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(54) Title: SUBSTITUTED BENZYL AMINE COMPOUNDS

(57) Abstract: Certain substituted benzyl amine compounds are histamine H3 receptor and/or serotonin transporter modulators useful in the treatment of histamine H3 receptor- and/or serotonin-mediated diseases.



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SUBSTITUTED BENZYL AMINE COMPOUNDS

Field of the Invention

The present invention relates to certain benzyl amine compounds, pharmaceutical compositions containing them, and methods of using them for the treatment of disease states, disorders, and conditions mediated by the histamine H₃ receptor and/or the serotonin transporter.

Background of the Invention

The histamine H₃ receptor is primarily expressed in the mammalian central nervous system (CNS), with some minimal expression in peripheral tissues such as vascular smooth muscle. Several indications for histamine H₃ antagonists and inverse agonists have been proposed based on animal pharmacology and other experiments with known histamine H₃ antagonists (e.g. thioperamide). (See: "The Histamine H₃ Receptor-A Target for New Drugs", Leurs, R. and Timmerman, H., (Eds.), Elsevier, 1998; Morisset, S. et al., Nature 2000, 408, 860-864.) These include conditions such as cognitive disorders, sleep disorders, psychiatric disorders, and other disorders.

Compounds that possess histamine H₃ receptor activity and serotonin transporter (SERT) activity may be useful in the treatment of SERT-mediated disorders such as substance abuse disorders and sexual dysfunction (including premature ejaculation), and particularly beneficial in the treatment of depression. Activation of the H₃ receptor on neurons by histamine or an agonist decreases the release of several neurotransmitters including noradrenaline and serotonin, key neurotransmitters involved in depression (Hill, S.J. et al. *Pharmacol. Rev.* 1997, 49(3), 253-278). Although H₃ receptor antagonists alone may not be capable of increasing serotonin levels *in vivo* to those required for antidepressant effects, concomitant blockade of the SERT will simultaneously decrease the neuronal reuptake of these neurotransmitter molecules, leading to enhanced concentrations of serotonin in the synaptic cleft and an enhanced therapeutic effect and a potentially reduced side effect profile as compared to a compound with SERT activity alone.

Histamine H₃ antagonists have been shown to have pharmacological activity relevant to several key symptoms of depression, including sleep

disorders (e.g. sleep disturbances, fatigue, and lethargy) and cognitive difficulties (e.g. memory and concentration impairment), as described above. Therefore, a combined H₃/SERT modulating compound would provide symptomatic relief for the sleep disorders, fatigue, and cognitive problems during the first weeks of treatment, before the mood-elevating effect of the SERT modulation is noticed.

Compounds that have H₃ receptor activity and SERT activity have been disclosed in U.S. Pat. Publ. US 2006/0194837 A1 (published August 31, 2006; based on U.S. Pat. Appl. 11/300,880), U.S. Pat. Publ. US 2006/0293316 A1 (published December 28, 2006; based on U.S. Pat. Appl. 11/424,734), and U.S. Pat. Publ. US 2006/0287292 A1 (published December 21, 2006; based on U.S. Pat. Appl. 11/424,751), each of which is hereby incorporated by reference.

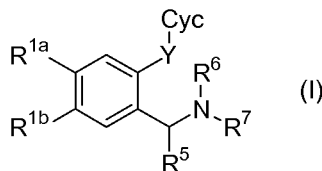
Aminomethyl phenyl ethers have been described by Pfizer, in Intl. Patent Appl. Publ. No. WO 01/72687, WO 02/18333, and U.S. Patent Appl. Publ. No. US 2002/0143003. Heteratom-linked aryl benzamides have been described by Glaxo SmithKline, in Intl. Patent Appl. Publ. No. WO 05/040144.

However, there remains a need for potent histamine H₃ receptor and/or serotonin transporter modulators with desirable pharmaceutical properties.

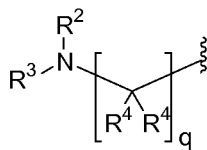
Summary of the Invention

Certain benzyl amine derivatives have now been found to have histamine H₃ receptor and/or serotonin transporter modulating activity. Thus, the invention is directed to the general and preferred embodiments defined, respectively, by the independent and dependent claims appended hereto, which are incorporated by reference herein.

In one general aspect the invention relates to a compound of the following Formula (I):



wherein



one of R^{1a} and R^{1b} is and the other is -H;

R² and R³ are each independently selected from the group consisting of: -H; a -C₁₋₆alkyl group unsubstituted or substituted with -OH, -OC₁₋₄alkyl, -NH₂, -N(R^a)R^b, or -F; -CO₂C₁₋₄alkyl; and a monocyclic cycloalkyl group

5 unsubstituted or substituted with -C₁₋₄alkyl, -OH, halo, or -CF₃;

where R^a and R^b are each independently -H, -C₁₋₆alkyl, or monocyclic cycloalkyl, or R^a and R^b taken together with their nitrogen of attachment form a monocyclic heterocycloalkyl group;

provided that R² and R³ are not both H;

10 or, alternatively,

R² and R³ taken together with the nitrogen to which they are attached form a saturated monocyclic heterocycloalkyl group unsubstituted or substituted on a carbon ring member with one, two, or three R^d moieties and substituted on a nitrogen ring member with an R^e moiety;

15 where each R^d moiety is independently selected from the group consisting of: -C₁₋₆alkyl; -C₁₋₄alkyl-OH; halo; -OH; -OC₁₋₆alkyl; ipso-substituted -OC₂₋₃alkylO-; -CN; -NO₂; -N(R^g)R^h; -C(O)N(R^g)R^h; -N(R^g)SO₂C₁₋₆alkyl; -C(O)C₁₋₆alkyl; -S(O)₀₋₂-C₁₋₆alkyl; -SO₂N(R^g)R^h; -SCF₃; -CF₃; -OCF₃; -CO₂H; and -CO₂C₁₋₆alkyl;

20 where R^g and R^h are each independently -H or -C₁₋₆alkyl, or R^g and R^h taken together with their nitrogen of attachment form a monocyclic heterocycloalkyl group; and

where R^e is selected from the group consisting of: -H; a -C₁₋₆alkyl or -C(O)C₁₋₆alkyl group unsubstituted or substituted with halo, -CN, -OH, -OC₁₋₄alkyl, or -CF₃; -C(O)CF₃; -S(O)₀₋₂-C₁₋₆alkyl; -CO₂C₁₋₆alkyl; and a phenyl, monocyclic carbon-linked heteroaryl, monocyclic cycloalkyl, or monocyclic carbon-linked heterocycloalkyl group, each unsubstituted or substituted with -C₁₋₄alkyl, halo, -CN, -OH, -OC₁₋₄alkyl, or -CF₃;

q is 0 or 1;

30 each R⁴ is independently -H or methyl, or both R⁴ substituents taken together form a carbonyl;

Y is -O-, -OCH₂-, -S-, -SO-, or -SO₂-;

R⁵ is -H or -C₁₋₆alkyl;

R⁶ is -H; or -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, monocyclic cycloalkyl, or
 -C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with -C₁₋₄alkyl, -OH, -OC₁₋₄alkyl, halo, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN,
 -CO₂H, or -CO₂C₁₋₄alkyl;

R⁷ is -H; or -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, monocyclic cycloalkyl, or
 -C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with -C₁₋₄alkyl, -OH, -OC₁₋₄alkyl, halo, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN,
 -CO₂H, or -CO₂C₁₋₄alkyl;

or R⁶ and R⁷ taken together with their nitrogen of attachment form a saturated monocyclic heterocycloalkyl group unsubstituted or substituted with -C₁₋₄alkyl, -OC₁₋₄alkyl, or halo; and

Cyc is a phenyl or monocyclic carbon-linked heteroaryl group, unsubstituted or substituted with one, two, or three R^k moieties;

where each R^k moiety is independently selected from the group consisting of: -C₁₋₆alkyl, -CHF₂, -CF₃, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -OH, -OC₁₋₆alkyl, -OCHF₂, -OCF₃, -OC₃₋₆alkenyl, -OC₃₋₆alkynyl, -CN, -NO₂, -N(R^l)R^m, -N(R^l)C(O)R^m, -N(R^l)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -S(O)₀₋₂-C₁₋₆alkyl, -C(O)N(R^l)R^m, -SO₂N(R^l)R^m, -SCF₃, halo, -CO₂H, and -CO₂C₁₋₆alkyl; or two R^k moieties on adjacent carbon atoms of attachment together are -OC₁₋₄alkyleneO- to form a cyclic ring which is unsubstituted or substituted with one or two fluoro substituents;

where R^l and R^m are each independently -H or -C₁₋₆alkyl;

provided that when both R⁴ substituents taken together form a carbonyl, then R² and R³ taken together are not diazepanyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite of such compound.

In a further general aspect, the invention relates to pharmaceutical compositions each comprising: (a) an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite thereof; and (b) a pharmaceutically acceptable excipient.

In another general aspect, the invention is directed to a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by histamine H₃ receptor and/or serotonin transporter activity, comprising administering to the subject in need of such treatment an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite thereof.

In certain preferred embodiments of the inventive method, the disease, disorder, or medical condition is selected from: cognitive disorders, sleep disorders, psychiatric disorders, and other disorders.

Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the invention.

Detailed Description

The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. For the sake of brevity, the disclosures of the publications, including patents, cited in this specification are herein incorporated by reference.

As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

The term "alkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Examples of alkyl groups include methyl (Me, which also may be structurally depicted by /), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

The term "alkylene" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain, where two hydrogen atoms are removed to form a diradical. Examples of alkylene groups include methylene (-CH₂-), ethylene, n-propylene, isopropylene, butylene, and groups that in light

The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

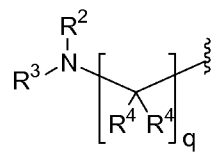
5 Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. In cases where a specified moiety or group is not expressly noted as being optionally substituted or substituted with any specified substituent, it is understood that such a moiety or group is intended to be unsubstituted.

10 Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. Additionally, any formula given herein is intended to embrace hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

15 Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{125}I , respectively. Such isotopically labeled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in

radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

When referring to any formula given herein, the selection of a particular moiety from a list of possible species for a specified variable is not intended to define the moiety for the variable appearing elsewhere. In other words, where a variable appears more than once, the choice of the species from a specified list is independent of the choice of the species for the same variable elsewhere in the formula.



In preferred embodiments of Formula (I), R^{1b} is

In preferred embodiments, R^2 and R^3 are each independently $-\text{H}$; or methyl, ethyl, propyl, isopropyl, sec-butyl, 2-methylpropyl, cyclopropyl, cyclobutyl, or cyclopentyl, each unsubstituted or substituted as previously described. In further preferred embodiments, R^2 and R^3 are each independently $-\text{H}$, methyl, ethyl, propyl, isopropyl, sec-butyl, 2-hydroxyethyl, 2-methoxyethyl, 2-methylaminoethyl, 2-dimethylaminoethyl, 2-(cyclopropylmethyl-amino)-ethyl, 2-pyrrolidin-1-yl-ethyl, 2-hydroxy-2-methylpropyl, 3-dimethylaminopropyl, cyclopropyl, cyclobutyl, or cyclopentyl. In still further preferred embodiments, R^2 and R^3 are each independently $-\text{H}$, methyl, cyclopropyl, dimethylaminoethyl, or dimethylaminopropyl.

In preferred embodiments, R^a and R^b are each independently $-\text{H}$, methyl, or cyclopropyl, or R^a and R^b taken together form pyrrolidinyl.

In alternative embodiments, R^2 and R^3 taken together with the nitrogen to which they are attached form azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-1 λ^6 -thiomorpholin-4-yl, homopiperidinyl,

diazepanyl, piperazinonyl, or diazepanonyl, each unsubstituted or substituted as previously described. In certain preferred embodiments, R² and R³ taken together with the nitrogen to which they are attached form azetidiny, 3,3-difluoroazetidiny, pyrrolidiny, 2-methylpyrrolidiny, 3-hydroxypyrrolidiny, 3-dimethylaminopyrrolidiny, 2,5-dimethylpyrrolidiny, 2-trifluoromethylpyrrolidiny, 2-hydroxymethylpyrrolidiny, 3,3-difluoropyrrolidiny, piperidiny, 3-fluoropiperidiny, 4-fluoropiperidiny, 3,3-difluoropiperidiny, 4,4-difluoropiperidiny, 3-trifluoromethylpiperidiny, 4-trifluoromethylpiperidiny, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, 4-cyanopiperidiny, 4-carboethoxypiperidiny, 3-hydroxypiperidiny, 4-hydroxypiperidiny, 2-hydroxymethylpiperidiny, 3-hydroxymethylpiperidiny, 4-hydroxymethylpiperidiny, 3-hydroxyethylpiperidiny, 4-hydroxyethylpiperidiny, 4-dimethylaminopiperidiny, 4-morpholin-4-yl-piperidin-1-yl, morpholinyl, 2-methylmorpholin-4-yl, 3-methylmorpholin-4-yl, 2,6-dimethylmorpholin-4-yl, 3-hydroxymethylmorpholin-4-yl, 2-hydroxymethylmorpholin-4-yl, piperazinyl, 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl, 4-(2-fluoroethyl)-piperazin-1-yl, 4-isopropyl-piperazin-1-yl, 4-cyclopropyl-piperazin-1-yl, 4-cyclobutyl-piperazin-1-yl, 4-cyclopentyl-piperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(2-methoxyethyl)-piperazin-1-yl, 4-(tert-butoxycarbonyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-(2-hydroxyphenyl)piperazinyl, 4-(4-trifluoromethyl-phenyl)-piperazin-1-yl, 4-thiazol-2-yl-piperazin-1-yl, 4-(2-thiophenyl)piperazinyl, 4-pyridin-4-yl-piperazin-1-yl, 4-acetyl-piperazin-1-yl, 4-isobutyryl-piperazin-1-yl, 4-piperazin-2-onyl, 1-isopropyl-4-piperazin-2-onyl, 4-isopropyl-1-piperazin-2-onyl, 1-cyclopropyl-4-piperazin-2-onyl, thiomorpholinyl, 1,1-dioxo-1λ⁶-thiomorpholin-4-yl, 4-isopropyl-[1,4]diazepan-1-yl, 4-cyclopropyl-[1,4]diazepan-1-yl, 1-cyclobutyl-4-diazepan-5-onyl, 4-isopropyl-1-diazepan-5-onyl, 1-isopropyl-4-diazepan-5-onyl, or 1-cyclopropyl-4-diazepan-5-onyl. In further preferred embodiments, R² and R³ taken together with the nitrogen to which they are attached form pyrrolidiny, 3-dimethylaminopyrrolidiny, piperidiny, 4-fluoropiperidiny, 4-dimethylaminopiperidiny, 4-morpholin-4-yl-piperidin-1-yl, morpholinyl, thiomorpholinyl, piperazinyl, 4-methyl-piperazin-1-yl, 4-isopropyl-piperazin-1-yl, 4-(2-fluoroethyl)-piperazin-1-yl, 4-cyclopropyl-piperazin-1-yl, 4-cyclobutyl-piperazin-1-yl, 4-cyclopentyl-piperazin-1-yl, 4-pyridin-4-yl-piperazin-1-yl, 4-

piperazin-2-onyl, 1-isopropyl-4-piperazin-2-onyl, 4-isopropyl-[1,4]diazepan-1-yl, or 1-isopropyl-4-diazepan-5-onyl.

