is an integer from 1 to 4;

(g) L is $-CH_2-$;

(h) Q is a saturated N-linked nitrogen-containing heterocyclyl;

(i) Q is substituted or unsubstituted piperidinyl, diazepanyl, azepanyl, decahydroisoquinolin-2-yl, piperazinyl, pyrrolinyl, pyrrolidinyl, thiomorpholinyl, or morpholinyl;

(j) Q is unsubstituted diazepanyl, azepanyl, morpholinyl, decahydroisoquinolin-2-yl, piperidinyl, or pyrrolidinyl;

(k) substituted Q are selected from N-(C_{1-6} alkyl)piperazinyl, N-phenyl-piperazinyl, 1,3,8-triaza-spiro{4.5}decyl, and 1,4-dioxa-8-aza-spiro{4.5}decyl;

(l) Q is a monovalent radical of an amine selected from aziridine, 1,4,7-trioxa-10-aza-cyclododecane, thiazolidine, 1-phenyl-1,3,8-triaza-spiro{4.5}decan-4-one, piperidine-3-carboxylic acid diethylamide, 1,2,3,4,5,6-hexahydro-{2,3'}bipyridinyl, 4-(3-trifluoromethyl-phenyl)-piperazine, 2-piperazin-1-yl-pyrimidine, piperidine-4-carboxylic acid amide, methyl-(2-pyridin-2-yl-ethyl)-amine, {2-(3,4-dimethoxy-phenyl)-ethyl}-methyl-amine, thiomorpholinyl, allyl-cyclopentyl-amine, {2-(1H-indol-3-yl)-ethyl}-methyl-amine, 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one, 2-(piperidin-4-yloxy)-pyrimidine, piperidin-4-yl-pyridin-2-yl-amine, phenylamine, and pyridin-2-ylamine;

(m) Q is selected from diazepanyl, azepanyl, morpholinyl, piperidinyl, and pyrrolidinyl, optionally substituted with between 1 and 3 substituents independently selected from hydroxy, halo, carboxamide, C_{1-6} alkyl, 5-9 membered or 6-9 membered heterocyclyl, -N(C_{1-6} alkyl)(5-9 membered or 6-9 membered heterocyclyl), -NH(5-9 membered or 6-9 membered heterocyclyl), -O(5-9 or 6-9 membered heterocyclyl), (5-9 membered or 6-9 membered heterocyclyl)C_{1-3} alkylene, C_{1-6} alkoxy, (C_{3-6} cycloalkyl)-O-, phenyl, (phenyl)C_{1-3} alkylene, and (phenyl)C_{1-3} alkylene-O-, where each of above heterocyclyl, phenyl, and alkyl groups may be optionally substituted with from 1 to 3

substituents independently selected from trifluoromethyl, methoxy, halo, nitro, cyano, hydroxy, and C_{1-3} alkyl;

(n) Q is substituted with a substituent comprising a 5-9 membered or 6-9 membered heterocyclyl group selected from: pyridyl, pyrimidyl, furyl, thiofuryl, imidazolyl, (imidazolyl)C_{1-6} alkylene, oxazolyl, thiazolyl, 2,3-dihydro-indolyl, benzimidazolyl, 2-oxobenzimidazolyl, (tetrazolyl)C_{1-6} alkylene, tetrazolyl, (triazolyl)C_{1-6} alkylene, triazolyl, (pyrrolyl)C_{1-6} alkylene, pyrrolidinyl, and pyrrolyl;

(o) Q is piperidinyl;

(p) R^8 is hydrogen;

(q) R^9 is C_{1-6} alkyl;

(r) R^9 is unsubstituted or substituted phenyl;

(s) R^8 and R^9 independently are C_{1-6} alkyl;

(t) R^8 and R^9 are methyl;

(u) R^8 and R^9 are ethyl;

(v) R^9 is selected from phenyl or 5-9 membered aromatic heterocyclyl, wherein said phenyl or aromatic heterocyclyl is optionally substituted with 1-3 substituents selected from methoxy, hydroxy, halo, nitro, cyano, trifluoromethyl, and C_{1-3} alkyl;

(w) R^9 is selected from substituted or unsubstituted phenyl, pyridyl, pyrimidyl, furyl, thiofuryl, imidazolyl, (imidazolyl)C_{1-6} alkylene, oxazolyl, thiazolyl, 2,3-dihydro-indolyl, benzimidazolyl, 2-oxobenzimidazolyl, (tetrazolyl)C_{1-6} alkylene, tetrazolyl, (triazolyl)C_{1-6} alkylene, triazolyl, (pyrrolyl)C_{1-6} alkylene, pyrrolidinyl, and pyrrolyl;

(x) R^9 is substituted or unsubstituted pyridyl;

(y) X is O; and

(z) combinations of (a) through (z) above.

Examples of compounds of the invention include:

(4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone;
(4-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;
(4-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;
(4-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone;
(4-Butyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone;
(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-Diethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;
(4-Dimethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;
(4-Dimethylaminomethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-(3-morpholin-4-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(3-piperidin-1-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-{[(2-methoxy-ethyl)-propyl-amino]-methyl}-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-(4-thiomorpholin-4-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-{4-(4-isopropyl-piperazin-1-ylmethyl)-phenyl}-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-methanone;
(4-Isopropyl-piperazin-1-yl)-[4-(pyridin-2-ylaminomethyl)-phenyl]-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-{(5-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-{(6-trifluoromethyl-pyridin-3-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Methyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

(4-Methyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{3-(4-Benzyl-piperidin-1-ylmethyl)-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(decahydro-isoquinolin-2-ylmethyl)-phenyl}-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone dihydrochloride;

{4-(1-Methyl-heptyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone;

{4-(1-Methyl-heptyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(Benzylamino-methyl)-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

{4-(Benzylamino-methyl)-phenyl}-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone; and

{4-{(5-Chloro-pyridin-2-ylamino)-methyl}-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride.

Preferred example compounds include:

(4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone;

(4-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;

(4-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone;

(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Diethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(3-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-{[(2-methoxy-ethyl)-propyl-amino]-methyl}-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-(4-thiomorpholin-4-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-{4-(4-isopropyl-piperazin-1-ylmethyl)-phenyl}-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-methanone;
(4-Isopropyl-piperazin-1-yl)-[4-(pyridin-2-ylaminomethyl)-phenyl]-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-{(5-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-{4-{(6-trifluoromethyl-pyridin-3-ylamino)-methyl}-phenyl}-methanone dihydrochloride;
(4-Methyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;
(4-Methyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone dihydrochloride;
(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;
(4-*sec*-Butyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(decahydro-isoquinolin-2-ylmethyl)-phenyl}-methanone;

{4-(Benzylamino-methyl)-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

{4-(Benzylamino-methyl)-phenyl}-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone; and

{4-{(5-Chloro-pyridin-2-ylamino)-methyl}-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride.

More preferred example compounds include:

(4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone;

(4-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Diethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(4-{[(2-methoxy-ethyl)-propyl-amino]-methyl}-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-(4-thiomorpholin-4-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-methanone;
(4-Isopropyl-piperazin-1-yl)-[4-(pyridin-2-ylaminomethyl)-phenyl]-methanone;
(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;
(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(decahydro-isoquinolin-2-ylmethyl)-phenyl}-methanone;
{4-(Benzylamino-methyl)-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride; and
{4-(Benzylamino-methyl)-phenyl}-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone.

Even more preferred example compounds include:
(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;
(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;
(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;
(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;
(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone; and
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone.

Yet even more preferred example compounds include:
(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;
(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;
(4-sec-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride; and
{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride.

The invention also provides compounds that are useful as synthetic intermediates of the compounds of the invention. Such compounds, which themselves may or may not have pharmaceutical activity, include those provided in the schemes and synthetic examples.

The invention also contemplates compounds isotopically-labelled to be detectable by positron emission tomography (PET) or single-photon emission computed tomography (SPECT) useful for studying H_3-mediated disorders.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. In addition, compounds of the invention may be modified by using protecting groups; such compounds, precursors, or prodrugs are also within the scope of the invention. This may be achieved by means of conventional protecting groups, such as those described in "Protective Groups in Organic Chemistry", ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, "Protective Groups in Organic Synthesis", 3rd ed., John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

HYDROXYL PROTECTING GROUPS

Protection for the hydroxyl group includes methyl ethers, substituted methyl ethers, substituted ethyl ethers, substitute benzyl ethers, and silyl ethers.

Substituted Methyl Ethers

Examples of substituted methyl ethers include methyoxymethyl, methylthiomethyl, *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, (4-methoxyphenoxy)methyl, guaiacolmethyl, *t*-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxido, 1-{(2-chloro-4-methyl)phenyl}-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl.

Substituted Ethyl Ethers

Examples of substituted ethyl ethers include 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-

methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

Substituted Benzyl Ethers

Examples of substituted benzyl ethers include *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, *p, p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4 ',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl S,S-dioxido.

Silyl Ethers

Examples of silyl ethers include trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxyphenylsilyl.

Esters

In addition to ethers, a hydroxyl group may be protected as an ester. Examples of esters include formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate(levulinate), 4,4-(ethylenedithio)pentanoate, pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate(mesitoate)

Carbonates

Examples of carbonates include methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

Assisted Cleavage

Examples of assisted cleavage include 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate, 4-(methylthiomethoxy)butyrate, and 2-(methylthiomethoxymethyl)benzoate.

Miscellaneous Esters

Examples of miscellaneous esters include 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenoate(tigloate), *o*-(methoxycarbonyl)benzoate, *p*-P-benzoate, α-naphthoate, nitrate, alkyl N,N,N′,N′-tetramethylphosphorodiamidate, N-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate

Sulfonates

Examples of sulfonates include sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

PROTECTION FOR 1,2- AND 1,3-DIOLS

Cyclic Acetals and Ketals

Examples of cyclic acetals and ketals include methylene, ethylidene, 1-*t*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl)ethylidene, 2,2,2-

trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

Cyclic Ortho Esters

Examples of cyclic ortho esters include methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidine, 1,2-dimethoxyethylidene, α-methoxybenzylidene, 1-(N,N-dimethylamino)ethylidene derivative, α-(N,N-dimethylamino)benzylidene derivative, and 2-oxacyclopentylidene.

Silyl Derivatives

Examples of silyl derivatives include di- *t*-butylsilylene group, and 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) derivative.

AMINO PROTECTING GROUPS

Protection for the amino group includes carbamates, amides, and special –NH protective groups.

Examples of carbamates include methyl and ethyl carbamates, substituted ethyl carbamates, assisted cleavage carbamates, photolytic cleavage carbamates, urea-type derivatives, and miscellaneous carbamates.

Carbamates

Examples of methyl and ethyl carbamates include methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-{9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)}methyl, and 4-methoxyphenacyl.

Substituted Ethyl

Examples of substituted ethyl carbamates include 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-

haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2′- and 4′-pyridyl)ethyl, 2-(N,N-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, N-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl and diphenylmethyl.

Assisted Cleavage

Examples of assisted cleavage include 2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, {2-(1,3-dithianyl)}methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, and 2-(trifluoromethyl)-6-chromonylmethyl.

Photolytic Cleavage

Examples of photolytic cleavage include *m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl.

Urea-Type Derivatives

Examples of urea-type derivatives include phenothiazinyl-(10)-carbonyl derivative, N′-*p*-toluenesulfonylaminocarbonyl, and N′-phenylaminothiocarbonyl.

Miscellaneous Carbamates

Examples of miscellaneous carbamates include *t*-amyl, S-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(N,N-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*-(*p*′-

methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, and 2,4,6-trimethylbenzyl.

Examples of amides include:

Amides

N-formyl, N-acetyl, N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, N-phenylacetyl, N-3-phenylpropionyl, N-picolinoyl, N-3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, N-benzoyl, N-*p*-phenylbenzoyl.

Assisted Cleavage

N-*o*-nitrophenylacetyl, N-*o*-nitrophenoxyacetyl, N-acetoacetyl, (N'-dithiobenzyloxycarbonylamino)acetyl, N-3-(*p*-hydroxyphenyl)propionyl, N-3-(*o*-nitrophenyl)propionyl, N-2-methyl-2-(*o*-nitrophenoxy)propionyl, N-2-methyl-2-(*o*-phenylazophenoxy)propionyl, N-4-chlorobutyryl, N-3-methyl-3-nitrobutyryl, N-*o*-nitrocinnamoyl, N-acetylmethionine derivative, N-*o*-nitrobenzoyl, N-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

Cyclic Imide Derivatives

N-phthalimide, N-dithiasuccinoyl, N-2,3-diphenylmaleoyl, N-2,5-dimethylpyrrolyl, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

SPECIAL – NH PROTECTIVE GROUPS

Examples of special NH protective groups include:

N-Alkyl and N-Aryl Amines

N-methyl, N-allyl, N-{2-(trimethylsilyl)ethoxy}methyl, N-3-acetoxypropyl, N-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, N-benzyl, N-4-methoxybenzyl, N-di(4-methoxyphenyl)methyl, N-5-dibenzosuberyl, N-triphenylmethyl, N-(4-methoxyphenyl)diphenylmethyl, N-9-phenylfluorenyl, N-2,7-dichloro-9-fluorenylmethylene, N-ferrocenylmethyl, and N-2-picolylamine N′-oxide.

Imine Derivatives

N-1,1-dimethylthiomethylene, N-benzylidene, N-*p*-methoxybenzylidene, N-diphenylmethylene, N-{(2-pyridyl)mesityl}methylene, and N-(N′ ,N′-dimethylaminomethylene).