In preferred embodiments, each R^d moiety is independently selected from the group consisting of: methyl, ethyl, isopropyl, hydroxyethyl, fluoro, methoxy, dimethylamino, piperidinyl, morpholinyl, acetyl, trifluoromethyl, -CO₂H, and -CO₂-methyl.

In preferred embodiments, R^g and R^h are each independently -H, methyl, ethyl, or isopropyl, or R^g and R^h taken together with their nitrogen of attachment form pyrrolidinyl, piperidinyl, morpholinyl, or thiomorpholinyl.

In preferred embodiments, R^e is selected from the group consisting of: -H, methyl, ethyl, isopropyl, 2-fluoroethyl, hydroxyethyl, methoxypropyl, acetyl, tert-butoxycarbonyl, phenyl, 4-pyridyl, cyclopropyl, cyclobutyl, cyclopentyl, and piperidinyl. In further preferred embodiments, R^e is selected from the group consisting of: -H, isopropyl, and cyclopropyl.

In preferred embodiments, q is 1 and both R⁴ substituents taken together form a carbonyl. In other preferred embodiments, q is 0. In still other preferred embodiments, q is 1 and each R⁴ is -H.

In preferred embodiments, Y is -O- or -S-.

In preferred embodiments, Cyc is a phenyl or pyridyl group unsubstituted or substituted with one, two, or three R^k moieties. In further preferred embodiments, Cyc is a thiophenyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, or pyrazinyl group unsubstituted or substituted with one, two, or three R^k moieties.

In further preferred embodiments, Cyc is phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-2-methylphenyl, 4-hydroxy-3-fluorophenyl, 3,4-dihydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 3-ethynylphenyl, 4-ethynylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3-iodophenyl, 4-iodophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-fluoro-3-

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5 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 4-difluoromethoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-acetylphenyl, 4-acetylphenyl, 3-nitrophenyl, 4-nitrophenyl, 4-aminophenyl, 4-dimethylaminophenyl, 4-carbamoylphenyl, 4-methanesulfanylphenyl, 4-methanesulfinylphenyl,

10 4-methanesulfonylphenyl, 4-trifluoromethanesulfanylphenyl, 3-methyl-4-methylsulfanylphenyl, benzo[1,3]dioxol-4-yl, benzo[1,3]dioxol-5-yl, thiophen-2-yl, thiophen-3-yl, oxazol-5-yl, thiazol-5-yl, thiazol-2-yl, 2H-pyrazol-3-yl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 4-trifluoromethyl-pyridin-2-yl, 2,6-dimethyl-pyridin-3-yl, 6-methyl-pyridin-3-yl, 2-chloro-5-pyridinyl, 2-dimethylamino-5-pyridinyl, 6-methoxy-pyridin-3-yl, 6-methylsulfanyl-pyridin-3-yl, 2-hydroxy-5-pyridinyl, 6-bromo-pyridin-3-yl, or pyrazin-2-yl.

In certain particular embodiments, Cyc is phenyl, 3-methoxyphenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-2-fluorophenyl, 4-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 4-trifluoromethylphenyl, 4-methanesulfanylphenyl, 3-methyl-4-methanesulfanylphenyl, 2-pyridinyl, 3-pyridinyl, or 6-methyl-3-pyridinyl.

In preferred embodiments, each R^k moiety is independently selected from the group consisting of: methyl, methoxy, fluoro, chloro, trifluoromethyl, methanesulfanyl, trifluoromethanesulfanyl, cyano, and trifluoromethoxy.

25 In preferred embodiments, R^l and R^m are each independently -H or methyl.

In preferred embodiments, R^5 is -H or methyl. In further preferred embodiments, R^5 is -H.

30 In preferred embodiments, R^6 is -H, methyl, ethyl, isopropyl, sec-butyl, cyclopropyl, cyclobutyl, or cyclopentyl, each unsubstituted or substituted as previously described. In further preferred embodiments, R^6 is -H or methyl.

In preferred embodiments, R^7 is -H, methyl, ethyl, propyl, isopropyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl,

cyclobutylmethyl, or cyclopentylmethyl, each unsubstituted or substituted as previously described. In further preferred embodiments, R⁷ is methyl, ethyl, isopropyl, sec-butyl, cyclopropyl, cyclobutyl, or cyclopentyl. In still further preferred embodiments, R⁷ is methyl, ethyl, isopropyl, or cyclopropyl.

- 5 In alternative embodiments, R⁶ and R⁷ taken together with their nitrogen of attachment form azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, thiomorpholiny, 1,1-dioxo-1λ⁶-thiomorpholin-4-yl, homopiperidiny, diazepany, or homomorpholiny, each unsubstituted or substituted as previously described.
- 10 In further preferred embodiments, R⁶ and R⁷ taken together with their nitrogen of attachment form piperidiny, pyrrolidiny, morpholiny, 4-isopropyl-piperazin-1-yl, or homomorpholiny.

In certain preferred embodiments, the compound of Formula (I) is selected from the group consisting of:

Ex.	Compound Name
1	[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
2	(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone;
3	(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone;
4	(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(3-methyl-4-methylsulfanyl-phenoxy)-phenyl]-methanone;
5	(4-Cyclopropyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
6	(4-Isopropyl-piperazin-1-yl)-[4-(3-methoxy-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
7	[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
8	[4-(4-Chloro-phenoxy)-3-cyclopropylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
9	(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-methanone;

10	(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-methanone;
11	[4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
12	(4-Cyclopropyl-piperazin-1-yl)-(3-methylaminomethyl-4-phenoxy-phenyl)-methanone;
13	(4-Cyclopropyl-piperazin-1-yl)-[4-(3-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
14	(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-trifluoromethyl-phenoxy)-phenyl]-methanone;
15	[3-Cyclopropylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
16	(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(3-methyl-4-methylsulfanyl-phenoxy)-phenyl]-methanone;
17	[3-Cyclopropylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
18	[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
19	(4-Cyclopropyl-piperazin-1-yl)-[4-(4-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
20	(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-methanone;
21	[4-(3-Chloro-4-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
22	[4-(4-Chloro-2-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
23	[3-Methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-(4-morpholin-4-yl-piperidin-1-yl)-methanone;
24	[4-(3-Chloro-2-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
25	(S)-3-Dimethylamino-pyrrolidin-1-yl]-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone;

26	4-(3-Chloro-phenoxy)-N-(2-dimethylamino-ethyl)-3-methylaminomethyl-benzamide;
27	4-(3-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-methylaminomethyl-benzamide;
28	[4-(4-Chloro-phenylsulfanyl)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
29	(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-2-ylsulfanyl)-phenyl]-methanone;
30	[4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
31	[4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
32	[4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(3-dimethylamino-pyrrolidin-1-yl)-methanone;
33	(4-Isopropyl-piperazin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone;
34	(4-Cyclopropyl-piperazin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone;
35	(3-Dimethylamino-pyrrolidin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone;
36	[3-(4-Chloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
37	[3-(3,4-Dichloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
38	[3-(3-Chloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
39	(4-Cyclopropyl-piperazin-1-yl)-[3-(3,4-dichloro-phenoxy)-4-methylaminomethyl-phenyl]-methanone
40	[5-(4-Isopropyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;
41	Methyl-[5-(4-methyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;

42	[5-(4-Cyclobutyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;
43	Methyl-[2-(4-methylsulfanyl-phenoxy)-5-(4-pyridin-4-yl-piperazin-1-yl)-benzyl]-amine;
44	[5-[4-(2-Fluoro-ethyl)-piperazin-1-yl]-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;
45	[5-(4-Cyclopropyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine
46	[5-(4-Cyclopropyl-piperazin-1-yl)-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine;
47	[2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-piperazin-1-yl)-benzyl]-methyl-amine;
48	1-[3-Methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-piperazin-2-one;
49	4-Isopropyl-1-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-piperazin-2-one;
50	1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-4-isopropyl-piperazin-2-one;
51	Methyl-[2-(4-methylsulfanyl-phenoxy)-5-(4-morpholin-4-yl-piperidin-1-yl)-benzyl]-amine;
52	[5-(4-Isopropyl-[1,4]diazepan-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;
53	[5-(4-Cyclopropyl-[1,4]diazepan-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;
54	1-Isopropyl-4-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-[1,4]diazepan-5-one;
55	[2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-[1,4]diazepan-1-yl)-benzyl]-methyl-amine;
56	[5-(4-Cyclopropyl-[1,4]diazepan-1-yl)-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine;
57	1-Cyclopropyl-4-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-[1,4]diazepan-5-one;

58	(S)-Dimethyl-{1-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-pyrrolidin-3-yl}-amine;
59	(4-Cyclopropyl-piperazin-1-yl)-[4-(3,4-dichloro-benzyloxy)-3-methylaminomethyl-phenyl]-methanone;
60	Cyclopropyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;
61	[5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;
62	[5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-dimethyl-amine;
63	Ethyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;
64	Isopropyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;
65	5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzylamine;
66	4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-1-isopropyl-piperazin-2-one;
67	1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-4-isopropyl-piperazin-2-one;
68	1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-4-isopropyl-[1,4]diazepan-5-one;
69	4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-1-isopropyl-[1,4]diazepan-5-one;
70	1-Cyclobutyl-4-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-benzyl]-[1,4]diazepan-5-one;
71	4-(3-Chloro-phenoxy)-3-methylaminomethyl-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
72	[4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclobutyl-piperazin-1-yl)-methanone;
73	4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-1-isopropyl-[1,4]diazepan-5-one;

74	(4-Cyclobutyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
75	(4-Cyclopentyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
76	[4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopentyl-piperazin-1-yl)-methanone;
77	[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclobutyl-piperazin-1-yl)-methanone;
78	[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopentyl-piperazin-1-yl)-methanone;
79	(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-trifluoromethyl-pyridin-2-ylsulfanyl)-phenyl]-methanone;
80	(4-Cyclopropyl-piperazin-1-yl)-[4-dimethylaminomethyl-3-(2,6-dimethyl-pyridin-3-yloxy)-phenyl]-methanone;
81	(3-Benzyloxy-4-dimethylaminomethyl-phenyl)-(4-cyclopropyl-piperazin-1-yl)-methanone;
82	[4-{{Bis-(2-methoxy-ethyl)-amino}-methyl}-3-(2,6-dimethyl-pyridin-3-yloxy)-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
83	[3-(2,6-Dimethyl-pyridin-3-yloxy)-4-morpholin-4-ylmethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
84	(4-Dimethylaminomethyl-3-phenoxy-phenyl)-piperidin-1-yl-methanone;
85	(4-{{Bis-(2-methoxy-ethyl)-amino}-methyl}-3-phenoxy-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;
86	[4-{{Bis-(2-methoxy-ethyl)-amino}-methyl}-3-(pyridin-3-yloxy)-phenyl]-(4-dimethylamino-piperidin-1-yl)-methanone;
87	[4-(4-Isopropyl-piperazin-1-ylmethyl)-3-phenoxy-phenyl]-piperidin-1-yl-methanone;
88	[4-(4-Isopropyl-piperazin-1-ylmethyl)-3-(pyridin-3-yloxy)-phenyl]-piperidin-1-yl-methanone;
89	4-Dimethylaminomethyl-N-(2-methylamino-ethyl)-3-(pyridin-3-yloxy)-benzamide;

90	N-[2-(Cyclopropyl-methyl-amino)-ethyl]-4-dimethylaminomethyl-3-(pyridin-3-yloxy)-benzamide; and
91	[5-(4-Isopropyl-piperazine-1-carbonyl)-2-(3-methoxy-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester;

and pharmaceutically acceptable salts thereof.

The invention includes also pharmaceutically acceptable salts of the compounds represented by Formula (I), preferably of those described above and of the specific compounds exemplified herein, and methods of treatment
5 using such salts.

A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid or base of a compound represented by Formula (I) that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, et al., "Pharmaceutical Salts", J. Pharm.
10 Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. Preferred pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. A compound of Formula
15 (I) may possess a sufficiently acidic group, a sufficiently basic group, or both types of functional groups, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates,
20 monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates,
25 benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, methane-sulfonates,

propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the compound of Formula (I) contains a basic nitrogen, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology.

If the compound of Formula (I) is an acid, such as a carboxylic acid or sulfonic acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide, alkaline earth metal hydroxide, any compatible mixture of bases such as those given as examples herein, and any other base and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, carbonates, bicarbonates, primary, secondary, and tertiary amines, and cyclic amines, such as benzylamines, pyrrolidines, piperidine, morpholine, and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

The invention also relates to pharmaceutically acceptable prodrugs of the compounds of Formula (I), and treatment methods employing such pharmaceutically acceptable prodrugs. The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of Formula (I)). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Examples of prodrugs include compounds having an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of a compound of Formula (I). Examples of amino acid residues include the twenty naturally occurring amino acids, commonly designated by three letter symbols, as well as 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone.

Additional types of prodrugs may be produced, for instance, by derivatizing free carboxyl groups of structures of Formula (I) as amides or alkyl esters. Examples of amides include those derived from ammonia, primary C₁₋₆alkyl amines and secondary di(C₁₋₆alkyl) amines. Secondary amines include 5- or 6-membered heterocycloalkyl or heteroaryl ring moieties. Examples of amides include those that are derived from ammonia, C₁₋₃alkyl primary amines, and di(C₁₋₂alkyl)amines. Examples of esters of the invention include C₁₋₇alkyl, C₅₋₇cycloalkyl, phenyl, and phenyl(C₁₋₆alkyl) esters. Preferred esters include methyl esters. Prodrugs may also be prepared by derivatizing free hydroxy groups using groups including hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, following procedures such as those outlined in *Adv. Drug Delivery Rev.* 1996, 19, 115.

Carbamate derivatives of hydroxy and amino groups may also yield prodrugs. Carbonate derivatives, sulfonate esters, and sulfate esters of hydroxy groups may also provide prodrugs. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group may be an alkyl ester, optionally substituted with one or more ether, amine, or carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, is also useful to yield prodrugs. Prodrugs of this type may be prepared as described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphoramides. All of these prodrug moieties may incorporate groups including ether, amine, and carboxylic acid functionalities.

The present invention also relates to pharmaceutically active metabolites of compounds of Formula (I), and uses of such metabolites in the methods of the invention. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of Formula (I) or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini, et al. *J. Med. Chem.* 1997, 40, 2011-2016; Shan, et al. *J. Pharm. Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 224-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen, et al., eds., Harwood Academic Publishers, 1991).

The compounds of Formula (I) and their pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of the present invention are useful as modulators of the histamine H₃ receptor and/or the serotonin transporter in the methods of the invention. Accordingly, the invention relates to methods of using the compounds of the invention to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated by histamine H₃ receptor and/or serotonin transporter activity, such as those described herein.

The term "treat" or "treating" as used herein is intended to refer to administration of a compound or composition of the invention to a subject for

the purpose of effecting a therapeutic or prophylactic benefit through modulation of histamine H₃ receptor and/or the serotonin transporter activity. Treating includes reversing, ameliorating, alleviating, inhibiting the progress of, lessening the severity of, or preventing a disease, disorder, or condition, or one
5 or more symptoms of such disease, disorder or condition mediated through modulation of histamine H₃ receptor and/or the serotonin transporter activity. The term "subject" refers to a mammalian patient in need of such treatment, such as a human. "Modulators" include both inhibitors and activators, where "inhibitors" refer to compounds that decrease, prevent, inactivate, desensitize
10 or down-regulate histamine H₃ receptor and/or the serotonin transporter expression or activity, and "activators" are compounds that increase, activate, facilitate, sensitize, or up-regulate histamine H₃ receptor and/or the serotonin transporter expression or activity.

Accordingly, the invention relates to methods of using the compounds
15 described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated by histamine H₃ receptor and/or the serotonin transporter activity, such as: cognitive disorders, sleep disorders, psychiatric disorders, and other disorders. Symptoms or disease states are intended to be included within the scope of "medical conditions, disorders, or diseases."

20 Cognitive disorders include, for example, dementia, Alzheimer's disease (Panula, P. et al., Soc. Neurosci. Abstr. 1995, 21, 1977), cognitive dysfunction, mild cognitive impairment (pre-dementia), attention deficit hyperactivity disorders (ADHD), attention-deficit disorders, and learning and memory
25 and memory disorders include, for example, learning impairment, memory impairment, age-related cognitive decline, and memory loss. H₃ antagonists have been shown to improve memory in a variety of memory tests, including the elevated plus maze in mice (Miyazaki, S. et al. *Life Sci.* 1995, 57(23), 2137-2144), a two-trial place recognition task (Orsetti, M. et al. *Behav. Brain Res.*
30 2001, 124(2), 235-242), the passive avoidance test in mice (Miyazaki, S. et al. *Meth. Find. Exp. Clin. Pharmacol.* 1995, 17(10), 653-658) and the radial maze in rats (Chen, Z. *Acta Pharmacol. Sin.* 2000, 21(10), 905-910). Also, in the spontaneously hypertensive rat, an animal model for the learning impairments

in attention-deficit disorders, H₃ antagonists were shown to improve memory (Fox, G.B. et al. *Behav. Brain Res.* 2002, 131(1-2), 151-161).

Sleep disorders include, for example, insomnia, disturbed sleep, narcolepsy (with or without associated cataplexy), cataplexy, disorders of
5 sleep/wake homeostasis, idiopathic somnolence, excessive daytime sleepiness (EDS), circadian rhythm disorders, fatigue, lethargy, jet lag, and REM-behavioral disorder. Fatigue and/or sleep impairment may be caused by or associated with various sources, such as, for example, sleep apnea, perimenopausal hormonal shifts, Parkinson's disease, multiple sclerosis (MS),
10 depression, chemotherapy, or shift work schedules.

Psychiatric disorders include, for example, schizophrenia (Schlicker, E. and Marr, I., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1996, 353, 290-294), bipolar disorders, manic disorders, depression (Lamberti, C. et al. *Br. J. Pharmacol.* 1998, 123(7), 1331-1336; Perez-Garcia, C. et al. *Psychopharmacology* 1999, 142(2), 215-220) (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.), obsessive-compulsive disorder, and post-traumatic stress disorder.

Other disorders include, for example, motion sickness, vertigo (e.g. vertigo or benign postural vertigo), epilepsy (Yokoyama, H. et al., *Eur. J. Pharmacol.* 1993, 234, 129-133), migraine, neurogenic inflammation, eating disorders (Machidori, H. et al., *Brain Res.* 1992, 590, 180-186), obesity, substance abuse disorders, tinnitus, movement disorders (e.g. restless leg syndrome), eye-related disorders (e.g. macular degeneration and retinitis pigmentosa), and sexual dysfunction (including premature ejaculation).
25

Particularly, as modulators of the histamine H₃ receptor and/or the serotonin transporter, the compounds of the present invention are useful in the treatment or prevention of depression, disturbed sleep, narcolepsy, fatigue, lethargy, cognitive impairment, memory impairment, memory loss, learning
30 impairment, attention-deficit disorders, and eating disorders.

In a treatment method according to the invention, an effective amount of a compound according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. An

“effective amount” means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment.

Effective amounts or doses of the compounds of the present invention
5 may be ascertained by routine methods such as modeling, dose escalation
studies or clinical trials, and by taking into consideration routine factors, e.g.,
the mode or route of administration or drug delivery, the pharmacokinetics of
the agent, the severity and course of the disease, disorder, or condition, the
subject's previous or ongoing therapy, the subject's health status and response
10 to drugs, and the judgment of the treating physician. An exemplary dose is in
the range of from about 0.001 to about 200 mg of compound per kg of subject's
body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35
mg/kg/day, or about 0.1 to 10 mg/kg daily in single or divided dosage units
(e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable
15 dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5
g/day.

Once improvement of the patient's disease, disorder, or condition has
occurred, the dose may be adjusted for preventative or maintenance treatment.
For example, the dosage or the frequency of administration, or both, may be
20 reduced as a function of the symptoms, to a level at which the desired
therapeutic or prophylactic effect is maintained. Of course, if symptoms have
been alleviated to an appropriate level, treatment may cease. Patients may,
however, require intermittent treatment on a long-term basis upon any
recurrence of symptoms.

25 In addition, the compounds of the invention may be used in combination
with additional active ingredients in the treatment of the above conditions. In
an exemplary embodiment, additional active ingredients are those that are
known or discovered to be effective in the treatment of conditions, disorders, or
diseases mediated by histamine H₃ receptor and/or the serotonin transporter
30 activity or that are active against another target associated with the particular
condition, disorder, or disease, such as H₁ receptor antagonists, H₂ receptor
antagonists, H₃ receptor antagonists, topiramate (TopamaxTM), and
neurotransmitter modulators such as serotonin-norepinephrine reuptake

inhibitors, selective serotonin reuptake inhibitors (SSRIs), noradrenergic reuptake inhibitors, non-selective serotonin re-uptake inhibitors (NSSRIs), acetylcholinesterase inhibitors (such as tetrahydroaminoacridine, Donepezil (Aricept™), Rivastigmine, or Galantamine (Reminyl™)), or modafinil. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of a compound according to the invention), decrease one or more side effects, or decrease the required dose of the compound according to the invention.

More particularly, compounds of the invention in combination with modafinil are useful for the treatment of narcolepsy, excessive daytime sleepiness (EDS), Alzheimer's disease, depression, attention-deficit disorders, MS-related fatigue, post-anesthesia grogginess, cognitive impairment, schizophrenia, spasticity associated with cerebral palsy, age-related memory decline, idiopathic somnolence, or jet-lag. Preferably, the combination method employs doses of modafinil in the range of about 20 to 300 mg per dose.

The compounds of the invention are used, alone or in combination with one or more other active ingredients, to formulate pharmaceutical compositions of the invention. A pharmaceutical composition of the invention comprises: (a) an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite thereof; and (b) a pharmaceutically acceptable excipient.

A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a compound of the invention and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

Delivery forms of the pharmaceutical compositions containing one or more dosage units of the compounds of the invention may be prepared using suitable pharmaceutical excipients and compounding techniques now or later known or available to those skilled in the art. The compositions may be

administered in the inventive methods by oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid
5 preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

For oral administration, the compounds of the invention can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds may be formulated to yield a
10 dosage of, e.g., from about 0.05 to about 100 mg/kg daily, or from about 0.05 to about 35 mg/kg daily, or from about 0.1 to about 10 mg/kg daily.

Oral tablets may include a compound according to the invention mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents,
15 flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP),
20 sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal
25 tract, or may be coated with an enteric coating.

Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, compounds of the invention may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the compound of the invention with water, an oil such as peanut oil,
30 sesame oil, or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be presented as a dry product for

reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; 5 preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

The compounds of this invention may also be administered by non-oral 10 routes. For example, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the compounds of the invention may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. 15 Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms will be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses 20 may range from about 1 to 1000 $\mu\text{g}/\text{kg}/\text{minute}$ of compound, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

For topical administration, the compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug 25 to vehicle. Another mode of administering the compounds of the invention may utilize a patch formulation to affect transdermal delivery.

Compounds of the invention may alternatively be administered in methods of this invention by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

30 Exemplary compounds useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably

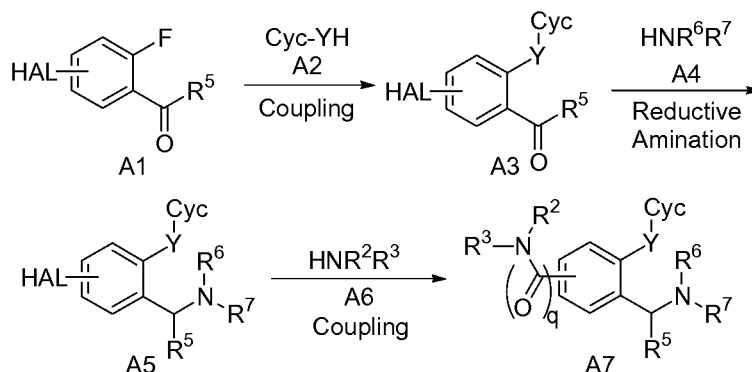
selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Unless otherwise specified, the variables are as defined above in reference to Formula (I).

10

Table of Acronyms and Abbreviations

Term	Acronym or Abbreviation
tert-Butoxycarbonyl	Boc
1,8-Diazabicyclo[5.4.0]undec-7-ene	DBU
1,2-Dichloroethane	DCE
Dichloromethane	DCM
Diethyl azodicarboxylate	DEAD
Diisopropyl azodicarboxylate	DIAD
Ethylene glycol dimethyl ether	DME
N,N-Dimethylformamide	DMF
Diethyl ether	Et ₂ O
Ethyl acetate	EtOAc
Ethanol	EtOH
Methanol	MeOH
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA

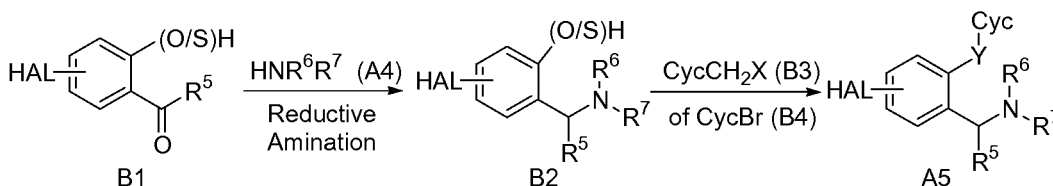
SCHEME A



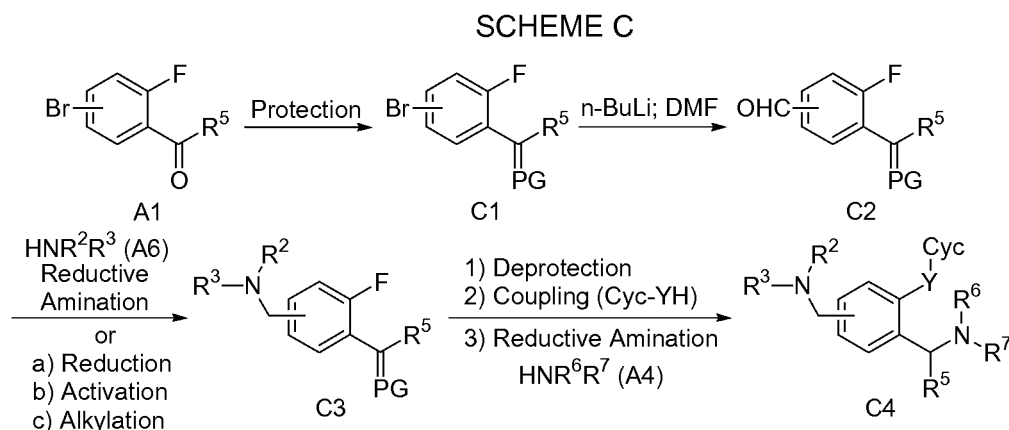
Referring to Scheme A, fluorobenzenes A1, where HAL is Br or Cl, are commercially available or are prepared according to methods known to one skilled in the art. Aromatic substitution of compounds A1 with reagents Cyc-YH, where Y is -O- or -S-, in the presence of a suitable base such as K_2CO_3 , Na_2CO_3 , or Cs_2CO_3 , in a solvent such as DMF, DME, or toluene, or a mixture thereof, at temperatures between room temperature and the reflux temperature of the solvent, provides ethers and thioethers A3. Ethers and thioethers A3 are reacted with amines A4 to form benzyl amines A5 under reductive amination conditions known to one skilled in the art. Preferred conditions include a reducing agent such as $NaBH_4$, $NaCNBH_3$, or $NaBH(OAc)_3$, in a solvent such as MeOH, EtOH, or DCE, and with optional additives such as acetic acid or a Lewis acid. Where a primary amine H_2NR^7 is used for the reductive amination, the resulting benzyl amine may be protected in a subsequent step with a suitable nitrogen protecting group, such as a Boc or other suitable carbamoyl group, under conditions known to one skilled in the art. Coupling with amines A6 is accomplished using two methods. First, aryl amination with amines A6, in the presence of a palladium catalyst such as $(PPh_3)_2PdCl_2$ or $Pd_2(dba)_3$, a phosphine ligand such as 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPHOS), and a base such as $tBuONa$, in a solvent such as DMF, DME, or toluene, at temperatures between room temperature and the reflux temperature of the solvent, provides anilines A7 (where q is 0). Aminocarbonylation of aryl bromides A5 with amines A6 to give amides A7 (where q is 1) may be performed in the presence of a suitable catalyst, such as Hermann's catalyst (trans-di- μ -acetatobis[2-(di-o-tolylphosphino)benzyl]-dipalladium), coupling aids such as tri-*t*-butylphosphonium tetrafluoroborate, a CO equivalent such as

- Mo(CO)₆, a suitable base such as DBU, in a solvent such as THF or toluene, at temperatures between room temperature and 150 °C in a microwave reactor. If a nitrogen protecting group is used, removal is accomplished under conditions known in the art, such as acidic or hydrogenation conditions, following the
- 5 coupling step. Where the synthesis provides compounds where Y is –S–, oxidation to the corresponding sulfoxides and sulfones (Y is –SO– or –SO₂–) may be performed under conditions known in the art.