PROTECTION FOR THE CARBONYL GROUP

Acyclic Acetals and Ketals

Examples of acyclic acetals and ketals include dimethyl, bis(2,2,2-trichloroethyl), dibenzyl, bis(2-nitrobenzyl) and diacetyl.

Cyclic Acetals and Ketals

Examples of cyclic acetals and ketals include 1,3-dioxanes, 5-methylene-1,3-dioxane, 5,5-dibromo-1,3-dioxane, 5-(2-pyridyl)-1,3-dioxane, 1,3-dioxolanes, 4-bromomethyl-1,3-dioxolane, 4-(3-butenyl)-1,3-dioxolane, 4-phenyl-1,3-dioxolane, 4-(2-nitrophenyl)-1,3-dioxolane, 4,5-dimethoxymethyl-1,3-dioxolane, *O,O′*-phenylenedioxy and 1,5-dihydro-3H-2,4-benzodioxepin.

Acyclic Dithio Acetals and Ketals

Examples of acyclic dithio acetals and ketals include S,S′-dimethyl, S,S′-diethyl, S,S′-dipropyl, S,S′-dibutyl, S,S′-dipentyl, S,S′-diphenyl, S,S′-dibenzyl and S,S′-diacetyl.

Cyclic Dithio Acetals and Ketals

Examples of cyclic dithio acetals and ketals include 1,3-dithiane, 1,3-dithiolane and 1,5-dihydro-3H-2,4-benzodithiepin.

Acyclic Monothio Acetals and Ketals

Examples of acyclic monothio acetals and ketals include *O*-trimethylsilyl-S-alkyl, *O*-methyl-S-alkyl or -S-phenyl and *O*-methyl-S-2-(methylthio)ethyl.

Cyclic Monothio Acetals and Ketals

Examples of cyclic monothio acetals and ketals include 1,3-oxathiolanes.

MISCELLANEOUS DERIVATIVES

O-Substituted Cyanohydrins

Examples of *O*-substituted cyanohydrins include *O*-acetyl, *O*-trimethylsilyl, *O*-1-ethoxyethyl and *O*-tetrahydropyranyl.

Substituted Hydrazones

Examples of substituted hydrazones include N,N-dimethyl and 2,4-dinitrophenyl.

Oxime Derivatives

Examples of oxime derivatives include *O*-methyl, *O*-benzyl and *O*-phenylthiomethyl.

Imines

Substituted Methylene Derivatives, Cyclic Derivatives

Examples of substituted methylene and cyclic derivatives include oxazolidines, 1-methyl-2-(1′-hydroxyalkyl)imidazoles, N,N′-dimethylimidazolidines, 2,3-dihydro-1,3-benzothiazoles, diethylamine adducts, and methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)(MAD)complex.

MONOPROTECTION OF DICARBONYL COMPOUNDS

Selective Protection Of α-and β-Diketones

Examples of selective protection of α-and β-diketones include enamines, enol acetates, enol ethers, methyl, ethyl, *i*-butyl, piperidinyl, morpholinyl, 4-methyl-1,3-dioxolanyl, pyrrolidinyl, benzyl, S-butyl, and trimethylsilyl.

Cyclic Ketals, Monothio and Dithio Ketals

Examples of cyclic ketals, monothio and dithio ketals include bismethylenedioxy derivatives and tetramethylbismethylenedioxy derivatives.

PROTECTION FOR THE CARBOXYL GROUP

Esters

Substituted Methyl Esters

Examples of substituted methyl esters include 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl, α-methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and N-phthalimidomethyl.

2-Substituted Ethyl Esters

Examples of 2-substituted ethyl esters include 2,2,2-trichloroethyl, 2-haloethyl, ω-chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(p-toluenesulfonyl)ethyl, 2-(2′-pyridyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl, α-methylcinnamyl, phenyl, *p*-(methylmercapto)phenyl and benzyl.

Substituted Benzyl Esters

Examples of substituted benzyl esters include triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzosuberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-

nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, piperonyl, 4-picolyl and *p*-P-benzyl.

Silyl Esters

Examples of silyl esters include trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl and di-*t*-butylmethylsilyl.

Activated Esters

Examples of activated esters include thiols.

Miscellaneous Derivatives

Examples of miscellaneous derivatives include oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group and pentaaminocobalt(III) complex.

Stannyl Esters

Examples of stannyl esters include triethylstannyl and tri-*n*-butylstannyl.

AMIDES AND HYDRAZIDES

Amides

Examples of amides include N,N-dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophenanthridinyl, *o*-nitroanilides, N-7-nitroindolyl, N-8-Nitro-1,2,3,4-tetrahydroquinolyl, and *p*-P-benzenesulfonamides.

Hydrazides

Examples of hydrazides include N-phenyl and N,N′-diisopropyl.

The compounds of the invention can be prepared according to the methods described in the next section.

C. Synthesis

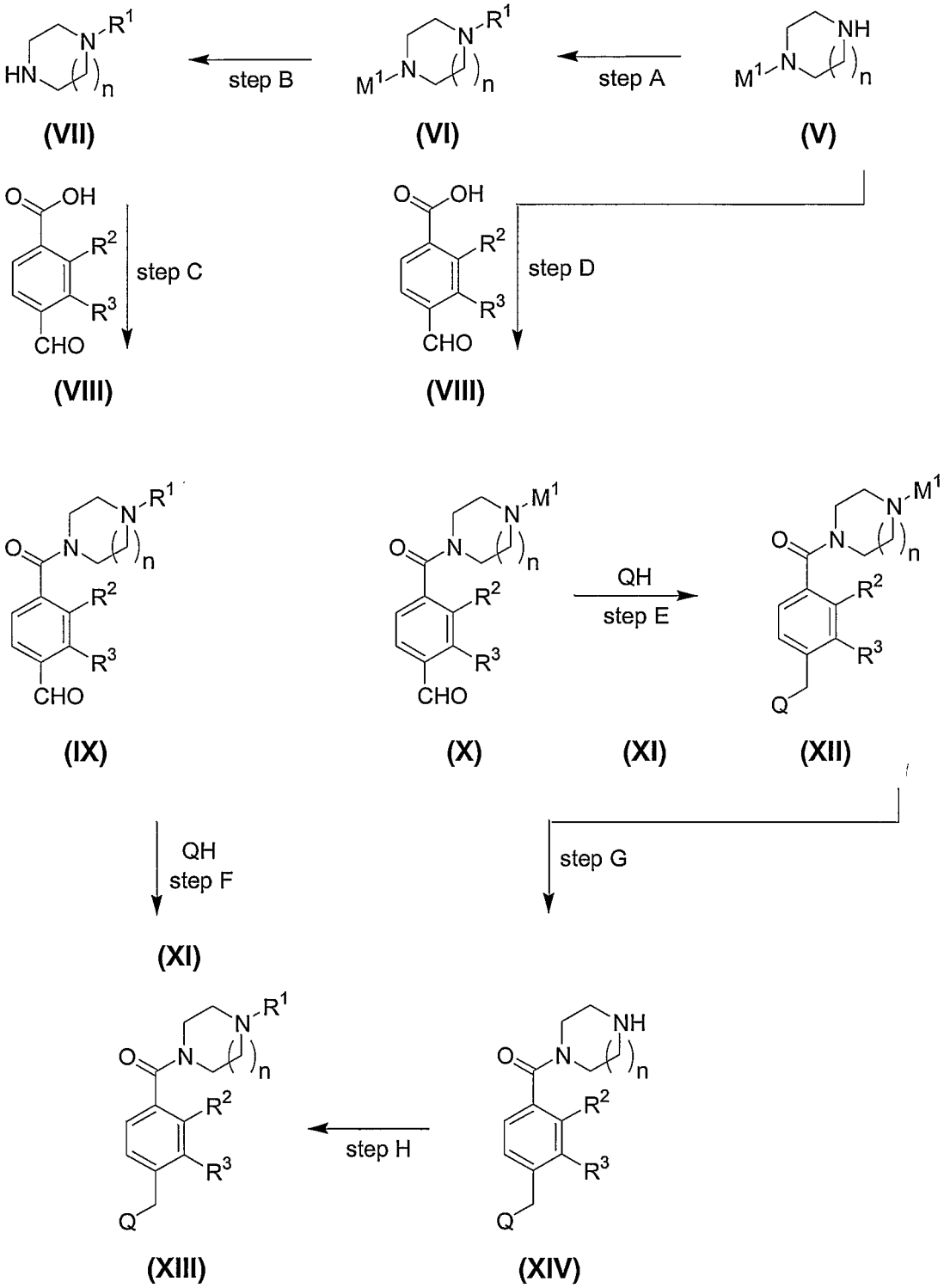
The compounds of the invention can be prepared according to traditional synthetic organic methods and matrix or combinatorial chemistry methods, as shown in Scheme 1 below and in Examples 1–72. A person of ordinary skill will be aware of variations and adaptations of the schemes and examples provided to achieve the compounds of the invention.

One skilled in the art will recognize that synthesis of the compounds of the present invention may be effected by purchasing intermediate or protected intermediate compounds described in any of the Schemes disclosed herein. Throughout the schemes when the reacting functionality is located at R^4, one skilled in the art will recognize that the choice of R^4 is illustrative only and that the reacting functionality could also be located at R^3 or R^2 also.

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

Compounds of formula **(XIII)** may be prepared according to the processes outlined in Scheme 1. One skilled in the art will recognize that the location of formyl functionality at R^4 is for illustrative purposes only and that the formyl group may also be located at R^2 or R^3.

Scheme 1.



A compound of formula **(XIII)** is prepared as outlined in Scheme 1 from a compound of formula **(V)**, in which the group M^1 represents a nitrogen-protecting group. One skilled in the art will be capable of selecting a protecting group that is compatible with the transformations in Scheme 1. In a particularly

preferred embodiment, the group M^1 is *tert*-butyl-carbamoyl. A compound of formula **(VI)** is obtained from a compound of formula **(V)** by reacting a compound of formula **(V)** with an aldehyde or ketone under reductive amination conditions in the presence of a reductant such as sodium triacetoxyborohydride, sodium cyanoborohydride, or phenylsilane in a solvent such as THF, DCE, DCM, methanol, ethanol, or ether at a temperature between 0 and 80 °C. One skilled in the art will recognize that the use of a promotor or catalyst with acidic character such as organometallic complexes or carboxylic acids may increase the rate of the reaction and/or reduce the formation of by-products. In a particularly preferred embodiment, a compound of formula **(V)** is reacted with an aldehyde or ketone, acetic acid, and sodium triacetoxyborohydride in DCE at room temperature. A compound of formula **(VII)** is obtained from a compound of formula **(VI)** by reacting a compound of formula **(VI)** with a reagent capable of removing the protecting group M^1 under nitrogen-deprotection conditions. In a preferred embodiment a compound of formula **(VI)**, in which the protecting group M^1 is *tert*-butyl carbamoyl, is reacted with an acid such as anhydrous hydrogen chloride in a solvent such as dioxane or ether at room temperature. A compound of formula **(IX)** is obtained by reacting a compound of formula **(VII)** with a compound of formula **(VIII)** under amide-formation conditions. In a preferred embodiment, a compound of formula **(VII)**, either as a free base or as a mineral acid salt, is reacted with a compound of formula **(VIII)** in the presence of a dehydrating agent and a base in a solvent at a temperature between 0 °C and 60 °C. In a particularly preferred embodiment, a compound of formula **(VII)** as a hydrochloride salt is used, the dehydrating agent is 1-{3-(dimethylamino)propyl}-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, and the base is *N*-methylmorpholine. A compound of formula **(XIII)** is obtained by reacting a compound of formula **(IX)** with a compound of formula **(XI)** in the presence of a reducing agent under reductive amination conditions, as outlined in step A. A compound of formula **(X)** is obtained by reacting a compound of formula **(V)** with a compound of formula **(VIII)** under amide formation conditions as outlined in step C. A compound of formula **(XII)** is obtained by reacting a compound of formula **(X)** with a compound of formula **(XI)** under reductive amination

conditions, as described in step A. A compound of formula **(XIV)** is obtained by reacting a compound of formula **(XII)** with a reagent capable of removing the protecting group M^1 under nitrogen-deprotection conditions, as outlined in step B. A compound of formula **(XIII)** is obtained by reacting a compound of formula **(XIV)** with an aldehyde or ketone under reductive amination conditions as outlined in step A. Compounds of the present invention may also be conveniently prepared using various other chemical intermediates. For example, variants of aldehyde **(VIII)** or amide **(IX)** could be accessed from a corresponding aryl halide, such as an aryl bromide, via a palladium mediated coupling with a formyl, carbonyl, or nitrile equivalent.

D. Formulation, Administration, and Therapy

The disclosed compounds, alone or in combination (with, for example, a histamine H_1 receptor antagonist), are useful for treating or preventing neurologic disorders including sleep/wake and arousal/vigilance disorders (e.g. insomnia and jet lag), attention deficit hyperactivity disorders (ADHD), learning and memory disorders, cognitive dysfunction, migraine, neurogenic inflammation, dementia, mild cognitive impairment (pre-dementia), Alzheimer's disease, epilepsy, narcolepsy, eating disorders, obesity, motion sickness, vertigo, schizophrenia, substance abuse, bipolar disorders, manic disorders and depression, as well as other histamine H_3 receptor mediated disorders such as upper airway allergic response, asthma, itch, nasal congestion and allergic rhinitis in a subject in need thereof.