SCHEME B



- 10 Referring to Scheme B, phenols or thiophenols B1 may be converted to amines B2 by reductive amination methods as described in Scheme A. Alkylation of phenols and thiols B2 with CycCH₂X (where X is a suitable leaving group, such as Br, Cl, OTs, or the like), in the presence of a suitable base such as K₂CO₃, Na₂CO₃, NaH, or the like, in a solvent such as CH₃CN or THF,
- 15 provides ethers and thioethers A5, where Y is –O– or –S–. In another embodiment, phenols or thiophenols B2 may be reacted under Mitsunobu conditions with CycCH₂X, where X is OH or SH, in the presence of PPh₃ and DEAD or DIAD, in a solvent such as CH₃CN or THF, to form ethers and thioethers A5, where Y is –OCH₂–. Aromatic substitution with activated CycBr
- 20 reagents (where Cyc is a suitable heteroaryl group) may be accomplished in the presence of a suitable base such as K₂CO₃, Na₂CO₃, or Cs₂CO₃, in the presence of dehydrating agents such as molecular sieves or Ca₂O or a mixture thereof, and salicylaldehyde, in a solvent such as DMF, DME, or toluene, or a mixture thereof, at temperatures between room temperature and
- 25 the reflux temperature of the solvent, to form ethers or thioethers A5 where where Y is –O– or –S–. All such ethers and thioethers A5 may be processed into compounds of Formula (I) as described in Scheme A.



Compounds of Formula (I) may also be prepared according to Scheme C. The carbonyl functionality of aryl bromides A1 is protected with a suitable protecting group, such as an acetal or ketal, using methods known in the art. Aldehydes are preferably protected by treatment with ethylene glycol and a catalyst such as p-toluenesulfonic acid, in a solvent such as benzene or toluene, preferably at reflux temperature. Removal of water is accomplished with molecular sieves or a Dean-Stark trap. The resulting bromides C1 are converted to benzaldehydes C2 by halogen-metal exchange with an organolithium reagent such as n-BuLi, in a solvent such as THF or Et₂O, and trapping of the resultant lithium anion with DMF. Reductive amination with amines A6 using methods as described in Scheme A provides benzyl amines C3. Aldehydes C2 may alternatively be reduced to the corresponding benzyl alcohols, activated (e.g., as a benzyl chloride, bromide, or tosylate), and displaced with suitable reagents A6 to provide benzyl amines C3. The carbonyl group may be deprotected, such as with 6 N HCl, and subsequent coupling with Cyc-YH and reductive amination as in Scheme A gives rise to compounds C4. One skilled in the art will recognize that this Scheme may also be accomplished with phenols and thiols rather than fluorobenzenes A1 to access compounds where Y is -OCH₂- and where Cyc is a suitable heteroaryl group.

Those skilled in the art will recognize that several of the chemical transformations described above may be performed in a different order than that depicted in the above Schemes. In addition, one skilled in the art will recognize that compounds of formulae A7 and C4 are compounds of Formula (I).

Additional applicable methodologies are described in U.S. Pat. Publ. US 2006/0194837 A1, U.S. Pat. Publ. US 2006/0293316 A1, and U.S. Pat. Publ. US 2006/0287292 A1.

5 Compounds of Formula (I) may be converted to their corresponding salts using methods known to those skilled in the art. For example, amines of Formula (I) may be treated with trifluoroacetic acid, HCl, or citric acid in a solvent such as Et₂O, DCM, THF, or MeOH to provide the corresponding salt forms.

10 Compounds prepared according to the schemes described above may be obtained as single enantiomers, diastereomers, or regioisomers, by enantio-, diastereo-, or regiospecific synthesis, or by resolution. Compounds prepared according to the schemes above may alternately be obtained as racemic (1:1) or non-racemic (not 1:1) mixtures or as mixtures of diastereomers or regioisomers. Where racemic and non-racemic mixtures of enantiomers are
15 obtained, single enantiomers may be isolated using conventional separation methods known to one skilled in the art, such as chiral chromatography, recrystallization, diastereomeric salt formation, derivatization into diastereomeric adducts, biotransformation, or enzymatic transformation. Where regioisomeric or diastereomeric mixtures are obtained, single isomers
20 may be separated using conventional methods such as chromatography or crystallization.

The following examples are provided to further illustrate the invention and various preferred embodiments.

25

EXAMPLES

Chemistry:

Where solutions or mixtures are "concentrated", they are typically concentrated under reduced pressure using a rotary evaporator.

30 Normal phase flash column chromatography (FCC) was typically performed with RediSep® silica gel columns using 2 M NH₃ in MeOH/DCM as eluent, unless otherwise indicated.

Preparative Reversed-Phase high performance liquid chromatography (HPLC) was typically performed using a Gilson® instrument with a YMC-Pack

ODS-A, 5 μm , 75x30 mm column, a flow rate of 25 mL/min, detection at 220 and 254 nm, with a 15% to 99% acetonitrile/water/0.05% TFA gradient.

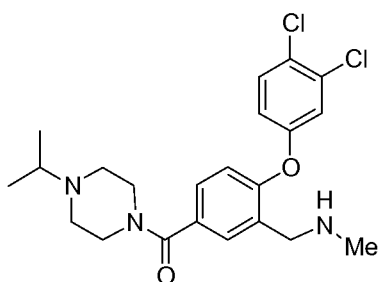
Analytical Reversed-Phase HPLC was typically performed using 1) a Hewlett Packard Series 1100 instrument with an Agilent ZORBAX® Bonus RP, 5 μm , 4.6x250 mm column, a flow rate of 1 mL/min, detection at 220 and 254 nm, with a 1% to 99% acetonitrile/water/0.05% TFA gradient; or 2) a Hewlett Packard HPLC instrument with an Agilent ZORBAX® Eclipse XDB-C8, 5 μm , 4.6x150 mm column, a flow rate of 1 mL/min, detection at 220 and 254 nm, with a 1% to 99% acetonitrile/water/0.05% TFA gradient.

Where trifluoroacetic acid salts were obtained, they were obtained from preparative reversed-phase HPLC or from deprotection of a Boc group with TFA in a final step. Where hydrochloride salts were obtained, they were obtained by treatment of a solution of the corresponding free base in DCM with an excess of 2.5 M HCl in MeOH, and concentration of the reaction solution.

In obtaining the characterization data described in the examples below, the following analytical protocols were followed as indicated.

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

NMR spectra were obtained on either a Bruker model DPX400 (400 MHz), DPX500 (500 MHz), DRX600 (600 MHz) spectrometer. The format of the ^1H NMR data below is: chemical shift in ppm down field of the tetramethylsilane reference (multiplicity, coupling constant J in Hz, integration).



Example 1: [4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone.

Step A: 5-Bromo-2-(3,4-dichloro-phenoxy)-benzaldehyde. To a solution of 5-bromo-2-fluoro-benzaldehyde (5.13 g, 25.4 mmol) in DMF (25 mL) were added K₂CO₃ (7.15 g, 51.8 mmol) and 3,4-dichloro-phenol (4.67 g, 28.8 mmol). The mixture was heated at 90 °C for 24 h and then was allowed to cool to room temperature (rt). Water was added and the mixture was extracted with Et₂O. The combined organic layers were dried (MgSO₄) and concentrated. The residue was diluted with DCM and hexanes and the resulting solids were collected by vacuum filtration to provide the desired product (4.74 g, 54%). ¹H NMR (CDCl₃): 10.36 (s, 1H), 8.06 (d, J = 2.5, 1H), 7.67 (dd, J = 8.8, 2.6, 1H), 7.46 (d, J = 8.8, 1H), 7.17 (d, J = 2.8, 1H), 6.92 (dd, J = 8.8, 2.8, 1H), 6.84 (d, J = 8.8, 1H).

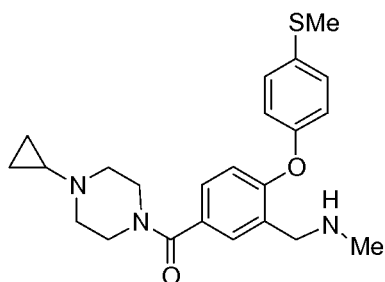
Step B: [5-Bromo-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine. To a mixture of 5-bromo-2-(3,4-dichloro-phenoxy)-benzaldehyde (4.74 g, 13.8 mmol) in MeOH (250 mL) was added MeNH₂ (40% aq.; 20 mL, 260 mmol), and the resulting mixture was stirred at rt until homogeneous. The mixture was cooled to 0 °C and treated with NaBH₄ (1.05 g, 27.8 mmol) portionwise. After 24 h, the mixture was concentrated and the residue was diluted with 1 N NaOH and extracted with DCM. The combined organic layers were dried (Na₂SO₄) and concentrated. The crude product was purified by FCC to provide the desired product (4.80 g, 97%). MS (ESI): mass calcd. for C₁₄H₁₂BrCl₂NO, 358.95; m/z found, 360.1 [M+H]⁺. ¹H NMR (CDCl₃): 7.61 (d, J = 2.5, 1H), 7.40-7.37 (m, 2H), 7.03 (d, J = 2.8, 1H), 6.82-6.79 (m, 2H), 3.72 (s, 2H), 2.44 (s, 3H), 1.30-1.21 (m, 1H).

Step C: [5-Bromo-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester. To a solution of [5-bromo-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine (4.61 g, 12.8 mmol) in DCM (250 mL) were added Et₃N (3.6 mL, 25.8 mmol) and di-tert-butyl dicarbonate (3.44 g, 15.8 mmol). After 1 h, the mixture was diluted with 1 N NaOH and extracted with DCM. The combined organic layers were dried (Na₂SO₄) and concentrated. The crude material was carried forward without purification (6.35 g, >100%). ¹H NMR (CDCl₃): 7.47-7.31 (m, 3H), 7.03 (d, J = 2.8, 1H), 6.80-6.74 (m, 2H), 4.46-4.32 (m, 2H), 2.93-2.78 (m, 3H), 1.45 (br s, 9H).

Step D. [2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-piperazine-1-carbonyl)-benzyl]-methyl-carbamic acid tert-butyl ester. To a solution of [5-bromo-2-(3,4-dichloro-phenoxy)-benzyl]-carbamic acid tert-butyl ester (327.0 mg, 0.71 mmol) in THF (2 mL) were added DBU (0.30 mL, 2.0 mmol), 1-
 5 isopropyl piperazine (0.30 mL, 2.5 mmol), Hermann's catalyst (31.9 mg, 0.034 mmol), tri-*t*-butylphosphium tetrafluoroborate (26.4 mg, 0.091 mmol), and Mo(CO)₆ (211.0 mg, 0.80 mmol). After 6 min in a microwave reactor at 125 °C, the mixture was cooled to rt and concentrated. Purification by FCC gave the desired product (212.5 mg, 56%).

10 Step E. To a solution of [2-(3,4-dichloro-phenoxy)-5-(4-isopropyl-piperazine-1-carbonyl)-benzyl]-methyl-carbamic acid tert-butyl ester (212.5 mg, 0.40 mmol) in DCM (2 mL) was added TFA (1 mL). After 30 min, the mixture was concentrated and the residue was purified by FCC to give the desired product (119.3 mg, 69%). MS (ESI): mass calcd. for C₂₂H₂₇Cl₂N₃O₂, 435.15; m/z found, 436.3 [M+H]⁺. ¹H NMR (CDCl₃): 7.50 (d, J = 2.0, 1H), 7.38 (d, J =
 15 8.8, 1H), 7.30 (dd, J = 8.3, 2.1, 1H), 7.06 (d, J = 2.8, 1H), 6.88 (d, J = 8.3, 1H), 6.82 (dd, J = 8.8, 2.8, 1H), 3.81-3.69 (m, 4H), 3.53-3.37 (m, 2H), 2.78-2.68 (m, 1H), 2.64-2.43 (m, 4H), 2.43 (s, 3H), 1.93 (br s, 1H), 1.04 (d, J = 6.5, 6H).

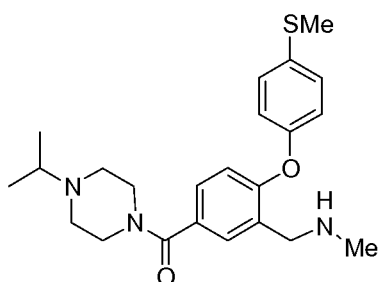
20 The compounds in Examples 2-27 were prepared by a sequence similar to that described in Example 1.



Example 2: (4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone.

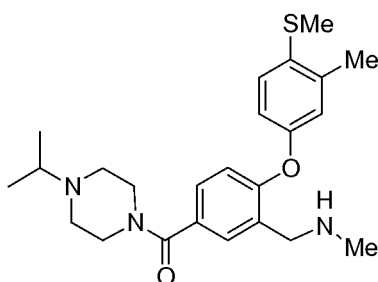
25 MS (ESI): mass calcd. for C₂₃H₂₉N₃O₂S, 411.20; m/z found, 412.3 [M+H]⁺. ¹H NMR (CDCl₃): 7.49 (d, J = 2.1, 1H), 7.30-7.26 (m, 3H), 6.94 (d, J = 8.7, 2H), 6.85 (d, J = 8.3, 1H), 3.83 (s, 2H), 3.80-3.68 (m, 2H), 3.51-3.38 (m,

2H), 2.72-2.54 (m, 4H), 2.50 (s, 3H), 2.47 (s, 3H), 2.04 (s, 2H), 1.68-1.64 (m, 1H), 1.63-1.55 (m, 3H).



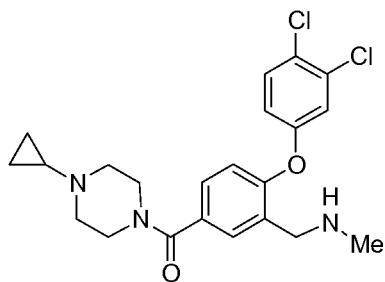
Example 3: (4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone.

5 MS (ESI): mass calcd. for $C_{23}H_{31}N_3O_2S$, 413.21; m/z found, 414.4
 [M+H]⁺. ¹H NMR (CDCl₃): 7.47 (d, J = 2.1, 1H), 7.30-7.24 (m, 3H), 6.93 (d, J =
 8.8, 2H), 6.83 (d, J = 8.3, 1H), 3.81 (s, 2H), 3.81-3.70 (m, 2H), 3.56-3.40 (m,
 2H), 2.77-2.68 (m, 1H), 2.63-2.44 (m, 4H), 2.48 (s, 3H), 2.45 (s, 3H), 1.56 (br s,
 10 1H), 1.05 (d, J = 6.5, 6H).



Example 4: (4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(3-methyl-4-methylsulfanyl-phenoxy)-phenyl]-methanone.

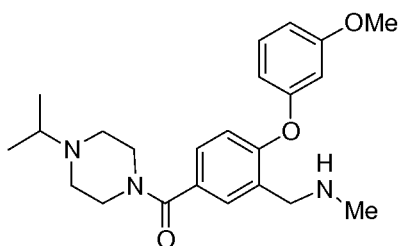
15 ¹H NMR (CDCl₃): 7.47 (d, J = 2.0, 1H), 7.26 (dd, J = 8.3, 2.1, 1H), 7.17
 (d, J = 9.3, 1H), 6.84-6.80 (m, 3H), 3.83 (s, 2H), 3.82-3.70 (m, 2H), 3.56-3.41
 (m, 2H), 2.77-2.70 (m, 1H), 2.64-2.47 (m, 4H), 2.46 (s, 3H), 2.45 (s, 3H), 2.34
 (s, 3H), 2.04 (br s, 1H), 1.05 (d, J = 6.5, 6H).



Example 5: (4-Cyclopropyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone.

MS (ESI): mass calcd. for $C_{22}H_{25}Cl_2N_3O_2$, 433.13; m/z found, 434.2

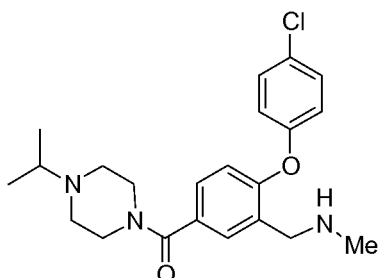
[M+H]⁺. ¹H NMR (CDCl₃): 7.51 (d, J = 2.0, 1H), 7.38 (d, J = 8.8, 1H), 7.30 (dd, J = 8.3, 2.1, 1H), 7.06 (d, J = 2.8, 1H), 6.88 (d, J = 8.3, 1H), 6.83 (dd, J = 8.8, 2.8, 1H), 3.79-3.63 (m, 4H), 3.50-3.31 (m, 2H), 2.75-2.50 (m, 4H), 2.44 (s, 3H), 1.99 (br s, 1H), 1.67-1.60 (m, 1H), 0.50-0.38 (m, 4H).



Example 6: (4-Isopropyl-piperazin-1-yl)-[4-(3-methoxy-phenoxy)-3-methylaminomethyl-phenyl]-methanone.

10

¹H NMR (CDCl₃): 7.47 (d, J = 2.1, 1H), 7.29-7.21 (m, 2H), 6.89 (d, J = 8.3, 1H), 6.70-6.66 (m, 1H), 6.57-6.53 (m, 2H), 3.83 (s, 2H), 3.79 (s, 3H), 3.55-3.44 (m, 1H), 2.77-2.69 (m, 1H), 2.64-2.47 (m, 3H), 2.46 (s, 3H), 1.75-1.63 (m, 5H), 1.05 (d, J = 6.5, 6H).

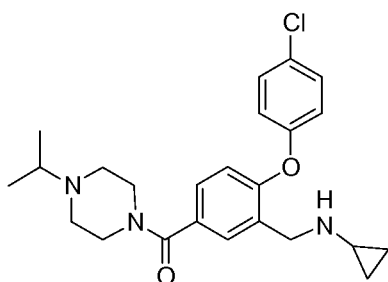


15

Example 7: [4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-[4-isopropyl-piperazin-1-yl]-methanone.

¹H NMR (CDCl₃): 7.51 (d, J = 2.1, 1H), 7.32 (d, J = 8.9, 2H), 7.30-7.26 (m, 1H), 6.93 (d, J = 8.9, 2H), 6.86 (d, J = 8.3, 1H), 3.83 (s, 2H), 3.83-3.68 (m, 2H), 3.59-3.40 (m, 2H), 2.78-2.72 (m, 1H), 2.66-2.47 (m, 4H), 2.47 (s, 3H), 1.75 (br s, 1H), 1.07 (d, J = 6.5, 6H).

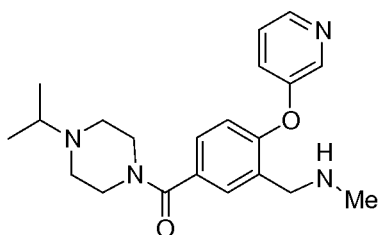
20



Example 8: [4-(4-Chloro-phenoxy)-3-cyclopropylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{24}H_{30}ClN_3O_2$, 427.20; m/z found, 428.3

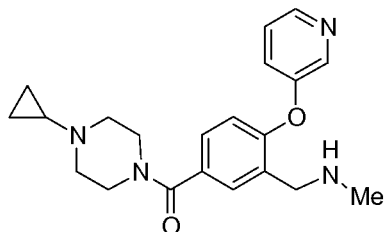
- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.48 (d, J = 2.0, 1H), 7.33-7.24 (m, 3H), 6.92 (d, J = 9.3, 2H), 6.84 (d, J = 8.3, 1H), 3.89 (s, 2H), 3.83-3.42 (m, 4H), 2.78-2.69 (m, 1H), 2.63-2.43 (m, 4H), 2.15-2.09 (m, 1H), 1.05 (d, J = 6.5, 6H), 0.45-0.34 (m, 4H).



- 10 Example 9: (4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-methanone.

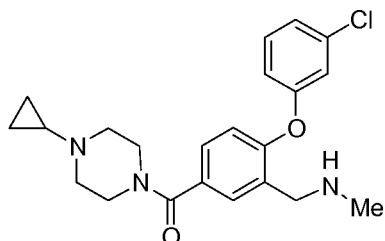
MS (ESI): mass calcd. for $C_{21}H_{28}N_4O_2$, 368.22; m/z found, 369.4 $[M+H]^+$.

- 1H NMR (MeOD): 8.90-8.86 (m, 1H), 8.74 (d, J = 5.3, 1H), 8.39-8.35 (m, 1H), 8.12-8.07 (m, 1H), 7.84 (d, J = 1.9, 1H), 7.67 (dd, J = 8.5, 2.0, 1H), 7.23 (d, J = 8.5, 1H), 4.98-4.58 (m, 1H), 4.42 (s, 2H), 4.27-3.96 (m, 1H), 3.74-3.96 (m, 1H), 3.74-3.35 (m, 5H), 3.30-3.22 (m, 2H), 2.84 (s, 3H), 1.41 (d, J = 6.7, 6H).



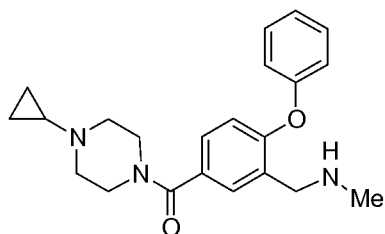
Example 10: (4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-methanone.

MS (ESI): mass calcd. for $C_{21}H_{26}N_4O_2$, 366.21; m/z found, 367.4 $[M+H]^+$.
 1H NMR (MeOD): 8.83 (s, 1H), 8.71 (d, J = 5.1, 1H), 8.30-8.26 (m, 1H), 8.04-8.00 (m, 1H), 7.82 (d, J = 2.1, 1H), 7.60 (dd, J = 8.5, 2.1, 1H), 7.20 (d, J = 8.5, 1H), 4.42 (s, 2H), 4.18-3.65 (m, 2H), 3.62-3.48 (m, 4H), 2.99-2.88 (m, 1H), 2.84 (s, 3H), 1.43 (d, J = 12.7, 3H), 1.15-1.11 (m, 2H), 1.02-0.97 (m, 2H).



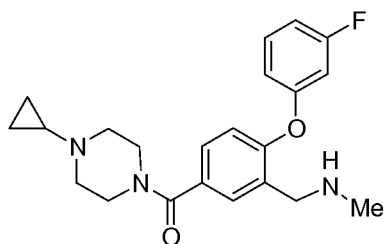
Example 11: [4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{22}H_{26}ClN_3O_2$, 399.17; m/z found, 400.3
 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.68 (d, J = 2.0, 1H), 7.40-7.34 (m, 2H), 7.26-7.23 (m, 1H), 7.08 (t, J = 2.1, 1H), 6.96 (ddd, J = 8.2, 2.3, 0.92, 1H), 6.82 (d, J = 8.5, 1H), 4.32-4.27 (m, 2H), 4.18-2.98 (m, 7H), 2.79 (s, 3H), 2.57-2.49 (m, 1H), 1.27-1.19 (m, 3H), 0.93-0.82 (m, 2H).



Example 12: (4-Cyclopropyl-piperazin-1-yl)-(3-methylaminomethyl-4-phenoxy-phenyl)-methanone.

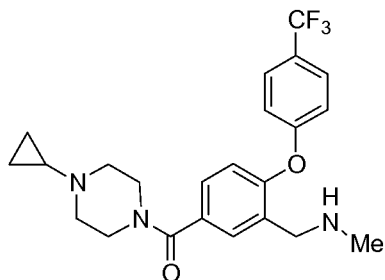
MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_2$, 365.21; m/z found, 366.3 $[M+H]^+$.
 1H NMR ($CDCl_3$): 7.48 (d, J = 2.1, 1H), 7.38-7.33 (m, 2H), 7.28-7.25 (m, 1H), 7.16-7.11 (m, 1H), 7.01-6.97 (m, 2H), 6.85 (d, J = 8.3, 1H), 3.83 (s, 2H), 3.81-3.66 (m, 2H), 3.52-3.38 (m, 2H), 2.74-2.52 (m, 4H), 2.45 (s, 3H), 1.68-1.62 (m, 1H), 0.51-0.46 (m, 2H), 0.46-0.40 (m, 2H).



Example 13: (4-Cyclopropyl-piperazin-1-yl)-[4-(3-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-methanone.

MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$, 383.20; m/z found, 384.40

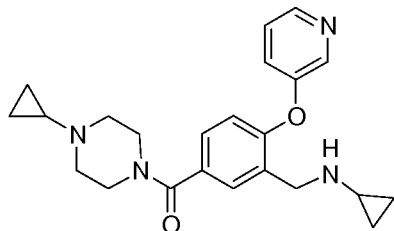
- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.54 (d, J = 2.2, 1H), 7.33-7.27 (m, 2H), 6.91 (d, J = 8.4, 1H), 6.87-6.81 (m, 1H), 6.80-6.76 (m, 1H), 6.72 (tt, J = 10.0, 2.4, 1H), 3.86 (br s, 2H), 3.81-3.64 (m, 2H), 3.55-3.32 (m, 2H), 2.75-2.50 (m, 4H), 2.48 (s, 3H), 1.70-1.59 (m, 1H), 0.52-0.38 (m, 4H).



- 10 Example 14: (4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-trifluoromethyl-phenoxy)-phenyl]-methanone.

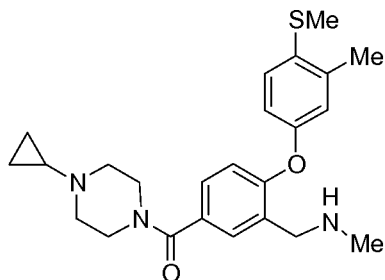
MS (ESI): mass calcd. for $C_{23}H_{26}F_3N_3O_2$, 433.20; m/z found, 434.4

- 15 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.64-7.56 (m, 2H), 7.56-7.52 (m, 1H), 7.32 (dd, J = 8.2, 2.2, 1H), 7.06-7.01 (m, 2H), 6.94 (d, J = 8.2, 1H), 3.83-3.63 (m, 4H), 3.54-3.33 (m, 2H), 2.78-2.50 (m, 4H), 2.44 (s, 3H), 1.78-1.56 (m, 1H), 0.54-0.38 (m, 4H).



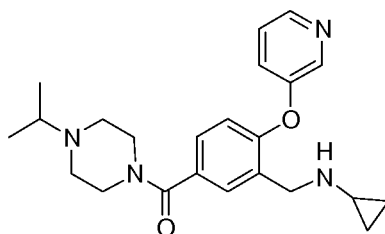
Example 15: [3-Cyclopropylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-[4-cyclopropyl-piperazin-1-yl]-methanone.

- MS (ESI): mass calcd. for $C_{23}H_{28}N_4O_2$, 392.22; m/z found, 393.4 $[M+H]^+$.
 1H NMR (MeOD): 8.82 (d, J = 2.5, 1H), 8.68 (d, J = 5.4, 1H), 8.30 (dd, J = 8.7, 1.6, 1H), 8.05-8.01 (m, 1H), 7.80 (d, J = 1.9, 1H), 7.62 (dd, J = 8.5, 2.0, 1H), 7.18 (d, J = 8.5, 1H), 4.48 (s, 2H), 4.00-3.31 (m, 6H), 2.89-2.80 (m, 2H), 1.38 (d, J = 12.8, 2H), 1.10-1.05 (m, 2H), 0.96-0.86 (m, 6H).



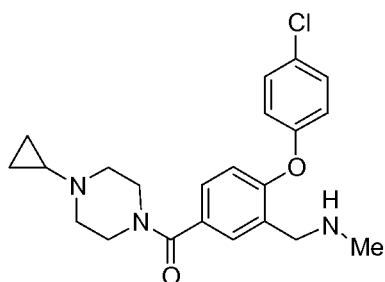
Example 16: (4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(3-methyl-4-methylsulfanyl-phenoxy)-phenyl]-methanone.