1. Formulation and Administration

The compounds or compositions of the invention may be formulated and administered to a subject by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral administration. The quantity of the compound which is effective for treating each condition may vary, and can be determined by one of ordinary skill in the art.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be

useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts that may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

Thus, representative pharmaceutically acceptable salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound that may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier,

1985. In addition to salts, the invention provides the esters, amides, and other protected or derivatized forms of the described compounds.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier and optionally additional pharmaceutical agents such as H_1 antagonists or SSRIs. Preferably these compositions are in unit dosage forms such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), powders, granules, sterile parenteral solutions or suspensions (including syrups and emulsions), metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these pre-formulation compositions as homogeneous, it is meant

that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid pre-formulation composition is then subdivided into unit dosage forms of the type described above containing from 5 to about 1000 mg of the active ingredient of the present invention. Examples include 5 mg, 7 mg, 10 mg, 15 mg, 20 mg, 35 mg, 50 mg, 75 mg, 100 mg, 120 mg, 150 mg, and so on. The tablets or pills of the disclosed compositions can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt

formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

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

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

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

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with

soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment is required.

The daily dosage of the products may be varied over a wide range from 1 to 1,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 20 mg/kg of body weight per day. Preferably, the range is from about 0.02 mg/kg to about 10 mg/kg of body weight per day, and especially from about 0.05 mg/kg to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

2. Combination Therapy

The disclosed compounds are useful in combination with other therapeutic agents, including H_1 receptor antagonists, H_2 receptor antagonists,

and neurotransmitter modulators such as SSRIs and non-selective serotonin re-uptake inhibitors (NSSRIs).

Methods are known in the art for determining effective doses for therapeutic and prophylactic purposes for the disclosed pharmaceutical compositions or the disclosed drug combinations, whether or not formulated in the same composition. For therapeutic purposes, the term "jointly effective amount" as used herein, means that amount of each active compound or pharmaceutical agent, alone or in combination, that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. For prophylactic purposes (i.e., inhibiting the onset or progression of a disorder), the term "jointly effective amount" refers to that amount of each active compound or pharmaceutical agent, alone or in combination, that inhibits in a subject the onset or progression of a disorder as being sought by a researcher, veterinarian, medical doctor or other clinician, the delaying of which disorder is mediated, at least in part, by the modulation of one or more histamine receptors. Thus, the present invention provides combinations of two or more drugs wherein, for example, (a) each drug is administered in an independently therapeutically or prophylactically effective amount; (b) at least one drug in the combination is administered in an amount that is sub-therapeutic or sub-prophylactic if administered alone, but is therapeutic or prophylactic when administered in combination with the second or additional drugs according to the invention; or (c) both drugs are administered in an amount that is sub-therapeutic or sub-prophylactic if administered alone, but are therapeutic or prophylactic when administered together. Combinations of three or more drugs are analogously possible. Methods of combination therapy include co-administration of a single formulation containing all active agents; essentially contemporaneous administration of more than one formulation; and administration of two or more active agents separately formulated.

E. Examples

In order to illustrate the invention, the following examples are included. These examples do not limit the invention. They are only meant to suggest a method of practicing the invention. Those skilled in the art may find other methods of practicing the invention, which are obvious to them. However, those methods are deemed to be within the scope of this invention.

Protocol for Preparative Reversed-Phase HPLC

Gilson®

Column: YMC-Pack ODS-A, 5 μm, 75x30 mm

Flow rate: 25 mL/min

Detection: λ = 220 & 254 nm

Gradient (acetonitrile/water, 0.05% trifluoroacetic acid)

1) 0.0 min 15% acetonitrile/85% water

2) 20.0 min 99% acetonitrile/1% water

Protocol for HPLC (Reversed-Phase)

Hewlett Packard Series 1100

Column: Agilent ZORBAX® Bonus RP, 5 μm, 4.6x250 mm

Flow rate: 1 mL/min

Detection: λ = 220 & 254 nm

Gradient (acetonitrile/water, 0.05% trifluoroacetic acid)

1) 0.0 min 1% acetonitrile/99% water

2) 20.0 min 99% acetonitrile/1% water

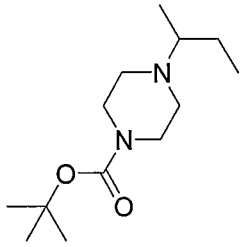
Mass spectra were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in either positive or negative modes as indicated.

Thin-layer chromatography was performed using Merck silica gel 60 F_{254} 2.5 cm x 7.5 cm 250 μm or 5.0 cm x 10.0 cm 250 μm pre-coated silica gel plates. Preparative thin-layer chromatography was performed using EM Science silica gel 60 F_{254} 20 cm x 20 cm 0.5 mm pre-coated plates with a 20 cm x 4 cm concentrating zone.

NMR spectra were obtained on either a Bruker model DPX400 (400 MHz) or DPX500 (500 MHz) spectrometer. The format of the ^{1}H NMR data

below is: chemical shift in ppm down field of the tetramethylsilane reference (multiplicity, coupling constant *J* in Hz, integration).

Example 1

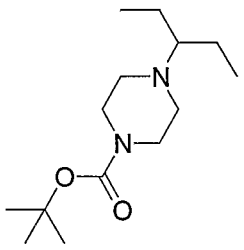


4-sec-Butyl-piperazine-1-carboxylic acid tert-butyl ester

A mixture of piperazine-1-carboxylic acid tert-butyl ester (7.00 g), 3-pentanone (3.89 g), glacial acetic acid (2.22 mL) and sodium triacetoxyborohydride (11.95 g) in dichloromethane (DCM, 200 mL) was stirred for 18 h at room temperature. The reaction mixture was quenched with 1 N aqueous NaOH (80 mL) and stirred for 2.5 h at room temperature. Additional water (100 mL) was added, and the resulting mixture was extracted with DCM (3 x 100 mL). Extracts were combined and washed with water (2 x 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure, yielding the title compound (6.28 g).

The products of Example 2 through Example 5 were prepared in analogy with the procedure of Example 1 using the specified carbonyl compound and amine.

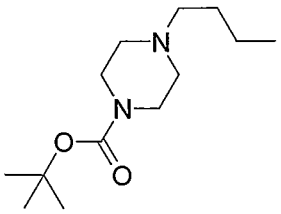
Example 2



4-(1-Ethyl-propyl)-piperazine-1-carboxylic acid tert-butyl ester

Prepared from 3-pentanone and piperazine-1-carboxylic acid tert-butyl ester.

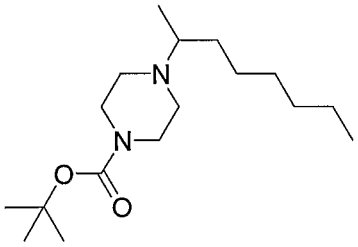
Example 3



4-Butyl-piperazine-1-carboxylic acid tert-butyl ester

Prepared from butanal and piperazine-1-carboxylic acid tert-butyl ester.

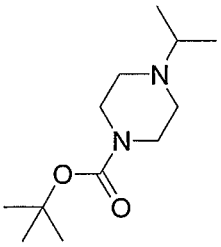
Example 4



4-(1-Methyl-heptyl)-piperazine-1-carboxylic acid tert-butyl ester

Prepared from 2-octanone and piperazine-1-carboxylic acid tert-butyl ester.

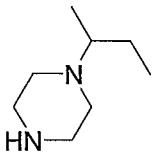
Example 5



4-Isopropyl-piperazine-1-carboxylic acid tert-butyl ester

Prepared from acetone and piperazine-1-carboxylic acid tert-butyl ester.

Example 6

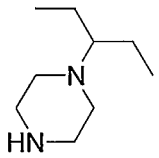


1-sec-Butyl-piperazine dihydrochloride

To a solution of the product of Example 1 (6.28 g) in methanol (120 mL) at 5 °C was added 4 M HCl in dioxane (100 mL). The reaction mixture was stirred at room temperature. After 24 h, the solvent was evaporated under vacuum. Ethyl ether was added and evaporated to dryness under vacuum (2 x 100 mL). The resulting white solid was dried under vacuum for 24 h yielding the title compound as its dihydrochloride salt (4.93 g) as a white solid.

The products of Example 7 through Example 10 were prepared in analogy to the procedure of Example 6 from the specified tert-butylcarbamate.

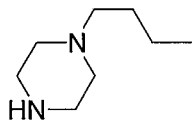
Example 7



1-(1-Ethyl-propyl)-piperazine dihydrochloride

Prepared from the product of Example 2.

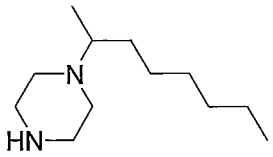
Example 8



1-Butyl-piperazine dihydrochloride

Prepared from the product of Example 3.

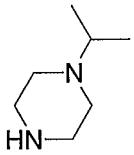
Example 9



1-(1-Methyl-heptyl)-piperazine dihydrochloride

Prepared from the product of Example 4.

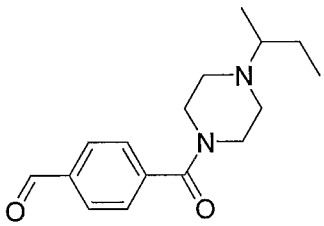
Example 10



1-Isopropyl-piperazine dihydrochloride

Prepared from the product of Example 5.

Example 11

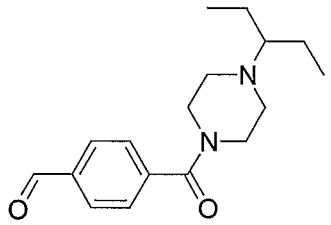


4-(4-sec-Butyl-piperazine-1-carbonyl)-benzaldehyde

The product of Example 6 (3.2 g) and 4-formylbenzoic acid (2.102 g) were suspended in DCM (130 mL) under nitrogen. 1-{3-(Dimethylamino)propyl}-3-ethylcarbodiimide hydrochloride (3.96 g), 1-hydroxybenzotriazole hydrate (3.06 g) and N-methylmorpholine (9.432 g) were added in sequence to the above suspension. The reaction mixture was stirred under nitrogen for 24 h. DCM (100 mL) was added, the resulting mixture was washed with 10 % aqueous NaOH solution (2 x 50 mL) and water (2 x 100 mL), and the separated organic phase was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield the crude product (3.75 g). Chromatography of the residue on silica gel (2-5% 2 M methanolic ammonia/DCM) yielded the title compound (2.75 g).

The products of Example 12 through Example 18 were prepared in analogy to the procedure of Example 11 using the specified piperazine derivatives and carboxylic acids.

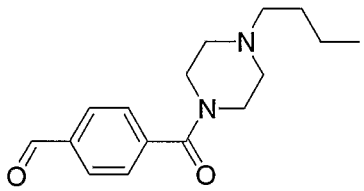
Example 12



4-{4-(1-Ethyl-propyl)-piperazine-1-carbonyl}-benzaldehyde

Prepared from the product of Example 7 and 4-formylbenzoic acid.

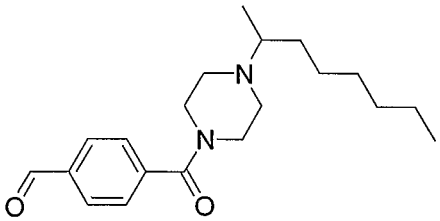
Example 13



4-(4-Butyl-piperazine-1-carbonyl)-benzaldehyde

Prepared from the product of Example 8 and 4-formybenzoic acid.

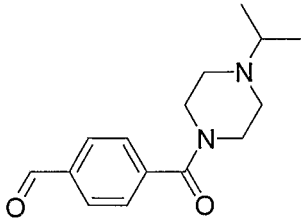
Example 14



4-{4-(1-Methyl-heptyl)-piperazine-1-carbonyl}-benzaldehyde

Prepared from the product of Example 9 and 4-formylbenzoic acid.

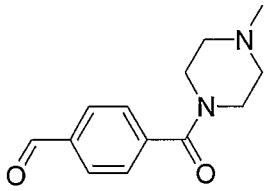
Example 15



4-(4-Isopropyl-piperazine-1-carbonyl)-benzaldehyde

Prepared from the product of Example 10 and 4-formylbenzoic acid.

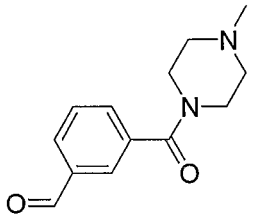
Example 16



4-(4-Methyl-piperazine-1-carbonyl)-benzaldehyde

Prepared from N-methylpiperazine and 4-formylbenzoic acid.

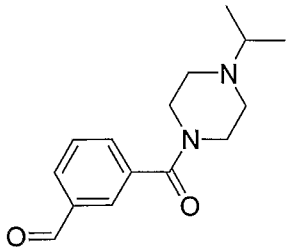
Example 17



3-(4-Methyl-piperazine-1-carbonyl)-benzaldehyde

Prepared from N-methylpiperazine and 4-formylbenzoic acid.

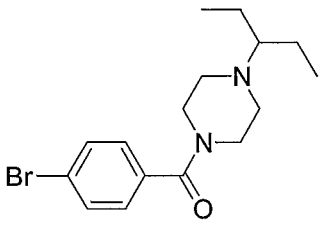
Example 18



3-(4-Isopropyl-piperazine-1-carbonyl)-benzaldehyde

Prepared from the product of Example 10 and 3-formylbenzoic acid.