- MS (ESI): mass calcd. for $C_{24}H_{31}N_3O_2S$, 425.21; m/z found, 426.4
 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.47 (d, J = 2.1, 1H), 7.27-7.24 (m, 2H), 7.19-7.16 (m, 1H), 6.84-6.81 (m, 3H), 3.83 (s, 2H), 3.80-3.86 (m, 2H), 3.53-3.33 (m, 2H), 2.74-2.51 (m, 4H), 2.47-2.46 (m, 3H), 2.45 (s, 3H), 2.34 (s, 3H), 1.89-1.80 (m, 3H), 1.68-1.61 (m, 1H).



- 15 Example 17: [3-Cyclopropylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-[4-isopropyl-piperazin-1-yl]-methanone.

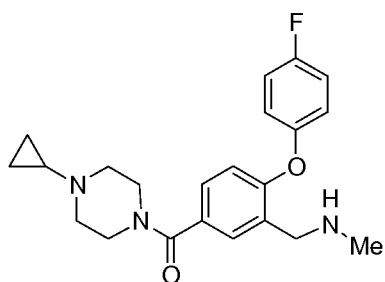
- MS (ESI): mass calcd. for $C_{23}H_{30}N_4O_2$, 394.24; m/z found, 395.4 $[M+H]^+$.
 1H NMR ($CDCl_3$): 8.83 (br s, 1H), 8.70 (br s, 1H), 8.27-8.24 (m, 1H), 8.03-7.98 (m, 1H), 7.85-7.83 (m, 1H), 7.67 (dd, J = 8.5, 2.0, 1H), 7.20 (d, J = 8.5, 1H), 4.91-4.65 (m, 1H), 4.53 (s, 2H), 4.24-3.95 (m, 1H), 3.70-3.38 (m, 5H), 3.28-3.19 (m, 2H), 2.91-2.85 (m, 1H), 1.42 (d, J = 6.6, 6H), 1.00-0.90 (m, 4H).



Example 18: [4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-[4-(4-cyclopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{22}H_{26}ClN_3O_2$, 399.17; m/z found, 400.3

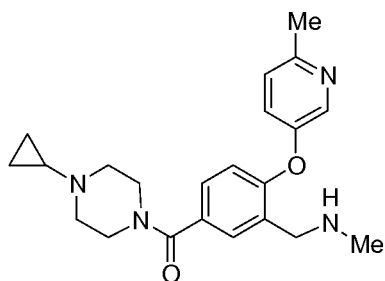
- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.48 (d, J = 2.1, 1H), 7.32-7.26 (m, 3H), 6.94-6.90 (m, 2H), 6.85 (d, J = 8.3, 1H), 3.80 (s, 2H), 3.78-3.66 (m, 2H), 3.53-3.37 (m, 2H), 2.76-2.51 (m, 4H), 2.45 (s, 3H), 1.78-1.69 (m, 1H), 1.68-1.62 (m, 1H), 0.52-0.40 (m, 4H).



- 10 Example 19: (4-Cyclopropyl-piperazin-1-yl)-[4-(4-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-methanone.

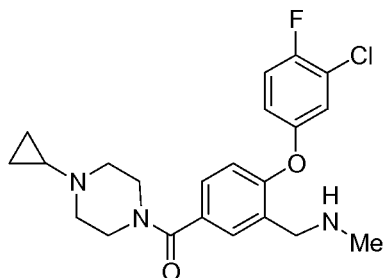
MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$, 383.20; m/z found, 384.4

- 15 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.47 (d, J = 2.0, 1H), 7.25 (dd, J = 8.4, 2.1, 1H), 7.08-7.02 (m, 2H), 6.99-6.94 (m, 2H), 6.78 (d, J = 8.4, 1H), 3.83 (s, 2H), 3.80-3.65 (m, 2H), 3.54-3.36 (m, 2H), 2.72-2.52 (m, 4H), 2.46 (s, 3H), 1.76-1.69 (m, 1H), 1.67-1.61 (m, 1H), 0.51-0.39 (m, 4H).



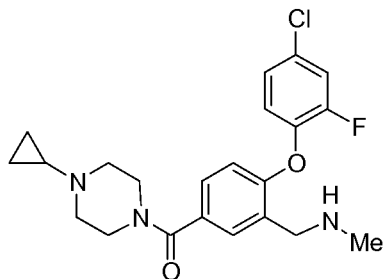
Example 20: (4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-methanone.

MS (ESI): mass calcd. for $C_{22}H_{28}N_4O_2$, 380.22; m/z found, 381.4 $[M+H]^+$.
 1H NMR ($CDCl_3$): 8.29 (d, $J = 2.8$, 1H), 7.51 (d, $J = 2.1$, 1H), 7.27 (dd, $J = 8.3$,
 2.2, 1H), 7.21 (dd, $J = 8.5$, 2.8, 1H), 7.15 (d, $J = 8.4$, 1H), 6.80 (d, $J = 8.3$, 1H),
 3.87 (s, 2H), 3.80-3.63 (m, 2H), 3.52-3.33 (m, 2H), 2.73-2.57 (m, 3H), 2.56 (s,
 5 3H), 2.48 (s, 3H), 2.31-2.20 (m, 1H), 1.68-1.62 (m, 1H), 0.51-0.40 (m, 4H).



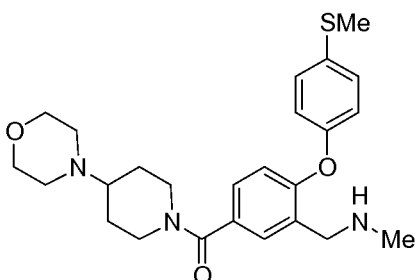
Example 21: [4-(3-Chloro-4-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{22}H_{25}ClFN_3O_2$, 417.16; m/z found, 418.3
 10 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.51 (d, $J = 2.1$, 1H), 7.29 (dd, $J = 8.3$, 2.2, 1H), 7.12
 (t, $J = 8.6$, 1H), 7.07-7.05 (m, 1H), 6.91-6.86 (m, 1H), 6.83 (d, $J = 8.3$, 1H), 3.85
 (s, 2H), 3.83-3.66 (m, 2H), 3.54-3.35 (m, 2H), 2.75-2.56 (m, 4H), 2.48 (s, 3H),
 2.06-1.90 (m, 1H), 1.69-1.62 (m, 1H), 0.52-0.40 (m, 4H).



15 Example 22: [4-(4-Chloro-2-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone.

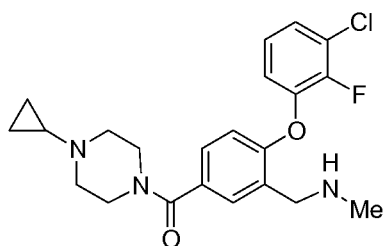
MS (ESI): mass calcd. for $C_{22}H_{25}ClFN_3O_2$, 417.16; m/z found, 418.3
 20 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.49 (d, $J = 2.0$, 1H), 7.28-7.21 (m, 2H), 7.15-7.10
 (m, 1H), 7.02 (t, $J = 8.6$, 1H), 6.72 (d, $J = 8.3$, 1H), 3.91 (s, 2H), 3.80-3.63 (m,
 2H), 3.54-3.34 (m, 2H), 2.74-2.52 (m, 4H), 2.48 (s, 3H), 2.14-1.96 (m, 1H),
 1.67-1.61 (m, 1H), 0.51-0.40 (m, 4H).



Example 23: [3-Methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-(4-morpholin-4-yl-piperidin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{25}H_{33}N_3O_3S$, 455.22; m/z found, 456.4

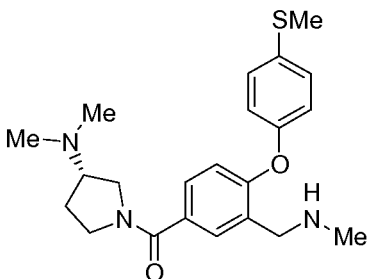
- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.41 (d, $J = 1.9$, 1H), 7.22-7.16 (m, 3H), 6.87 (d, $J = 8.7$, 2H), 6.75 (d, $J = 8.4$, 1H), 4.73-4.46 (m, 1H), 3.79 (s, 2H), 3.67-3.60 (m, 4H), 3.12-2.66 (m, 4H), 2.50-2.44 (m, 4H), 2.42-2.33 (m, 7H), 1.98-1.65 (m, 2H), 1.52-1.26 (m, 2H).



- 10 Example 24: [4-(3-Chloro-2-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone.

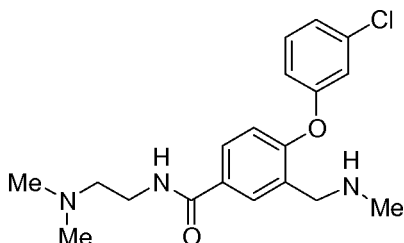
MS (ESI): mass calcd. for $C_{22}H_{25}ClFN_3O_2$, 417.16; m/z found, 418.3

- 15 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.49 (d, $J = 2.1$, 1H), 7.26 (dd, $J = 8.3$, 2.2, 1H), 7.24-7.19 (m, 1H), 7.06 (td, $J = 8.2$, 1.8, 1H), 6.96-6.91 (m, 1H), 6.76 (d, $J = 8.3$, 1H), 3.88 (s, 2H), 3.82-3.65 (m, 2H), 3.53-3.33 (m, 2H), 2.73-2.50 (m, 4H), 2.47 (s, 3H), 1.72 (br s, 1H), 1.68-1.61 (m, 1H), 0.51-0.40 (m, 4H).



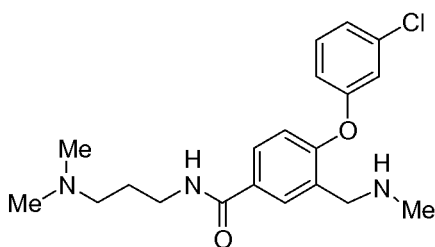
Example 25: (S)-(3-Dimethylamino-pyrrolidin-1-yl)-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone.

- MS (ESI): mass calcd. for $C_{22}H_{29}N_3O_2S$, 399.20; m/z found, 400.3
 [M+H]⁺. ¹H NMR (CDCl₃): 7.60 (s, 1H), 7.37 (dd, J = 8.4, 2.1, 1H), 7.27 (d, J = 7.2, 2H), 6.94 (t, J = 7.7, 2H), 6.82 (d, J = 8.4, 1H), 3.94-3.77 (m, 3H), 3.67-3.48 (m, 2H), 3.44-3.31 (m, 1H), 2.79-2.63 (m, 1H), 2.48 (s, 3H), 2.44 (s, 3H),
 5 2.32-2.25 (m, 4H), 2.24-2.04 (m, 4H), 1.89-1.76 (m, 1H).



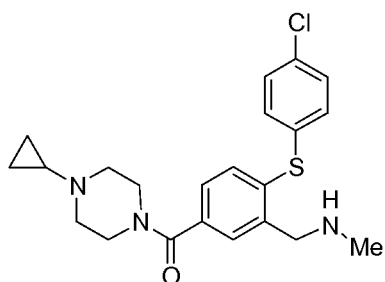
Example 26: 4-(3-Chloro-phenoxy)-N-(2-dimethylamino-ethyl)-3-methylaminomethyl-benzamide.

- MS (ESI): mass calcd. for $C_{19}H_{24}ClN_3O_2$, 361.16; m/z found, 362.7
 10 [M+H]⁺. ¹H NMR (CDCl₃): 7.89 (d, J = 2.2, 1H), 7.71 (dd, J = 8.5, 2.3, 1H), 7.28-7.24 (m, 1H), 7.12-7.09 (m, 1H), 6.97 (t, J = 2.2, 1H), 6.91-6.85 (m, 2H), 3.82 (s, 2H), 3.56-3.51 (m, 2H), 2.56 (t, J = 5.9, 2H), 2.46 (s, 3H), 2.30 (s, 6H).



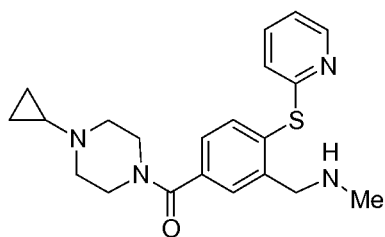
- Example 27: 4-(3-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-methylaminomethyl-benzamide.

- MS (ESI): mass calcd. for $C_{20}H_{26}ClN_3O_2$, 375.17; m/z found, 376.7
 15 [M+H]⁺. ¹H NMR (CDCl₃): 8.50-8.44 (m, 1H), 7.86 (d, J = 2.2, 1H), 7.67 (dd, J = 8.5, 2.3, 1H), 7.28-7.24 (m, 1H), 7.12-7.08 (m, 1H), 6.97 (d, J = 2.2, 1H), 6.90-6.84 (m, 2H), 3.81 (s, 2H), 3.59-3.54 (m, 2H), 2.52 (t, J = 5.8, 2H), 2.43 (s,
 20 3H), 2.31 (s, 6H), 1.80-1.74 (m, 2H).



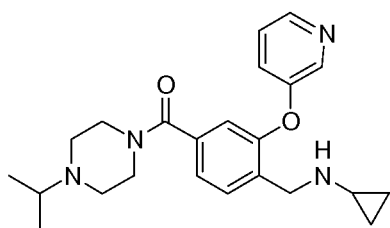
Example 28: [4-(4-Chloro-phenylsulfanyl)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone.

The title compound was prepared in an similar manner as Example 1,
 5 using [5-bromo-2-(4-chloro-phenylsulfanyl)-benzyl]-methyl-carbamic acid tert-butyl ester. MS (ESI): mass calcd. for $C_{22}H_{26}ClN_3OS$, 415.15; m/z found, 416.3 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.47-7.45 (m, 1H), 7.32-7.28 (m, 2H), 7.26-7.22 (m, 2H), 7.21-7.16 (m, 2H), 3.87 (s, 2H), 3.79-3.67 (m, 2H), 3.45-3.33 (m, 2H), 2.73-2.62 (m, 2H), 2.59-2.50 (m, 2H), 2.46 (s, 3H), 1.67-1.60 (m, 2H), 0.56-
 10 0.40 (m, 4H).



Example 29: (4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-2-ylsulfanyl)-phenyl]-methanone.

The title compound was prepared by a sequence similar to that
 15 described in Example 28. MS (ESI): mass calculated for $C_{21}H_{26}N_4OS$, 382.18; m/z found, 383.7 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.44-8.41 (m, 1H), 7.61 (d, J = 7.9, 1H), 7.59-7.58 (m, 1H), 7.49 (td, J = 7.6, 1.9, 1H), 7.32 (dd, J = 7.9, 1.9, 1H), 7.06-7.02 (m, 1H), 6.91-6.88 (m, 1H), 3.90 (s, 2H), 3.80-3.70 (m, 2H), 3.46-3.35 (m, 2H), 2.75-2.63 (m, 2H), 2.61-2.53 (m, 2H), 2.41 (s, 3H), 1.68-1.62 (m,
 20 1H), 0.50-0.40 (m, 4H).



Example 30: [4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone.

Step A: 4-Bromo-2-(pyridin-3-yloxy)-benzaldehyde. The title compound was prepared in a similar manner as in Example 1, Step A (2.85 g, 71%). MS (ESI): mass calcd. for $C_{12}H_8BrNO_2$, 276.97; m/z found, 278.0, 280.0 $[M+H]^+$.
5 1H NMR ($CDCl_3$): 10.47 (s, 1H), 8.53 (dd, J = 4.5, 1.3, 1H), 8.51 (d, J = 2.7, 1H), 7.83 (d, J = 8.4, 1H), 7.45-7.42 (m, 1H), 7.42-7.38 (m, 2H), 7.02-7.01 (m, 1H).

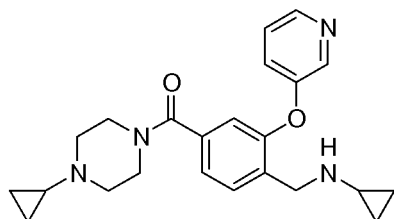
Step B: [4-Bromo-2-(pyridin-3-yloxy)-benzyl]-cyclopropyl-amine. To a mixture of 4-bromo-2-(pyridin-3-yloxy)-benzaldehyde (2.0 g, 7.19 mmol) in DCE (75 mL) were added cyclopropylamine (0.50 mL, 7.2 mmol), acetic acid (2.16 mL, 36.0 mmol), and $NaBH(OAc)_3$ (95%; 3.62 g, 18.0 mmol) portionwise. After 18 h, the mixture was diluted with 50 mL DCM and washed with 1 M NaOH (2x25 mL). The organic layer was dried (Na_2SO_4) and concentrated. FCC
15 purification (EtOAc/DCM) gave the desired product (1.74 g, 76%). MS (ESI): mass calcd. for $C_{15}H_{15}BrN_2O$, 318.04; m/z found, 319.1, 321.1 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.42-8.39 (m, 2H), 7.31-7.26 (m, 4H), 7.00-6.99 (m, 1H), 3.84 (s, 2H), 2.11-2.07 (m, 1H), 0.43-0.40 (m, 2H), 0.36-0.33 (m, 2H).

Step C: [4-Bromo-2-(pyridin-3-yloxy)-benzyl]-cyclopropyl-carbamic acid tert-butyl ester. The title compound was prepared in a similar manner as in Example 1, Step C. The crude material was carried forward without purification. MS (ESI): mass calcd. for $C_{20}H_{23}BrN_2O_3$, 418.09; m/z found, 419.1, 421.1 $[M+H]^+$.
20

Step D: Cyclopropyl-[4-(4-isopropyl-piperazine-1-carbonyl)-2-(pyridin-3-yloxy)-benzyl]-carbamic acid tert-butyl ester. The title compound was prepared in a similar manner as in Example 1, Step D. FCC purification (EtOAc/MeOH/DCM) gave the desired product. MS (ESI): mass calcd. for $C_{28}H_{38}N_4O_4$, 494.29; m/z found, 495.3 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.41-8.40 (m, 1H), 8.40-8.38 (m, 1H), 7.31-7.23 (m, 3H), 7.20-7.17 (m, 1H), 6.91-6.89 (m, 1H), 4.53 (s, 2H), 3.76-3.70 (m, 2H), 3.43-3.36 (m, 2H), 2.75-2.68 (m, 1H),
30 2.59-2.48 (m, 3H), 2.45-2.38 (m, 2H), 1.44 (s, 9H), 1.03 (d, J = 6.5, 6H), 0.72-0.60 (m, 4H).

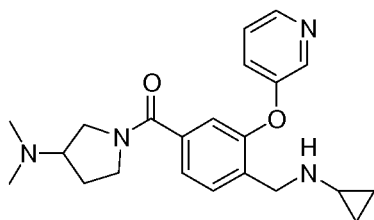
Step E. The title compound was prepared in a similar manner as in Example 1, Step E (66.4 mg, 51%). MS (ESI): mass calcd. for $C_{23}H_{30}N_4O_2$, 394.24; m/z found, 395.3 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.42-8.40 (m, 1H), 8.39 (t, J = 3.1, 1H), 7.46 (d, J = 7.7, 1H), 7.29-7.27 (m, 2H), 7.18 (dd, J = 7.7, 1.5, 1H), 6.91 (d, J = 1.4, 1H), 3.90 (s, 2H), 3.73 (br s, 2H), 3.39 (br s, 2H), 2.74-2.68 (m, 1H), 2.59-2.55 (m, 2H), 2.45-2.37 (m, 2H), 2.14-2.10 (m, 1H), 1.03 (d, J = 6.5, 6H), 0.44-0.40 (m, 2H), 0.38-0.34 (m, 2H).

The compounds in Examples 31-32 were prepared by a sequence similar to that described in Example 30.



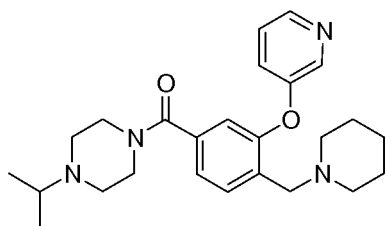
Example 31: [4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{23}H_{28}N_4O_2$, 392.22; m/z found, 393.2 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.42-8.41 (m, 1H), 8.40-8.38 (m, 1H), 7.47 (d, J = 7.7, 1H), 7.29-7.27 (m, 2H), 7.19-7.17 (m, 1H), 6.92-6.91 (m, 1H), 3.91 (s, 2H), 3.69 (br s, 2H), 3.34 (br s, 2H), 2.65 (br s, 2H), 2.50 (br s, 2H), 2.15-2.11 (m, 1H), 1.64-1.59 (m, 1H), 0.49-0.36 (m, 8H).



Example 32: [4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(3-dimethylamino-pyrrolidin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{22}H_{28}N_4O_2$, 380.22; m/z found, 381.2 $[M+H]^+$. 1H NMR ($CDCl_3$, mixture of rotamers): 8.41-8.37 (m, 2H), 7.46 (dd, J = 7.8, 2.4, 1H), 7.31-7.27 (m, 3H), 7.03-7.01 (m, 1H), 3.92-3.74 (m, 3H), 3.60-3.20 (m, 3H), 2.74-2.60 (m, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 2.18-1.90 (m, 3H), 1.84-1.75 (m, 1H), 0.45-0.34 (m, 4H).

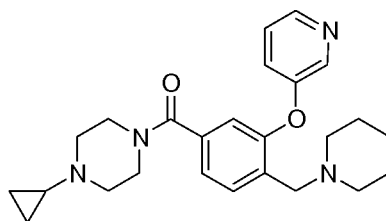


Example 33: (4-Isopropyl-piperazin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone.

Step A: 3-(5-Bromo-2-piperidin-1-ylmethyl-phenoxy)-pyridine. The title compound was prepared in a similar manner as in Example 30, Step B (0.91 g, 85%). MS (ESI): mass calcd. for $C_{17}H_{19}BrN_2O$, 346.07; m/z found, 347.1, 349.1 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.39-8.36 (m, 2H), 7.42 (d, J = 8.2, 1H), 7.32 (dd, J = 8.2, 1.9, 1H), 7.30-7.26 (m, 1H), 7.23-7.20 (m, 1H), 7.06 (d, J = 1.9, 1H), 3.46 (s, 2H), 2.38 (br s, 4H), 1.55-1.48 (m, 4H), 1.44-1.37 (m, 2H).

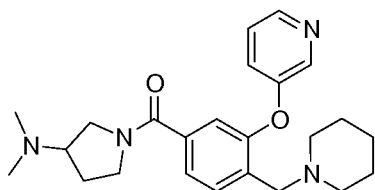
Step B. The title compound was prepared in a similar manner as in Example 1, Step D. MS (ESI): mass calcd. for $C_{25}H_{34}N_4O_2$, 422.27; m/z found, 423.3 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.36-8.32 (m, 2H), 7.56 (d, J = 7.8, 1H), 7.25-7.17 (m, 3H), 6.94-6.92 (m, 1H), 3.73 (br s, 2H), 3.49 (s, 2H), 3.40 (br s, 2H), 2.73-2.66 (m, 1H), 2.61-2.34 (m, 8H), 1.52-1.46 (m, 4H), 1.42-1.35 (m, 2H), 1.02 (d, J = 6.5, 6H).

The compounds in Examples 34-35 were prepared by a sequence similar to that described in Example 33.



Example 34: (4-Cyclopropyl-piperazin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone.

MS (ESI): mass calcd. for $C_{25}H_{32}N_4O_2$, 420.25; m/z found, 421.3 $[M+H]^+$. 1H NMR ($CDCl_3$): 8.36 (d, J = 2.8, 1H), 8.34 (dd, J = 4.6, 1.3, 1H), 7.57 (d, J = 7.8, 1H), 7.26-7.18 (m, 3H), 6.94 (d, J = 1.4, 1H), 3.70 (br s, 2H), 3.50 (s, 2H), 3.36 (br s, 2H), 2.66 (br s, 2H), 2.52 (br s, 2H), 2.42-2.33 (m, 4H), 1.65-1.60 (m, 1H), 1.53-1.48 (m, 4H), 1.43-1.36 (m, 2H), 0.49-0.40 (m, 4H).



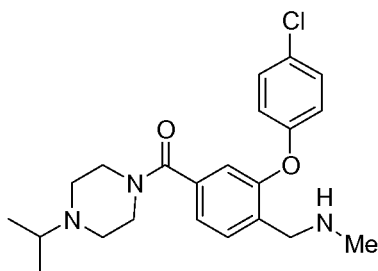
Example 35: (3-Dimethylamino-pyrrolidin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone.

MS (ESI): mass calcd. for $C_{24}H_{32}N_4O_2$, 408.25; m/z found, 409.3 $[M+H]^+$.

- 5 1H NMR ($CDCl_3$, mixture of rotamers): 8.35-8.32 (m, 2H), 7.57-7.54 (m, 1H), 7.33-7.30 (m, 1H), 7.24-7.16 (m, 2H), 7.04 (dd, $J = 5.6, 1.2$, 1H), 3.90-3.74 (m, 1H), 3.59-3.51 (m, 1.5H), 3.50 (s, 1H), 3.48 (s, 1H), 3.46-3.34 (m, 1H), 3.24 (t, $J = 9.5, 0.5$), 2.73-2.60 (m, 1H), 2.45-2.30 (m, 4H), 2.27 (s, 3H), 2.19 (s, 3H), 2.08-2.01 (m, 1H), 1.83-1.75 (m, 1H), 1.52-1.45 (m, 4H), 1.41-1.34 (m, 2H).

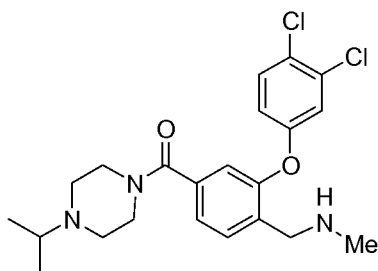
10

The compounds in Examples 36-39 were prepared by a sequence similar to that described in Example 30.



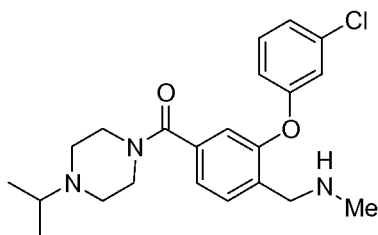
- 15 Example 36: [3-(4-Chloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{22}H_{28}ClN_3O_2$, 401.19; m/z found, 402.8 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.44 (d, $J = 7.7$, 1H), 7.29 (d, $J = 8.9$, 2H), 7.15 (dd, $J = 7.7, 1.5$, 1H), 6.91 (d, $J = 8.9$, 2H), 6.87 (d, $J = 1.4$, 1H), 3.79 (s, 2H), 3.76-3.67 (m, 2H), 3.42-3.32 (m, 2H), 2.73-2.67 (m, 1H), 2.58-2.50 (m, 2H), 2.44 (s, 20 3H), 2.42-2.34 (m, 2H), 1.02 (d, $J = 6.5$, 6H).



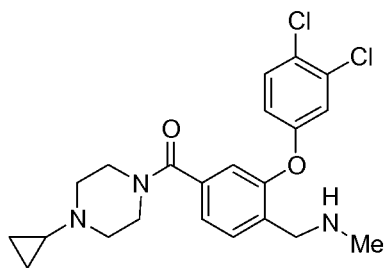
Example 37: [3-(3,4-Dichloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{22}H_{27}Cl_2N_3O_2$, 435.15; m/z found, 436.7
 [M+H]⁺. ¹H NMR (CDCl₃): 7.46 (d, J = 7.8, 1H), 7.37 (d, J = 8.8, 1H), 7.19 (dd,
 5 J = 7.7, 1.5, 1H), 7.05 (d, J = 2.8, 1H), 6.90 (d, J = 1.5, 1H), 6.81 (dd, J = 8.8,
 2.8, 1H), 3.77-3.66 (m, 4H), 3.44-3.33 (m, 2H), 2.74-2.66 (m, 1H), 2.58-2.50
 (m, 2H), 2.45-2.35 (m, 5H), 1.02 (d, J = 6.6, 6H).



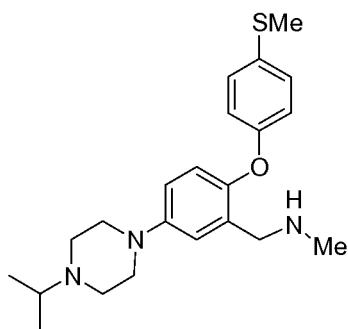
10 Example 38: [3-(3-Chloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone.