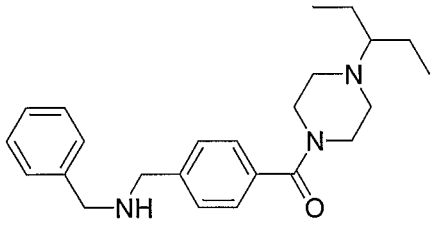
Example 19



(4-Bromo-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone

To a solution of 4-bromobenzoic acid (500 mg) and the product of Example 7 (710 mg) in DCM (20 mL) was added 1-{3-(dimethylamino) propyl}-3-ethylcarbodiimide hydrochloride (713 mg), 1-hydroxybenzotriazole hydrate (570 mg), and N-methyl morpholine (1.64 mL). After 16 h the reaction mixture was treated with 1 N NaOH (25 mL) and extracted with DCM (3 x 75 mL). The organic layers were dried (Na_2SO_4), concentrated, and chromatographed on silica gel (1-3% 2 M methanolic ammonia/DCM) to give the title compound as white-yellow solid (630 mg).

Example 20



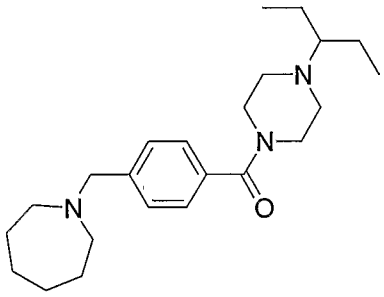
{4-(Benzylamino-methyl)-phenyl}-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone

To a solution of the product of Example 12 (150 mg) and benzylamine (0.062 mL) in DCM (5 mL) was added acetic acid (.03 mL) and sodium triacetoxyborohydride (165 mg). After 16 h the reaction was treated with 1 N NaOH (20 mL) and extracted with DCM (3 x 20 mL). The organic layers were dried (Na_2SO_4), concentrated, and chromatographed (2-3% 2 M methanolic ammonia-DCM) to give the title compound as an oil (150 mg).

^{1}H NMR (400 MHz, $CDCl_3$): 7.40-7.34 (m, 8H), 7.29-7.26 (m, 1H), 3.85 (d, J = 9.1 Hz, 4H), 3.75 (br s, 2H), 3.40 (br s, 2H), 2.59-2.45 (m, 4H), 2.21-2.18 (m, 1H), 1.67 (s, 1H), 1.50-1.43 (m, 2H), 1.35-1.28 (m, 2H), 0.92-0.89 (m, 6H).

The products of Example 21 through Example 42 were prepared in analogy with the procedure of Example 20 using the specified carbonyl compounds and amines.

Example 21

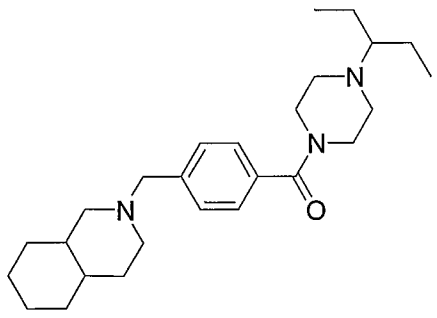


(4-Azepan-1-ylmethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone

Prepared from the product of Example 12 and azepine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.33 (m, 4H), 3.74 (br s, 2H), 3.65 (s, 2H), 3.40 (br s, 2H), 2.62-2.46 (m, 8H), 2.21-2.17 (m, 1H), 1.62 (br s, 8H), 1.50-1.43 (m, 2H), 1.34-1.27 (m, 2H), 0.92-0.89 (m, 6H).

Example 22

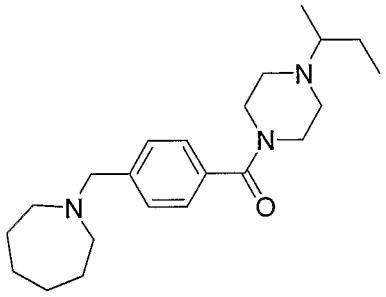


{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(decahydro-isoquinolin-2-ylmethyl)-phenyl}-methanone

Prepared from the product of Example 12 and decahydroisoquinoline.

^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.33 (m, 4H), 3.73 (br s, 2H), 3.52-3.39 (m, 4H), 2.59-2.45 (m, 6H), 2.20-2.17 (m, 2H), 1.70-1.29 (m, 17H), 0.92-0.88 (m, 6H).

Example 23

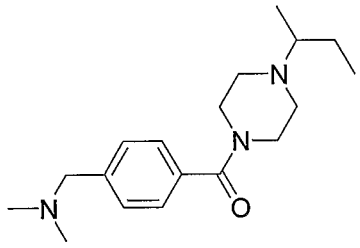


(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone

Prepared from the product of Example 11 and azepine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.35 (dd, J = 9.1, 8.1 Hz, 4H), 3.76 (br s, 2H), 3.63 (s, 2H), 3.42 (br s, 2H), 2.68-2.32 (m, 9H), 1.69-1.47 (m, 9H), 1.36-1.20 (m, 1H), 0.96 (d, J = 6.6, 3H), 0.89 (t, J = 7.3, 3H).

Example 24

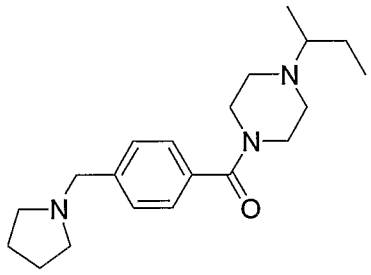


(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone

Prepared from the product of Example 11 and dimethylamine hydrochloride.

^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.29 (m, 4H), 3.75 (br s, 2H), 3.42 (br s, 4H), 2.66-2.30 (m, 5H), 2.22 (s, 6H), 1.58-1.46 (m, 1H), 1.34-1.20 (m, 1H), 0.95 (d, J = 6.57 Hz, 3H), 0.92-0.88 (m, 3H).

Example 25

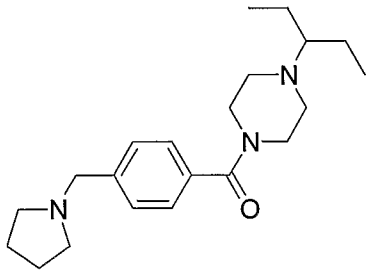


(4-sec-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 11 and pyrrolidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.29 (m, 4H), 3.74 (br s, 2H), 3.60 (s, 2H), 3.40 (br s, 2H), 2.64-2.34 (m, 9H), 1.81-1.70 (m, 4H), 1.59-1.45 (m, 1H), 1.33-1.19 (m, 1H), 0.94 (d, J = 6.57 Hz, 3H), 0.91-0.88 (m, 3H).

Example 26

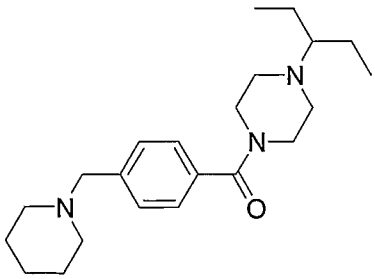


{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 12 and pyrrolidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.41-7.35 (m, 4H), 3.73-3.70 (m, 4H), 3.38 (br s, 2H), 2.59-2.45 (m, 8H), 2.20-2.17 (m, 1H), 1.83 (br s, 4H), 1.49-1.27 (m, 4H), 0.92-0.88 (m, 6H).

Example 27

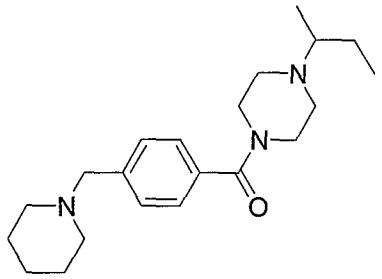


{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 12 and piperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.40-7.34 (m, 4H), 3.74 (br s, 2H), 3.53 (s, 2H), 3.39 (br s, 2H), 2.59-2.42 (m, 8H), 2.20-2.17 (m, 1H), 1.62-1.60 (m, 4H), 1.50-1.41 (m, 4H), 1.43-1.27 (m, 2H), 0.92-0.88 (m, 6H).

Example 28

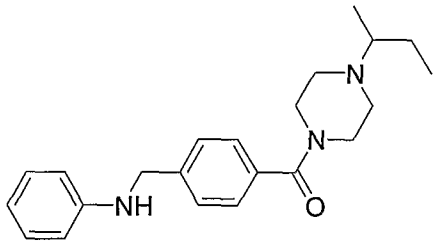


(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 11 and piperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.36-7.30 (m, 4H), 3.75 (br s, 2H), 3.50-3.32 (m, 4H), 2.55-2.24 (m, 9H), 1.60-1.48 (m, 5H), 1.46-1.36 (m, 2H), 1.34-1.20 (m, 1 H), 0.95 (d, J = 6.6 Hz, 3H), 0.92-0.88 (m, 3H).

Example 29

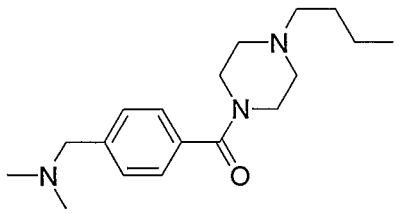


(4-sec-Butyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone

Prepared from the product of Example 11 and aniline.

^{1}H NMR (400 MHz, $CDCl_3$): 7.43-7.32 (m, 4H), 7.15 (tt, J = 7.4, 5.4 Hz, 2H), 6.74-6.66 (m, 1H), 6.59 (dd, J = 7.6, 1.0 Hz, 2H), 4.33 (s, 2H), 4.2 (br s, 1H), 3.76 (br s, 2H), 3.41 (br s, 2H), 2.66-2.27 (m, 5H), 1.62-1.45 (m, 1H), 1.36-1.20 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H).

Example 30

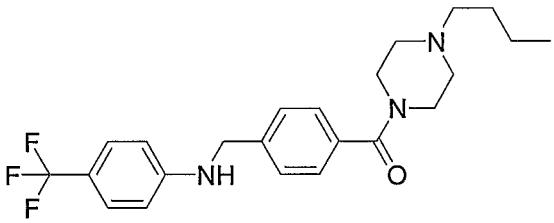


(4-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone

Prepared from the product of Example 13 and dimethylamine hydrochloride.

^{1}H NMR (400 MHz, $CDCl_3$): 7.41-7.31 (m, 4H), 3.79 (br s, 2H), 3.43 (s, 3H), 2.5 (br s, 2H), 2.37-2.34 (m, 3H), 2.24 (br s, 4H), 1.65 (br s, 4H), 1.52-1.40 (m, 2H), 1.39-1.26 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H).

Example 31

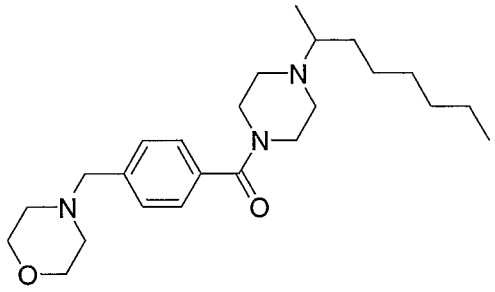


(4-Butyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone

Prepared from the product of Example 13 and 4-trifluoromethyl-phenylamine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.45-7.32 (m, 6H), 6.60 (d, J = 8.5 Hz, 2H), 4.59 (t, J = 5.6 Hz, 1H), 4.39 (d, J = 5.8 Hz, 2H), 3.79 (br s, 2H), 3.43 (br s, 2H), 2.60-2.30 (m, 6H), 1.55-1.43 (m, 2H), 1.40-1.25 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

Example 32

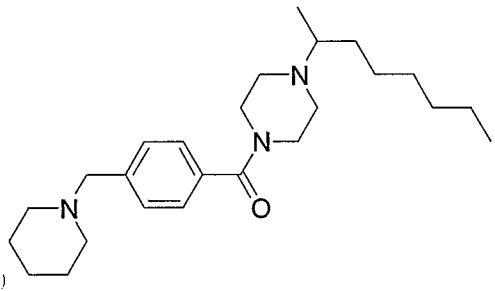


{4-(1-Methyl-heptyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone

Prepared from the product of Example 14 and morpholine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.35 (m, 4H), 3.76 (br s, 2H), 3.68-3.66 (m, 2H), 3.52 (s, 2H), 3.46 (br s, 2H), 2.64-2.45 (m, 10H), 1.51-1.47 (m, 1H), 1.30-1.26 (m, 10H), 1.02 (m, 3H), 0.90-0.87 (m, 3H).

Example 33

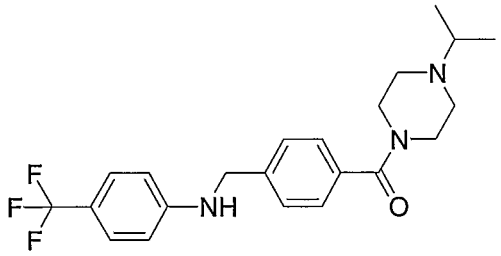


{4-(1-Methyl-heptyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 14 and piperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.42-7.35 (m, 4H), 3.77 (br s, 2H), 3.58 (s, 2H), 3.42 (br s, 2H), 2.60-2.47 (m, 10H), 1.65 (br s, 4H), 1.50-1.46 (m, 1H), 1.33-1.28 (m, 10H), 0.97 (d, J = 6.5 Hz, 3H), 0.90-0.87 (m, 3H).

Example 34

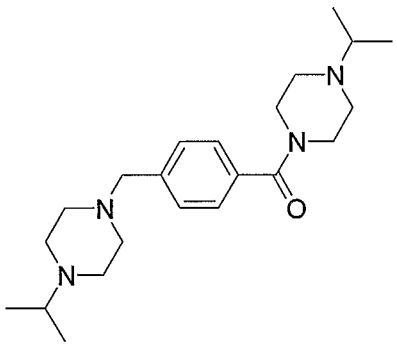


(4-Isopropyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone

Prepared from the product of Example 15 and 4-trifluoromethylaniline.

^{1}H NMR (400 MHz, $CDCl_3$): 7.41-7.36 (m, 6H), 6.62 (d, J = 8.5 Hz, 2H), 4.56-4.54 (m, 1H), 4.40 (d, J = 5.8 Hz, 2H), 3.83 (br s, 2H), 3.48 (br s, 2H), 2.80-2.77 (m, 1H), 2.63-2.50 (m, 4H), 1.08 (d, J = 6.6 Hz, 6H).

Example 35

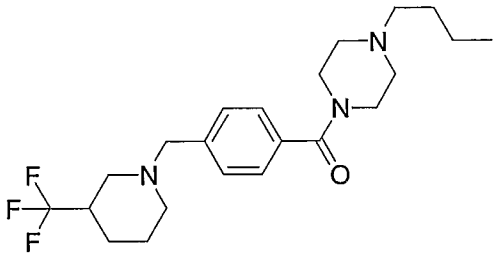


(4-Isopropyl-piperazin-1-yl)-{4-(4-isopropyl-piperazin-1-ylmethyl)-phenyl}-methanone

Prepared from the product of Example 15 and the product of Example 10.

^{1}H NMR (400 MHz, $CDCl_3$): 7.37 (m, 4H), 3.78 (br s, 2H), 3.54 (s, 2H), 3.44 (br s, 2H), 2.76-2.45 (m, 14H), 1.11 (d, J = 6.6 Hz, 6H), 1.05 (d, J = 6.6 Hz, 6H).

Example 36

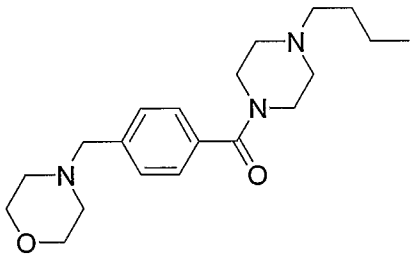


(4-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone

Prepared from the product of Example 13 and 3-trifluoromethylpiperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.74-7.47 (m, 4H), 4.96-4.74 (m, 5H), 4.46-4.26 (m, 2H), 4.00-3.38 (m, 5H), 2.97-2.69 (m, 6H), 2.04-1.58 (m, 4H), 1.16-0.9 (m, 6H).

Example 37

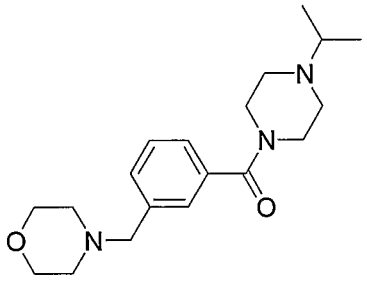


(4-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone

Prepared from the product of Example 13 and morpholine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.35-7.31 (m, 4H), 3.79 (br s, 2H), 3.68 (t, J = 4.5 Hz, 4H), 3.48 (s, 2H), 3.41 (br s, 2H), 2.48 (br s, 2H), 2.44-2.40, (m, 4H), 2.33 (t, J = 7.6 Hz, 4H), 1.48-1.41 (m, 2H), 1.35-1.26 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H).

Example 38

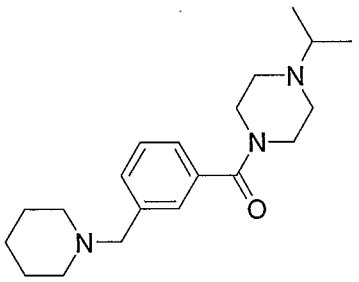


(4-Isopropyl-piperazin-1-yl)-(3-morpholin-4-ylmethyl-phenyl)-methanone

Prepared from the product of Example 18 and morpholine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.28 (m, 4H), 3.79 (br s, 2H), 3.71 (t, J = 4.6 Hz, 4H), 3.52 (s, 2H), 3.42 (br s, 2H), 2.76-2.70 (m, 1H), 2.60 (br s, 2H), 2.46-2.44 (m, 6H), 1.05 (d, J = 6.5 Hz, 6H).

Example 39

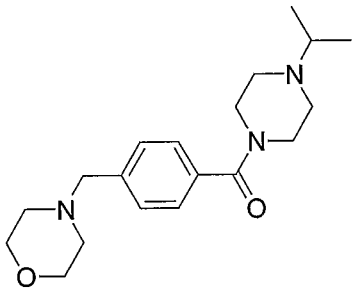


(4-Isopropyl-piperazin-1-yl)-(3-piperidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 18 and piperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.37 (m, 3H), 7.28 (d, J = 1.7 Hz, 1H), 3.79 (br s, 2H), 3.48 (s, 2H), 3.42 (br s, 2H), 2.76-2.69 (m, 1H), 2.69 (br s, 2H), 2.45 (br s, 2H), 2.37 (br s, 2H), 1.59-1.54 (m, 4H), 1.44-1.42 (m, 2H), 1.05 (d, J = 6.5 Hz, 6H).

Example 40

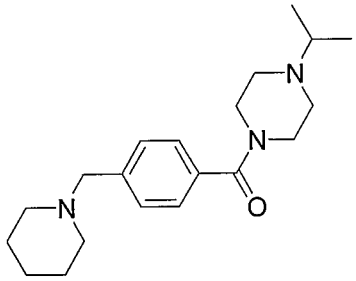


(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone

Prepared from the product of Example 15 and morpholine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (s, 4H), 3.79 (br s, 2H), 3.71 (t, J = 4.7 Hz, 4H), 3.51 (s, 2H), 3.44 (br s, 2H), 2.76-1.69 (m, 1H), 2.59 (br s, 2H), 2.44 (t, J = 4.4 Hz, 6H), 1.05 (d, J = 6.5 Hz, 6H).

Example 41

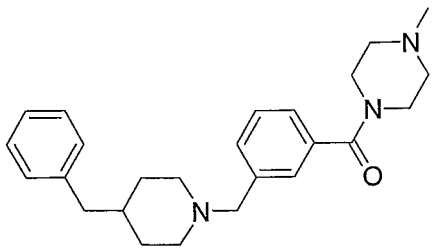


(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 15 and piperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.35 (s, 4H), 3.79 (br s, 2H), 3.48 (br s, 2H), 3.45 (br s, 2H), 2.72 (m, 1H), 2.59 (br s, 2H), 2.45 (br s, 2H), 2.38 (br s, 4H), 1.60-1.55 (m, 4H), 1.48-1.40 (m, 2H), 1.06 (d, J = 6.3 Hz, 6H).

Example 42

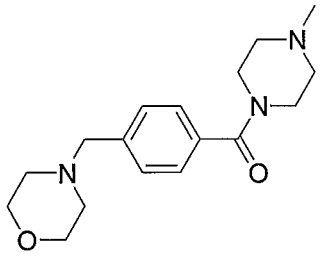


{3-(4-Benzyl-piperidin-1-ylmethyl)-phenyl}-(4-methyl-piperazin-1-yl)-methanone

Prepared from the product of Example 17 and 4-benzylpiperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.10 (m, 9H), 3.80 (br s, 2H), 3.48 (s, 2H), 3.41 (br s, 2H), 2.87-2.79 (m, 2H), 2.53 (d, J = 7.0 Hz, 2H), 2.47 (br s, 2H), 2.33 (br s, 2H), 2.32 (s, 3H), 1.90 (ddd, J = 11.7, 11.7, 2.2 Hz, 2H), 1.63-1.45 (m, 3H), 1.35-1.23 (m, 2H).

Example 43



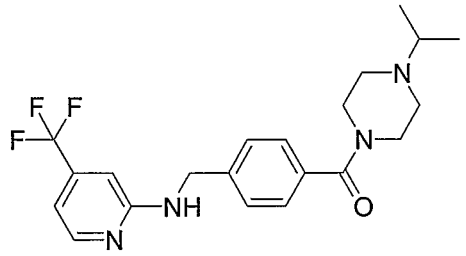
(4-Methyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride

To a solution of the product of Example 16 (60 mg) and morpholine (0.025 mL) in DCM (5 mL) was added acetic acid (0.015 mL) and sodium triacetoxyborohydride (83 mg). After 16 h the reaction was treated with 1 N NaOH (10mL) and extracted with DCM (3 x 20 mL). Organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed on silica gel (4% 2 M methanolic ammonia/DCM) to give the free base product. This material was converted into the dihydrochloride using methanol and 2 M HCl in ether to form a white solid (35 mg).

^{1}H NMR (400 MHz, CD_3OD): 7.71 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H), 4.45 (s, 2H), 4.07-4.03 (m, 2H), 3.88-3.86 (m, 1H), 3.80 (t, J = 11.6 Hz, 2H), 3.62-3.39 (m, 6H), 3.27-3.17 (m, 5H), 2.96 (s, 3H).

The products of Example 44 through Example 62 were prepared in analogy to the procedure of Example 43 using the specified carbonyl compounds and amines.

Example 44

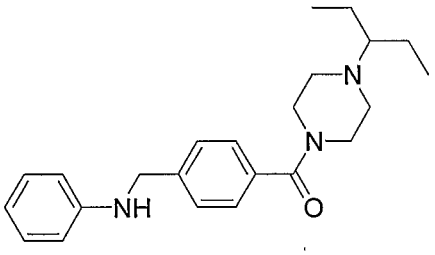


(4-Isopropyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride

Prepared from the product of Example 15 and 4-trifluoromethyl-pyridin-2-ylamine.

^{1}H NMR (400 MHz, CD_3OD): 8.08-8.06 (m, 1H), 7.58-7.45 (m, 4H), 7.39-7.35 (m, 1H), 7.14-7.10 (m, 1H), 4.76-4.70 (m, 2H), 3.58 (br s, 6H), 3.25-3.23 (m, 2H), 1.41-1.30 (m, 7H).

Example 45

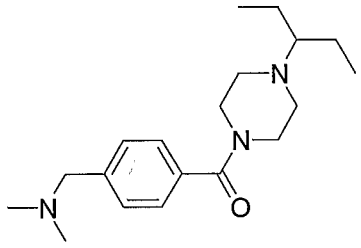


{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride

Prepared from the product of Example 12 and aniline.

^{1}H NMR (400 MHz, CD_3SOCD_3): 7.76-7.63 (m, 4H), 7.53-7.41 (tt, J = 7.3, 6.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 1H), 6.92 (dd, J = 7.6, 1.1 Hz, 2H), 5.60 (s, 1H), 4.66 (br s, 2H), 4.47 (br s, 1H), 4.05 (br s, 2H), 3.70 (br s, 2H), 2.90 (br s, 2H), 2.76 (br s, 2H), 1.84-1.70 (m, 2H), 1.68-1.55 (m, 2H), 1.30-1.20 (m, 6H).

Example 46

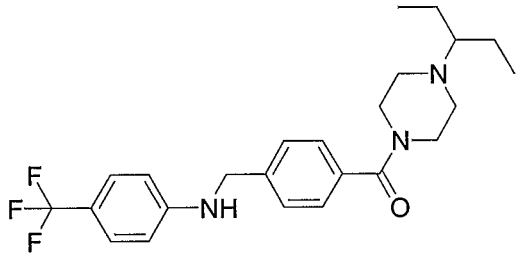


(4-Dimethylaminomethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone dihydrochloride

Prepared from the product of Example 12 and dimethylamine hydrochloride.

^{1}H NMR (400 MHz, CD_3OD): 7.78-7.44 (m, 4H), 4.52 (br s, 1H), 4.32-4.25 (m, 2H), 3.83-3.58 (m, 2H), 3.23-2.93 (m, 4H), 2.78-2.55 (m, 6H), 2.54-2.35 (m, 2H), 2.00-1.71 (m, 2H), 1.70-1.47 (m, 2H), 1.05-0.77 (m, 6H).

Example 47

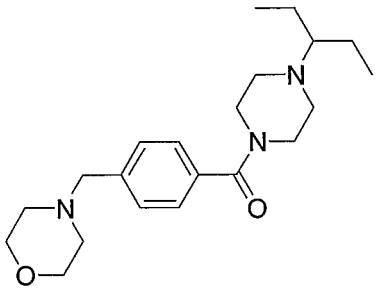


{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone dihydrochloride

Prepared from the product of Example 12 and 4-trifluoromethylaniline.

^{1}H NMR (400 MHz, CD_3OD): 7.56-7.12 (m, 6H), 6.69-6.49 (m, 2H), 4.81 (s, 2H), 4.47-4.28 (m, 2H), 3.37-3.03 (m, 8H), 1.97-1.56 (m, 4H), 1.13-0.89 (m, 6H).

Example 48

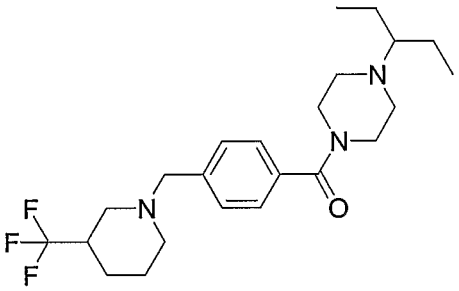


{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride

Prepared from the product of Example 12 and morpholine.

^{1}H NMR (400 MHz, dmso-d_6): 7.74 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 4.36 (d, J = 4.8 Hz, 2H), 4.00-3.67 (m, 10H), 3.52-3.41 (m, 2H), 3.25-3.18 (m, 2H), 3.11-2.99 (m, 3H), 1.97-1.80 (m, 2H), 1.69-1.52 (m, 2H), 0.96 (t, J = 7.58 Hz, 6H).

Example 49

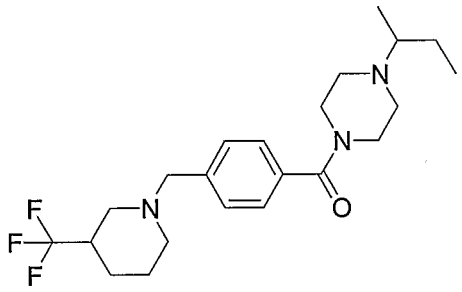


{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride

Prepared from the product of Example 12 and 3-trifluoromethylpiperidine.

^{1}H NMR (400 MHz, CD_3OD): 7.72 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 7.8, 2H), 4.87 (s, 2H), 4.50-4.40 (m, 2H), 3.75-3.41 (m, 8H), 3.20-2.84 (m, 4H), 2.09 (m, 2H), 2.00-1.50 (m, 6H), 1.12-1.02 (m, 6H).

Example 50

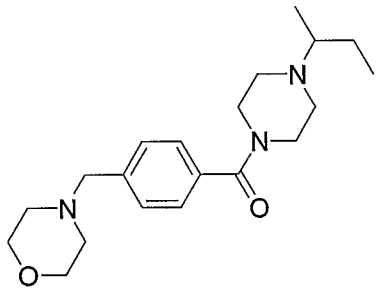


(4-*sec*-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride

Prepared from the product of Example 11 and 3-trifluoromethylpiperidine.

^{1}H NMR (400 MHz, CD_3OD): 7.71 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 4.86 (s, 2H), 4.52-4.40 (m, 2H), 3.75-3.45 (m, 8H), 3.23-2.96 (m, 5H), 2.17-2.00 (br m, 2H), 1.97-1.54 (m, 4H), 1.50-1.25 (m, 2H), 1.10-0.98 (m, 3H).

Example 51

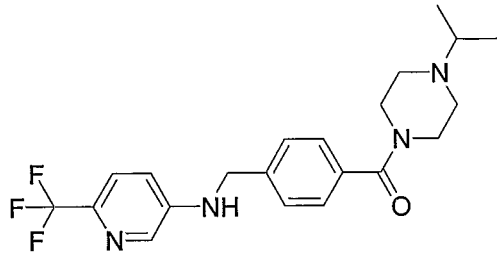


(4-*sec*-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride

Prepared from the product of Example 11 and morpholine.

^{1}H NMR (400 MHz, CD_3OD): 7.71-7.62 (m, 4H), 4.43 (s, 2H), 4.14-3.59 (m, 7H), 3.52-3.11 (m, 10H), 2.02-1.88 (m, 1H), 1.68-1.49 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H).

Example 52

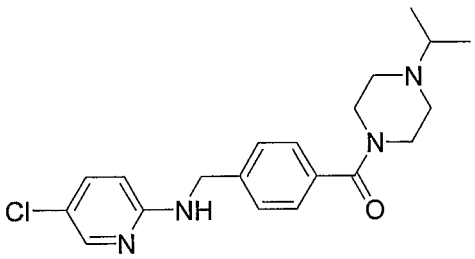


(4-Isopropyl-piperazin-1-yl)-{4-{(6-trifluoromethyl-pyridin-3-ylamino)-methyl}-phenyl}-methanone dihydrochloride

Prepared from the product of Example 15 and 6-trifluoromethyl-pyridin-3-ylamine.

^{1}H NMR (400 MHz, CD_3OD): 8.18-8.11 (m, 1H), 7.81-7.74 (m, 1H), 7.53-7.46 (m, 5H), 4.92-4.89 (m, 2H), 4.58-4.51 (m, 2H), 3.56-3.52 (m, 4H), 3.28-3.21 (m, 2H), 1.40-1.46 (m, 7H).

Example 53

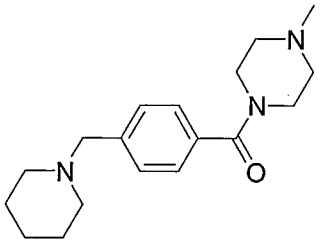


{4-{(5-Chloro-pyridin-2-ylamino)-methyl}-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride

Prepared from the product of Example 15 and 5-chloro-pyridin-2-ylamine.

^{1}H NMR (400 MHz, CD_3OD): 8.04 (d, J = 2.5 Hz, 1H), 7.38-7.33 (m, 5H), 6.32 (d, J = 8.8 Hz, 1H), 5.05 (t, J = 5.6 Hz, 1H), 4.52 (d, J = 6.1 Hz, 2H), 3.78 (br s, 2H), 3.43 (br s, 2H), 2.72 (m, 1H), 2.58-2.44 (m, 4H), 1.04 (d, J = 6.6 Hz, 6H).

Example 54

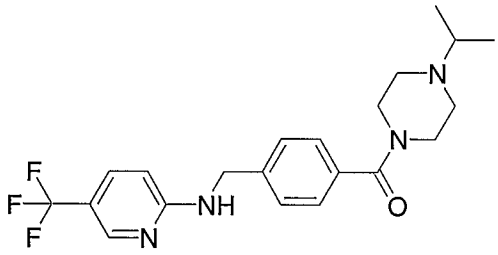


(4-Methyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone dihydrochloride

Prepared from the product of Example 16 and piperidine.

^{1}H NMR (400 MHz, CD_3OD): 7.68-7.60 (m, 4H), 4.36 (s, 2H), 3.73 (br s, 2H), 3.52-3.46 (m, 4H), 3.25 (br s, 4H), 3.00 (br s, 2H), 2.87 (s, 3H), 1.94-1.82 (m, 5H), 1.53 (br s, 1H).

Example 55

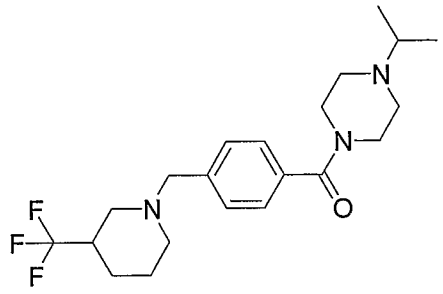


(4-Isopropyl-piperazin-1-yl)-{4-{(5-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride

Prepared from the product of Example 15 and 5-trifluoromethyl-pyridin-2-ylamine.

^{1}H NMR (400 MHz, CD_3OD): 8.31 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.57 (s, 4H), 7.24 (d, J = 9.6 Hz, 1H), 4.75 (s, 2H), 3.60-3.46 (m, 6H), 3.24-3.21 (m, 2H), 1.41-1.40 (m, 7H).

Example 56

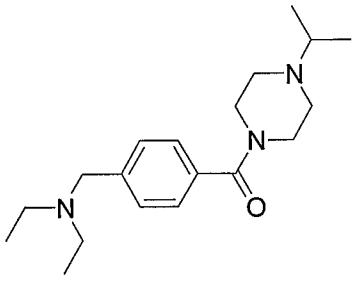


(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride

Prepared from the product of Example 15 and 3-trifluoromethyl-piperidine.

^{1}H NMR (400 MHz, CD_3OD): 7.74-7.64 (m, 4H), 4.88 (s, 2H), 4.52-4.41 (m, 2H), 3.70-3.50 (m, 6H), 3.26-3.13 (m, 4H), 3.07-2.92 (m, 2H), 2.14-2.07 (m, 2H), 1.94-1.84 (m, 1H), 1.68-1.58 (m, 1H), 1.42-1.39 (m, 6H).

Example 57

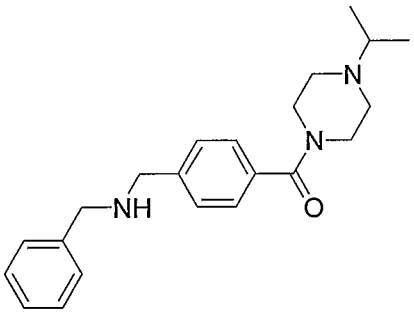


(4-Diethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride

Prepared from the product of Example 15 and diethylamine.

^{1}H NMR (400 MHz, CD_3OD): 7.70-7.64 (m, 4H), 4.42 (s, 2H), 3.61-3.57 (m, 6H), 3.25-3.22 (m, 6H), 1.42-1.30 (m, 13H).

Example 58

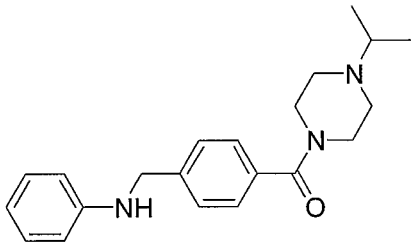


{4-(Benzylamino-methyl)-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride

Prepared from the product of Example 15 and benzylamine.

^{1}H NMR (400 MHz, CD_3OD): 7.67-7.43 (m, 9H), 4.33 (s, 2H) 4.29 (s, 2H), 3.61-3.56 (m, 6H), 3.26-3.22 (m, 2H), 1.42-1.41 (d, J = 6.6 Hz, 7H).

Example 59

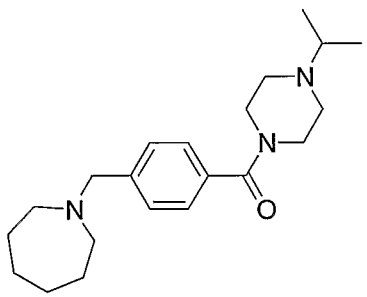


(4-Isopropyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride

Prepared from the product of Example 15 and aniline.

^{1}H NMR (400 MHz, CD_3OD): 7.57-7.54 (m, 7H), 7.47-7.44 (m, 2H), 4.69 (s, 2H), 3.62-3.52 (m, 6H), 3.25-3.19 (m, 2H), 1.42-1.41 (d, J = 6.6 Hz, 7H).

Example 60

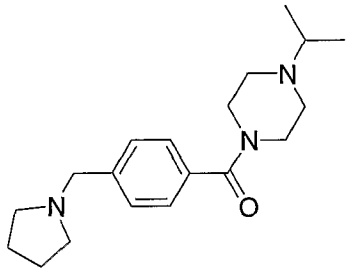


(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride

Prepared from the product of Example 15 and azepane.

^{1}H NMR (400 MHz, CD_3OD): 7.69 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 4.43 (s, 2H), 3.60-3.43 (m, 8H), 3.23-3.20 (m, 4H), 1.97-1.90 (m, 4H), 1.79-1.73 (m, 4H), 1.42-1.46 (d, J = 6.6 Hz, 7H).

Example 61

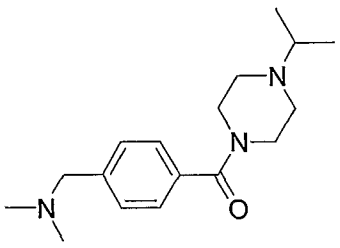


(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride

Prepared from the product of Example 15 and pyrrolidine.

^{1}H NMR (400 MHz, CD_3OD): 7.69 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 4.46 (s, 2H), 3.61-3.51 (m, 8H), 3.25-3.20 (m, 4H), 2.22-2.18 (m, 2H), 2.06-2.03 (m, 2H), 1.42 (d, J = 6.6 Hz, 7H).

Example 62

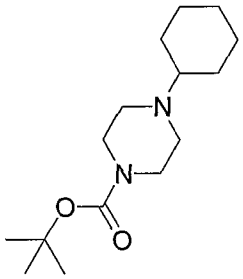


(4-Dimethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride

Prepared from the product of Example 15 and dimethylamine hydrochloride.

^{1}H NMR (400 MHz, CD_3OD): 7.66 (br s, 4H), 4.40 (s, 2H), 3.65-3.54 (m, 4H), 3.26-3.20 (m, 4H), 2.89 (br s, 6H), 1.41 (d, J = 6.6 Hz, 7H).

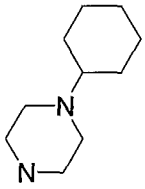
Example 63



4-Cyclohexyl-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to Example 1 from piperazine-1-carboxylic acid tert-butyl ester and cyclohexanone.

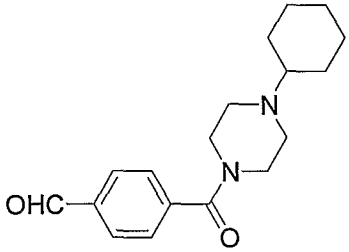
Example 64



1-Cyclohexyl-piperazine dihydrochloride

Prepared in analogy to Example 6 from the product of Example 63.

Example 65

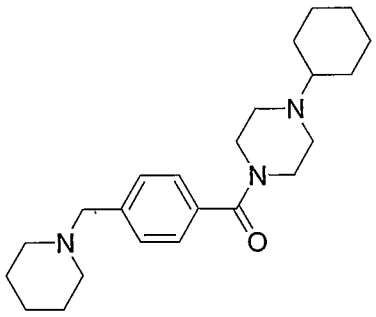


4-(4-Cyclohexyl-piperazine-1-carbonyl)-benzaldehyde

Prepared in analogy to Example 11 from the product of Example 64.

The products of Example 66 through Example 72 were prepared in analogy to the procedure of Example 20 from the specified carbonyl compounds and amines.

Example 66

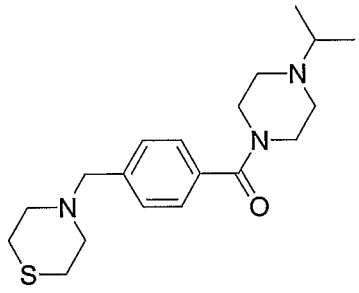


(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone

Prepared from the product of Example 65 and piperidine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.35 (s, 4H), 3.78 (br s, 2H), 3.48 (s, 2H), 3.44 (br s, 2H), 2.64-2.51 (m, 4H), 2.37 (br s, 2H), 2.30-2.29 (m, 2H), 1.86-1.80 (m, 4H), 1.65-1.55 (m, 7H), 1.45-1.44 (m, 2H), 1.24-1.19 (m, 4H).

Example 67

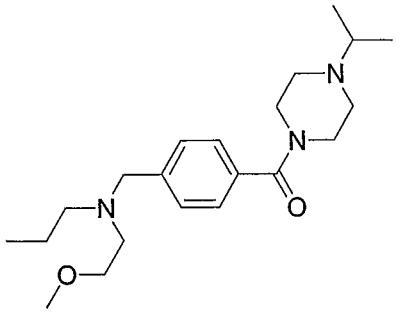


(4-Isopropyl-piperazin-1-yl)-(4-thiomorpholin-4-ylmethyl-phenyl)-methanone

Prepared from the product of Example 15 and thiomorpholine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.40-7.30 (m, 4H), 3.90-3.68 (br m, 2H), 3.53 (s, 2H), 3.49-3.37 (br m, 2H), 2.81-2.63 (m, 9H), 2.63-2.52 (br m, 2H), 2.51-2.35 (br m, 2H), 1.05 (d, J = 6.5 Hz, 6H).

Example 68

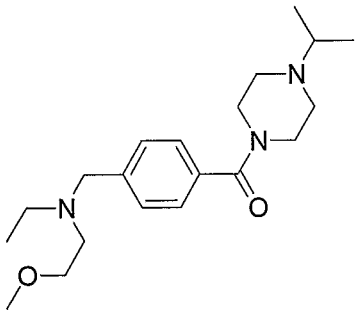


(4-Isopropyl-piperazin-1-yl)-(4-{[(2-methoxy-ethyl)-propyl-amino]-methyl}-phenyl)-methanone

Prepared from the product of Example 15 and (2-methoxy-ethyl)-propyl-amine.

^{1}H NMR (500 MHz, $CDCl_3$): 7.41-7.34 (m, 4H), 3.79 (br s, 2H), 3.65 (s, 2H), 3.51-3.46 (m, 4H), 3.32 (s, 3H), 2.76-2.71 (m, 1H), 2.69-2.65 (m, 2H), 2.53 (br s, 2H), 2.46-2.43 (m, 4H), 1.67 (br s, 1H), 1.53-1.46 (m, 2H), 1.06 (d, J = 6.5 Hz, 6H), .868 (t, J = 7.3 Hz, 3H).

Example 69

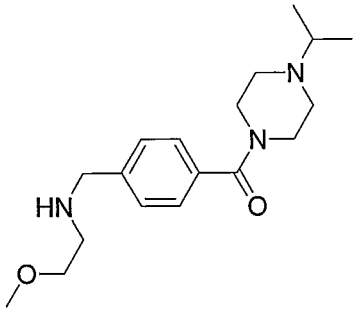


(4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone

Prepared from the product of Example 15 and (2-methoxy-ethyl)-ethyl-amine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.42-7.31 (m, 4H), 3.79 (br s, 2H), 3.70 (s, 2H), 3.53-3.45 (m, 4H), 3.33 (s, 3H), 2.76-2.71 (m, 1H), 2.69-2.67 (m, 2H), 2.60-2.56 (m, 4H), 2.46 (s, 2H), 1.62 (br s, 1H), 1.11-1.01 (m, 8H).

Example 70

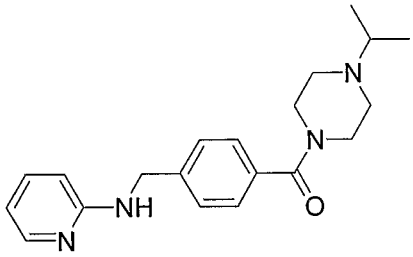


(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-methanone

Prepared from the product of Example 15 and (2-methoxy-ethyl)-amine.

^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (m, 4H), 3.84 (s, 2H), 3.75 (br s, 2H), 3.53-3.51 (m, 2H), 3.42 (br s, 2H), 3.62 (s, 3H), 2.81-2.79 (m, 2H), 2.77-2.74 (m, 1H), 2.62 (br s, 2H), 2.42 (br s, 2H), 1.70 (br s, 1H), 1.05 (d, J = 6.5 Hz, 6H).

Example 71

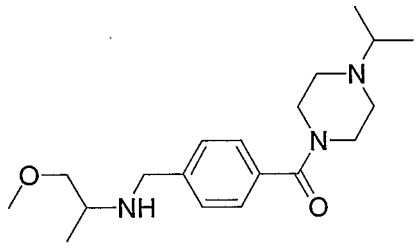


(4-Isopropyl-piperazin-1-yl)-[4-(pyridin-2-ylaminomethyl)-phenyl]-methanone

Prepared from the product of Example of 15 and 2-aminopyridine.

^{1}H NMR (400 MHz, $CDCl_3$): 8.16-8.10 (m, 1H), 7.46-7.36 (m, 5H), 6.65-6.59 (m, 1H), 6.42-6.36 (m, 1H), 5.04 (t, J = 6.1 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 3.91-3.68 (br m, 2H), 3.56-3.36 (br m, 2H), 2.80-2.67 (m, 1H), 2.69-2.54 (br m, 2H), 2.53-2.34 (br m, 2H), 1.07 (d, J = 6.6 Hz, 6H).

Example 72



(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-methanone

Prepared from the product of example 15 and 2-methoxy-1-methyl-ethylamine.

^{1}H NMR (500 MHz, $CDCl_3$): 7.35-7.38 (m, 4H), 3.89 (d, J = 13.3, 1H), 3.82-3.75 (m, 3H), 3.45 (br s, 2H), 3.43-3.32 (m, 4H), 3.28-3.25 (m, 1H), 2.96-2.92 (m, 1H), 2.75-2.58 (m, 1H), 2.65-2.20 (m, 5H), 1.06-1.04 (m, 9H).

BIOLOGICAL METHODS

In Vitro

Transfection of cells with human histamine receptor

A 10 cm tissue culture dish with a confluent monolayer of SK-N-MC cells was split two days prior to transfection. Using sterile technique the media was removed and the cells were detached from the dish by the addition of trypsin. One fifth of the cells were then placed onto a new 10 cm dish. Cells were grown in a 37 °C incubator with 5% CO_2 in Minimal Essential Media Eagle with 10% Fetal Bovine Serum. After two days cells were approximately 80% confluent. These were removed from the dish with trypsin and pelleted in a clinical centrifuge. The pellet was then re-suspended in 400 μL complete media and transferred to an electroporation cuvette with a 0.4 cm gap between the electrodes. One microgram of supercoiled H_3 receptor cDNA was added to the cells and mixed. The voltage for the electroporation was set at 0.25 kV, the capacitance was set at 960 μF. After electroporation the cells were diluted into 10 mL complete media and plated onto four 10 cm dishes. Because of the variability in the efficiency of electroporation, four different concentrations of cells were plated. The ratios used were; 1:20, 1:10, 1:5, with the remainder of

the cells being added to the fourth dish. The cells were allowed to recover for 24 h before adding the selection media (complete media with 600 μg/mL G418). After 10 days dishes were analyzed for surviving colonies of cells. Dishes with well-isolated colonies were used. Cells from individual colonies were isolated and tested. SK-N-MC cells were used because they give efficient coupling for inhibition of adenylate cyclase. The clones that gave the most robust inhibition of adenylate cyclase in response to histamine were used for further study.

{^{3}H}-*N*-methylhistamine binding

Cell pellets from histamine H_3 receptor-expressing SK-N-MC cells were homogenized in 20 mM TrisHCl/0.5 mM EDTA. Supernatants from an 800 g spin were collected, recentrifuged at 30,000 g for 30 min. Pellets were re-homogenized in 50 mM Tris/5 mM EDTA (pH 7.4). Membranes were incubated with 0.8 nM {^{3}H}-N-methylhistamine plus/minus test compounds for 45 min at 25 °C and harvested by rapid filtration over GF/C glass fiber filters (pretreated with 0.3 % polyethylenimine) followed by four washes with ice-cold buffer. Filters were dried, added to 4 mL scintillation cocktail and then counted on a liquid scintillation counter. Non-specific binding was defined with 10 μM histamine. The pK_i values were calculated based on a K_d of 800 pM and a ligand concentration ({L}) of 800 pM according to the formula:

$$K_i=(IC_{50})/(1 + (\{L\}/(K_d))$$

K_i values for exemplary compounds of the invention are listed in the table below:

EX	K_i (nM)	EX	K_i (nM)
20	2.0	45	54
21	2.0	46	2.0
22	2.0	47	81
23	0.9	48	1
24	1.5	49	4

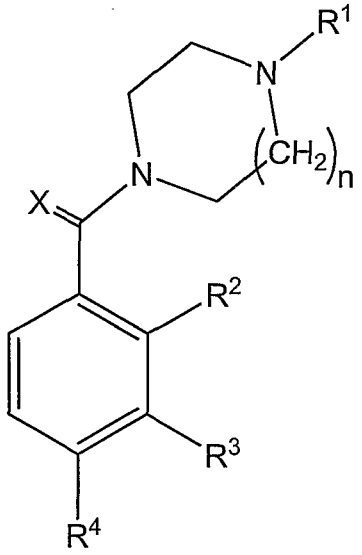
EX	K_i (nM)	EX	K_i (nM)
25	1.0	50	30
26	0.9	51	2
27	0.4	52	14
28	0.9	53	30
29	38	54	24
30	18	55	49
31	630	56	1.0
32	130	57	6.0
33	52	58	3.0
34	68	59	23
35	18	60	1.0
36	12	61	1.0
37	9	62	5.0
38	180	66	1
39	35	67	2
40	3.0	68	2
41	0.7	69	3
42	800	70	2
43	22	71	4
44	85	72	3

F. Other Embodiments

The features and advantages of the invention will be apparent to one of ordinary skill in view of the discussion, examples, embodiments, and claims relating to the invention. The invention also contemplates variations and adaptations, based on the disclosure herein concerning the key features and advantages of the invention, and within the abilities of one of ordinary skill.

What is claimed is:

1. A composition comprising a compound of formula **(I)**:



(I)

wherein

R^1 is C_{1-10} alkyl, C_{3-8} alkenyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{3-8} alkenyl, or (C_{1-8} alkylcarbonyl)C_{1-8} alkyl;

n is 1 or 2;

X is O or S;

one of R^2, R^3 and R^4 is G and the other two independently are hydrogen, fluoro, chloro, bromo, nitro, trifluoromethyl, methyl, or C_{1-3}alkoxy;

G is LQ;

L is unbranched $-(CH_2)_m-$ wherein m is an integer from 1 to 7;

Q is NR^8R^9 wherein R^8 is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, 3-9 membered carbocyclyl, 3-12 membered heterocyclyl, phenyl, (6-9-membered heterocyclyl)C_{1-6} alkylene, and (phenyl)C_{1-6} alkylene; and R^9 is independently selected from C_{1-6} alkyl, C_{3-6} alkenyl, 6-9 membered carbocyclyl, 3-12 membered heterocyclyl, phenyl, (6-9-membered heterocyclyl)C_{1-6} alkylene, and (phenyl)C_{1-6} alkylene; or

Q is a saturated 3-12 membered N-linked heterocyclyl, wherein, in addition to the N-linking nitrogen, the 3-12 membered

heterocyclyl may optionally contain between 1 and 3 additional heteroatoms independently selected from O, S, and NH;

wherein Q is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxy, halo, carboxamide, C_{1-6} alkyl, 5-9 membered or 6-9 membered heterocyclyl, -N(C_{1-6} alkyl)(5-9 membered or 6-9 membered heterocyclyl), -NH(5-9 membered or 6-9 membered heterocyclyl), -O(5-9 or 6-9 membered heterocyclyl), (5-9 membered or 6-9 membered heterocyclyl)C_{1-3} alkylene, C_{1-6} alkoxy, (C_{3-6} cycloalkyl)-O-, phenyl, (phenyl)C_{1-3} alkylene, and (phenyl)C_{1-3} alkylene-O-, where each of above heterocyclyl, phenyl, and alkyl groups may be optionally substituted with from 1 to 3 substituents independently selected from trifluoromethyl, methoxy, halo, nitro, cyano, hydroxy, and C_{1-3} alkyl;

provided however that when R^1 is methyl, G is not piperidin-1-ylmethyl; and

wherein each of the above alkyl, alkylene, alkenyl, heterocyclyl, cycloalkyl, carbocyclyl, and aryl groups may each be independently and optionally substituted with between 1 and 3 substituents independently selected from trifluoromethyl, methoxy, halo, amino, nitro, hydroxy, and C_{1-3} alkyl;

or a pharmaceutically acceptable salt, ester, tautomer, solvate or amide thereof.

2. A compound of claim 1, wherein R^1 is C_{1-10} alkyl.

3. A compound of claim 1, wherein R^1 is C_{3-5} alkyl.

4. A compound of claim 1, wherein wherein R^1 is isopropyl.

5. A compound of claim 1 wherein n is 1.

6. A compound of claim 1, wherein wherein X is O.

7. A compound of claim 1, wherein one of R^3 and R^4 is G.

8. A compound of claim 1, wherein R^4 is G.

9. A compound of claim 1, wherein L is unbranched $-(CH_2)_m-$, wherein m is an integer from 1 to 4.

10. A compound of claim 1, wherein L is $-CH_2-$.

11. A compound of claim 1, wherein L is $-CH_2CH_2-$.

12. A compound of claim 1 wherein Q is a saturated N-linked nitrogen-containing heterocyclyl.

13. A compound of claim1, wherein Q is selected from substituted or unsubstituted piperidinyl, diazepanyl, azepanyl, decahydroisoquinolin-2-yl, piperazinyl, pyrrolinyl, pyrrolidinyl, thiomorpholinyl, or morpholinyl.

14. A compound of claim 1, wherein Q is unsubstituted piperidinyl, diazepanyl, azepanyl, decahydroisoquinolin-2-yl, piperazinyl, pyrrolinyl, pyrrolidinyl, thiomorpholinyl, or morpholinyl.

15. A compound of claim 14, wherein Q is unsubstituted diazepanyl, azepanyl, morpholinyl, decahydroisoquinolin-2-yl, piperidinyl, or pyrrolidinyl;

16. A compound of claim 1, wherein substituted Q are selected from N-(C_{1-6} alkyl)piperazinyl, N-phenyl-piperazinyl, 1,3,8-triaza-spiro{4.5}decyl, and 1,4-dioxa-8-aza-spiro{4.5}decyl.

17. A compound of claim 1, wherein Q is a monovalent radical of an amine selected from aziridine, 1,4,7-trioxa-10-aza-cyclododecane, thiazolidine,

1-phenyl-1,3,8-triaza-spiro{4.5}decan-4-one, piperidine-3-carboxylic acid diethylamide, 1,2,3,4,5,6-hexahydro-{2,3'}bipyridinyl, 4-(3-trifluoromethyl-phenyl)-piperazine, 2-piperazin-1-yl-pyrimidine, piperidine-4-carboxylic acid amide, methyl-(2-pyridin-2-yl-ethyl)-amine, {2-(3,4-dimethoxy-phenyl)-ethyl}-methyl-amine, thiomorpholinyl, allyl-cyclopentyl-amine, {2-(1H-indol-3-yl)-ethyl}-methyl-amine, 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one, 2-(piperidin-4-yloxy)-pyrimidine, piperidin-4-yl-pyridin-2-yl-amine, phenylamine, pyridin-2-ylamine.

18. A compound of claim 1, wherein Q is selected from diazepanyl, azepanyl, morpholinyl, piperidinyl, and pyrrolidinyl, optionally substituted with between 1 and 3 substituents selected from hydroxy, halo, carboxamide, C_{1-6} alkyl, 5-9 membered or 6-9 membered heterocyclyl, -N(C_{1-6} alkyl)(5-9 membered or 6-9 membered heterocyclyl), -NH(5-9 membered or 6-9 membered heterocyclyl), -O(5-9 or 6-9 membered heterocyclyl), (5-9 membered or 6-9 membered heterocyclyl)C_{1-3} alkylene, C_{1-6} alkoxy, (C_{3-6} cycloalkyl)-O-, phenyl, (phenyl)C_{1-3} alkylene, and (phenyl)C_{1-3} alkylene-O-, where each of above heterocyclyl, phenyl, and alkyl groups may be optionally substituted with from 1 to 3 substituents independently selected from trifluoromethyl, methoxy, halo, nitro, cyano, hydroxy, and C_{1-3} alkyl.

19. A compound of claim 12, wherein Q is substituted with a substituent comprising a 5-9 membered heterocyclyl group selected from: pyridyl, pyrimidyl, furyl, thiofuryl, imidazolyl, (imidazolyl)C_{1-6} alkylene, oxazolyl, thiazolyl, 2,3-dihydro-indolyl, benzimidazolyl, 2-oxobenzimidazolyl, (tetrazolyl)C_{1-6} alkylene, tetrazolyl, (triazolyl)C_{1-6} alkylene, triazolyl, (pyrrolyl)C_{1-6} alkylene, pyrrolidinyl, and pyrrolyl.

20. A compound of claim 19, wherein Q is piperidinyl.

21. A compound of claim 1, wherein R^8 is hydrogen.

22. A compound of claim 1, wherein R^9 is C_{1-6} alkyl.

23. A compound of claim 1, wherein R^9 is unsubstituted or substituted phenyl.

24. A compound of claim 1, wherein R^8 and R^9 independently are C_{1-6} alkyl.

25. A compound of claim 1, wherein R^8 and R^9 are methyl.

26. A compound of claim 1, wherein R^8 and R^9 are ethyl.

27. A compound of claim 21, wherein R^9 is selected from phenyl or 5-9 membered aromatic heterocyclyl, wherein said phenyl or aromatic heterocyclyl is optionally substituted with 1-3 substituents selected from methoxy, hydroxy, halo, nitro, cyano, trifluoromethyl, and C_{1-3} alkyl.

28. A compound of claim 27, wherein R^9 is selected from substituted or unsubstituted phenyl, pyridyl, pyrimidyl, furyl, thiofuryl, imidazolyl, (imidazolyl)C_{1-6} alkylene, oxazolyl, thiazolyl, 2,3-dihydro-indolyl, benzimidazolyl, 2-oxobenzimidazolyl, (tetrazolyl)C_{1-6} alkylene, tetrazolyl, (triazolyl)C_{1-6} alkylene, triazolyl, (pyrrolyl)C_{1-6} alkylene, pyrrolidinyl, and pyrrolyl.

29. A compound of claim 28, wherein R^9 is phenyl.

30. A compound of claim 28, wherein R^9 is substituted or unsubstituted pyridyl.

31. A compound of claim 1 wherein

R^1 is C_{1-10} alkyl;

X is O;

R^4 is G;

L is $-CH_2-$; and

Q is a saturated N-linked nitrogen-containing heterocyclyl.

32. A compound of claim 31 wherein R^1 is branched.

33. A compound of claim 31 wherein R^1 is C_{3-5} alkyl.

34. A compound of claim 31, wherein wherein R^1 is isopropyl.

35. A compound of claim 31, wherein Q is selected from substituted or unsubstituted piperidinyl, diazepanyl, azepanyl, decahydroisoquinolin-2-yl, piperazinyl, pyrrolinyl, pyrrolidinyl, thiomorpholinyl, or morpholinyl.

36. A compound of claim 31, wherein Q is unsubstituted azepanyl, diazepanyl, morpholinyl, decahydroisoquinolin-2-yl, piperidinyl, or pyrrolidinyl.

37. A compound of claim 1 selected from the group consisting of:
(4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;
(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;
(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;
(4-Azepan-1-ylmethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone;
(4-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;
(4-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;
(4-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone;
(4-Butyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone;
(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;
(4-Diethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(3-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(3-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-{[(2-methoxy-ethyl)-propyl-amino]-methyl}-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(4-thiomorpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-(4-isopropyl-piperazin-1-ylmethyl)-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-[4-(pyridin-2-ylaminomethyl)-phenyl]-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-{(4-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-{(5-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-{(6-trifluoromethyl-pyridin-3-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Methyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

(4-Methyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{3-(4-Benzyl-piperidin-1-ylmethyl)-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(decahydro-isoquinolin-2-ylmethyl)-phenyl}-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-{(4-trifluoromethyl-phenylamino)-methyl}-phenyl}-methanone dihydrochloride;

{4-(1-Methyl-heptyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone;

{4-(1-Methyl-heptyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(Benzylamino-methyl)-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

{4-(Benzylamino-methyl)-phenyl}-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone; and

{4-{(5-Chloro-pyridin-2-ylamino)-methyl}-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride.

38. A compound of claim 1 selected from the group consisting of:

(4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone;

(4-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;

(4-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone;

(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Diethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(3-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-{[(2-methoxy-ethyl)-propyl-amino]-methyl}-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(4-thiomorpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-(4-isopropyl-piperazin-1-ylmethyl)-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-[4-(pyridin-2-ylaminomethyl)-phenyl]-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-{(5-trifluoromethyl-pyridin-2-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-{(6-trifluoromethyl-pyridin-3-ylamino)-methyl}-phenyl}-methanone dihydrochloride;

(4-Methyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

(4-Methyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-phenylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(decahydro-isoquinolin-2-ylmethyl)-phenyl}-methanone;

{4-(Benzylamino-methyl)-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

{4-(Benzylamino-methyl)-phenyl}-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone; and

{4-{(5-Chloro-pyridin-2-ylamino)-methyl}-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride.

39. A compound of claim 1 selected from the group consisting of:

(4-{[Ethyl-(2-methoxy-ethyl)-amino]-methyl}-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;

(4-Azepan-1-ylmethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone;

(4-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Diethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Dimethylaminomethyl-phenyl)-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(4-{[(2-methoxy-ethyl)-propyl-amino]-methyl}-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-(4-thiomorpholin-4-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-methanone;

(4-Isopropyl-piperazin-1-yl)-[4-(pyridin-2-ylaminomethyl)-phenyl]-methanone;

(4-Isopropyl-piperazin-1-yl)-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-{4-(decahydro-isoquinolin-2-ylmethyl)-phenyl}-methanone;

{4-(Benzylamino-methyl)-phenyl}-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride; and

{4-(Benzylamino-methyl)-phenyl}-{4-(1-ethyl-propyl)-piperazin-1-yl}-methanone.

40. A compound of claim 1 selected from the group consisting of:

(4-Azepan-1-ylmethyl-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride;

(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;

(4-Cyclohexyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone dihydrochloride;

(4-Isopropyl-piperazin-1-yl)-{4-(3-trifluoromethyl-piperidin-1-ylmethyl)-phenyl}-methanone dihydrochloride;

(4-*sec*-Butyl-piperazin-1-yl)-(4-dimethylaminomethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone; and

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone.

41. A compound of claim 1 selected from the group consisting of:

(4-Azepan-1-ylmethyl-phenyl)-(4-*sec*-butyl-piperazin-1-yl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

(4-*sec*-Butyl-piperazin-1-yl)-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-piperidin-1-ylmethyl-phenyl)-methanone;

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-pyrrolidin-1-ylmethyl-phenyl)-methanone;

(4-Isopropyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone;

(4-sec-Butyl-piperazin-1-yl)-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride; and

{4-(1-Ethyl-propyl)-piperazin-1-yl}-(4-morpholin-4-ylmethyl-phenyl)-methanone dihydrochloride.

42. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically-acceptable excipient.

43. A compound of claim 1 isotopically-labelled to be detectable by PET or SPECT.

44. A method of inhibiting histamine H_3 receptor activity in a subject, comprising administering an effective amount of a compound of claim 1 to a subject in need of such inhibition of histamine H_3 receptor activity.

45. A method of treating a subject having a disease or condition modulated by histamine H_3 receptor activity, comprising administering to the subject a therapeutically effective amount of a compound of claim 1.

46. A method of claim 45, wherein said disease or condition is selected from the group consisting of sleep/wake disorders, arousal/vigilance disorders, migraine, asthma, dementia, cognitive dysfunction, neurogenic inflammation, mild cognitive impairment (pre-dementia), Alzheimer's disease, epilepsy, narcolepsy, eating disorders, obesity, motion sickness, vertigo, attention deficit hyperactivity disorders, learning disorders, memory retention disorders, schizophrenia, substance abuse, bipolar disorders, manic disorders and depression,

nasal congestion, itch, allergic rhinitis, and upper airway allergic response.

47. A method for treating a disease or condition modulated by at least one receptor selected from the histamine H_1 receptor and the histamine H_3 receptor, said method comprising (a) administering to a subject a jointly effective amount of a histamine H_1 receptor antagonist compound, and (b) administering to the subject a jointly effective amount of a compound of claim 1, said method providing a jointly therapeutically effective amount of said compounds.

48. The method of claim 47 wherein the histamine H_1 receptor antagonist and the compound of claim 1 are present in the same dosage form.

49. A method for treating diseases or conditions modulated by at least one receptor selected from the histamine H_2 receptor and the histamine H_3 receptor in a subject, comprising (a) administering to the subject a jointly effective amount of a histamine H_2 receptor antagonist compound, and (b) administering to the subject a jointly effective amount of a compound of claim 1, said method providing a jointly therapeutically effective amount of said compounds.

50. The method of claim 39 wherein the histamine H_2 receptor antagonist and the compound of claim 1 are present in the same dosage form.

51. A method for treating one or more disorders or conditions selected from the group consisting of sleep/wake disorders, narcolepsy, and arousal/vigilance disorders, comprising administering to a subject a therapeutically effective amount of a compound of claim 1.

52. A method for treating attention deficit hyperactivity disorders (ADHD), comprising administering to a subject a therapeutically effective amount of a compound of claim 1.

53. A method for treating one or more disorders or conditions selected from the group consisting of dementia, mild cognitive impairment (pre-dementia), cognitive dysfunction, schizophrenia, depression, manic disorders, bipolar disorders, and learning and memory disorders, comprising administering to a subject a therapeutically effective amount of a compound of claim 1.

54. A method for treating or preventing upper airway allergic response, itch, nasal congestion, or allergic rhinitis, comprising administering to a subject a therapeutically effective amount of a compound of claim 1.

55. A method for studying disorders mediated by the histamine H_3 receptor, comprising using an ^{18}F-labeled or ^{11}C-labelled compound of claim 1 as a positron emission tomography (PET) molecular probe.