MS (ESI): mass calcd. for $C_{22}H_{28}ClN_3O_2$, 401.19; m/z found, 402.8
 [M+H]⁺. ¹H NMR (CDCl₃): 7.47 (d, J = 7.7, 1H), 7.27 (t, J = 8.1, 1H), 7.19 (dd, J
 = 7.7, 1.5, 1H), 7.11-7.07 (m, 1H), 6.97 (t, J = 2.2, 1H), 6.91 (d, J = 1.5, 1H),
 6.86 (ddd, J = 8.3, 2.3, 0.82, 1H), 3.81 (s, 2H), 3.77-3.67 (m, 2H), 3.45-3.33 (m,
 15 2H), 2.76-2.67 (m, 1H), 2.60-2.50 (m, 2H), 2.47-2.36 (m, 5H), 1.03 (d, J = 6.5,
 6H).



20 Example 39: (4-Cyclopropyl-piperazin-1-yl)-[3-(3,4-dichloro-phenoxy)-4-methylaminomethyl-phenyl]-methanone.

MS (ESI): mass calcd. for $C_{22}H_{25}Cl_2N_3O_2$, 433.13; m/z found, 434.7
 [M+H]⁺. ¹H NMR (CDCl₃): 7.48 (d, J = 7.7, 1H), 7.39 (d, J = 8.8, 1H), 7.20 (dd,
 J = 7.7, 1.5, 1H), 7.08 (d, J = 2.8, 1H), 6.92 (d, J = 1.5, 1H), 6.83 (dd, J = 8.8,
 2.8, 1H), 3.80 (s, 2H), 3.76=3.63 (m, 2H), 3.42-3.27 (m, 2H), 2.71-2.60 (m, 2H),
 2.58-2.47 (m, 2H), 2.46 (s, 3H), 1.66-1.59 (m, 1H), 0.51-0.38 (m, 4H).

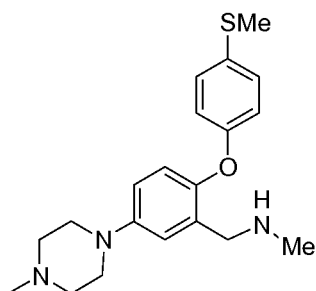


Example 40: [5-(4-Isopropyl-piperazin-1-yl)-2-(4-methylsulfonyl-phenoxy)-benzyl]-methyl-amine.

Step A: [5-(4-Isopropyl-piperazin-1-yl)-2-(4-methylsulfonyl-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester. A mixture of [5-bromo-2-(4-methylsulfonyl-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester (300 mg, 0.684 mmol) {prepared in an analogous fashion to Example 1, Steps A-C}, isopropyl piperazine (132 mg, 1.02 mmol), XPHOS (39 mg, 0.082 mmol), Pd₂(dba)₃ (62.6 mg, 0.0684 mmol), and t-BuONa (98.0 mg, 1.02 mmol) in toluene was heated in a sealed tube overnight at 120 °C. After cooling to rt, the mixture was filtered through diatomaceous earth and the filtrate was concentrated. Purification by FCC gave the desired product (180 mg, 54%). MS (ESI): mass calcd. for C₂₇H₃₉N₃O₃S, 485.27; m/z found, 486.4 [M+H]⁺. ¹H NMR (CDCl₃): 7.22 (d, J = 8.5, 2H), 6.86-6.83 (m, 1H), 6.83-6.80 (m, 4H), 4.42-4.35 (m, 2H), 3.19-3.16 (m, 4H), 2.87-2.83 (m, 2H), 2.80-2.75 (m, 1H), 2.75-2.71 (m, 1H), 2.71-2.67 (m, 4H), 2.44 (s, 3H), 1.48-1.40 (m, 9H), 1.10 (d, J = 6.5, 6H).

Step B. The title compound was prepared in an analogous fashion to Example 1, Step E. MS (ESI): mass calcd. for C₂₂H₃₁N₃OS, 385.22; m/z found, 386.4 [M+H]⁺. ¹H NMR (CDCl₃): 7.22 (d, J = 8.9, 2H), 6.99 (d, J = 2.7, 1H), 6.86-6.80 (m, 4H), 3.69 (s, 2H), 3.22-3.17 (m, 4H), 2.72-2.67 (m, 4H), 2.45 (s, 3H), 2.40 (s, 3H), 2.08-1.97 (br s, 1H), 1.10 (d, J = 6.5, 6H).

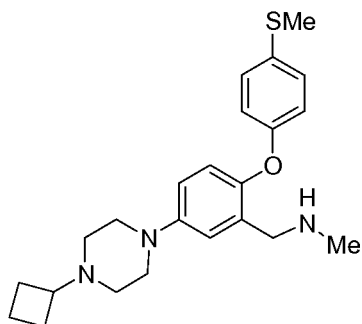
The compounds in Examples 41-58 were prepared by a sequence similar to that described in Example 40.



Example 41: Methyl-[5-(4-methyl-piperazin-1-yl)-2-(4-methylsulfonyl-phenoxy)-benzyl]-amine.

MS (ESI): mass calcd. for $C_{20}H_{27}N_3OS$, 357.19; m/z found, 358.3

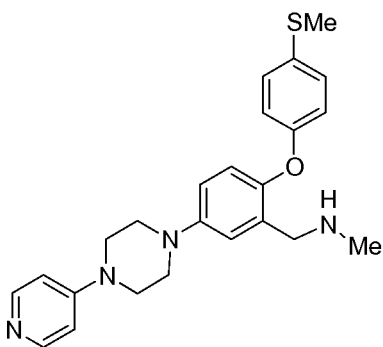
- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.22 (d, $J = 8.9$, 2H), 7.01 (d, $J = 2.5$, 1H), 6.85-6.81 (m, 4H), 3.78 (s, 2H), 3.20-3.16 (m, 4H), 2.59-2.56 (m, 4H), 2.45 (s, 3H), 2.44 (s, 3H), 2.35 (s, 3H).



Example 42: [5-(4-Cyclobutyl-piperazin-1-yl)-2-(4-methylsulfonyl-phenoxy)-benzyl]-methyl-amine.

MS (ESI): mass calcd. for $C_{23}H_{31}N_3OS$, 397.22; m/z found, 398.4

- 10 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.21 (d, $J = 8.8$, 2H), 6.97 (d, $J = 2.8$, 1H), 6.84-6.76 (m, 4H), 3.68 (s, 2H), 3.20-3.16 (m, 4H), 2.82-2.74 (m, 1H), 2.50-2.46 (m, 4H), 2.43 (s, 3H), 2.39 (s, 3H), 2.09-2.02 (m, 2H), 1.96-1.86 (m, 2H), 1.78-1.66 (m, 2H).
- 15

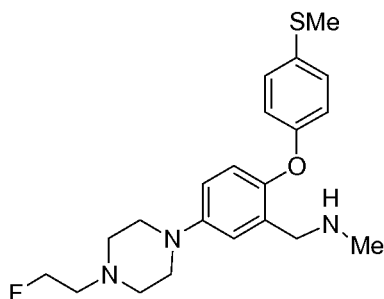


Example 43: Methyl-[2-(4-methylsulfanyl-phenoxy)-5-(4-pyridin-4-yl-piperazin-1-yl)-benzyl]-amine.

MS (ESI): mass calcd. for C₂₄H₂₈N₄OS, 420.20; m/z found, 421.3

[M+H]⁺. ¹H NMR (CDCl₃): 8.42-8.21 (m, 2H), 7.24 (d, J = 8.8, 2H), 7.09-7.05

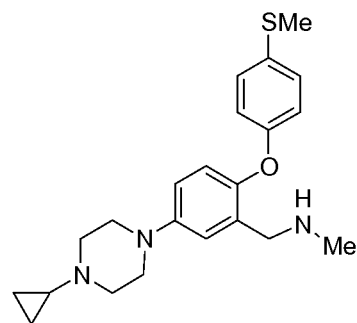
5 (m, 1H), 6.92-6.82 (m, 4H), 6.78-6.66 (m, 2H), 3.80-3.67 (m, 2H), 3.54-3.48 (m, 4H), 3.34-3.28 (m, 4H), 2.50-2.38 (m, 5H), 2.28-2.14 (m, 2H).



Example 44: [5-[4-(2-Fluoro-ethyl)-piperazin-1-yl]-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine.

10 MS (ESI): mass calcd. for C₂₁H₂₈FN₃OS, 389.19; m/z found, 390.3

[M+H]⁺. ¹H NMR (CDCl₃): 7.22 (d, J = 8.9, 2H), 6.99 (d, J = 2.8, 1H), 6.86-6.78 (m, 4H), 4.67 (t, J = 4.7, 1H), 4.57 (t, J = 4.7, 1H), 3.68 (s, 2H), 3.24-3.18 (m, 4H), 2.80 (t, J = 4.8, 1H), 2.75-2.69 (m, 5H), 2.45 (s, 3H), 2.40 (s, 3H), 2.01 (br s, 1H).



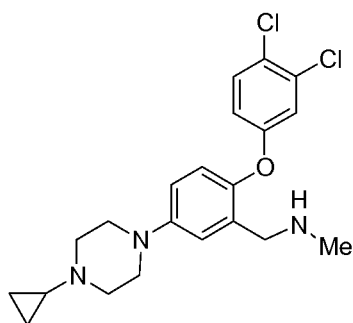
15

Example 45: [5-(4-Cyclopropyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine.

MS (ESI): mass calcd. for C₂₂H₂₉N₃OS, 383.20; m/z found, 384.3

[M+H]⁺. ¹H NMR (CDCl₃): 7.21 (d, J = 8.8, 2H), 7.02 (d, J = 2.5, 1H), 6.85 (d, J = 8.8, 2H), 6.80-6.78 (m, 2H), 3.93 (s, 2H), 3.11-3.08 (m, 4H), 2.75-2.72 (m, 4H), 2.49 (s, 3H), 2.44 (s, 3H), 1.67-1.62 (m, 1H), 0.50-0.41 (m, 4H).

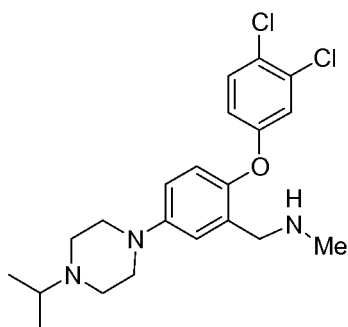
20



Example 46: [5-(4-Cyclopropyl-piperazin-1-yl)-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine.

MS (ESI): mass calcd. for $C_{21}H_{25}Cl_2N_3O$, 405.14; m/z found, 406.7

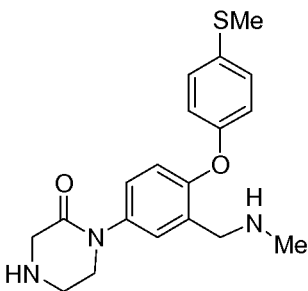
- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.36 (d, J = 8.8, 1H), 7.08 (d, J = 2.7, 1H), 7.01 (d, J = 2.8, 1H), 6.88-6.80 (m, 3H), 4.00 (s, 2H), 3.18-3.11 (m, 4H), 2.82-2.77 (m, 4H), 2.55 (s, 3H), 1.76-1.68 (m, 1H), 0.55-0.51 (m, 4H).



Example 47: [2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-piperazin-1-yl)-benzyl]-methyl-amine.

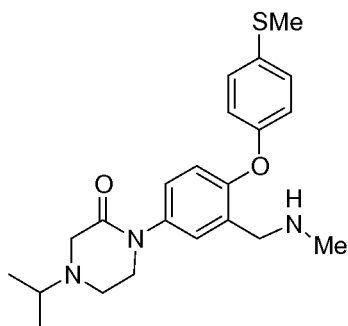
MS (ESI): mass calcd. for $C_{21}H_{27}Cl_2N_3O$, 407.15; m/z found, 408.2

- 10 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.32 (d, J = 8.9, 1H), 7.01 (d, J = 2.7, 1H), 6.96 (d, J = 2.8, 1H), 6.87-6.80 (m, 2H), 6.75 (dd, J = 8.9, 2.8, 1H), 3.68 (s, 2H), 3.24-3.20 (m, 4H), 2.80-2.73 (m, 1H), 2.73-2.70 (m, 4H), 2.42 (s, 3H), 1.11 (d, J = 6.5, 6H).
- 15



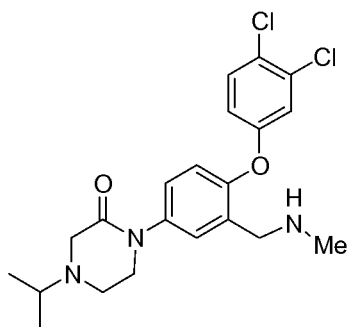
Example 48: 1-[3-Methylaminomethyl-4-(4-methylsulfonyl-phenoxy)-phenyl]-piperazin-2-one.

MS (ESI): mass calcd. for $C_{19}H_{23}N_3O_2S$, 357.15; m/z found, 358.4
 [M+H]⁺. ¹H NMR (CDCl₃): 7.42-7.38 (m, 1H), 7.28-7.24 (m, 2H), 7.134 (dd, J =
 5 8.6, 2.6, 1H), 6.96-6.92 (m, 2H), 6.85-6.82 (m, 1H), 3.91-3.79 (m, 2H), 3.72-
 3.64 (m, 4H), 3.24-3.18 (m, 2H), 2.47 (s, 6H).



Example 49: 4-Isopropyl-1-[3-methylaminomethyl-4-(4-methylsulfonyl-phenoxy)-phenyl]-piperazin-2-one.

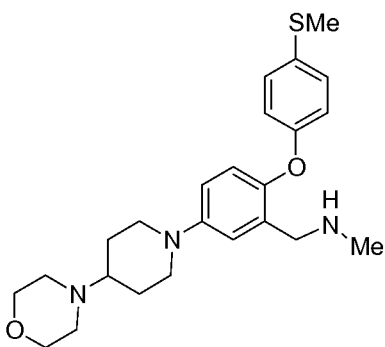
10 MS (ESI): mass calcd. for $C_{22}H_{29}N_3O_2S$, 399.20; m/z found, 400.2
 [M+H]⁺. ¹H NMR (CDCl₃): 7.36 (d, J = 2.6, 1H), 7.24 (d, J = 8.8, 2H), 7.13 (dd,
 J = 8.6, 2.6, 1H), 6.92 (d, J = 8.8, 2H), 6.81 (d, J = 8.7, 1H), 3.84 (s, 2H), 3.67-
 3.63 (m, 2H), 3.63-3.58 (m, 1H), 3.36 (s, 2H), 2.84-2.80 (m, 2H), 2.80-2.73 (m,
 1H), 2.46 (s, 6H), 1.09 (d, J = 6.5, 6H).



15

Example 50: 1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-4-isopropyl-piperazin-2-one.

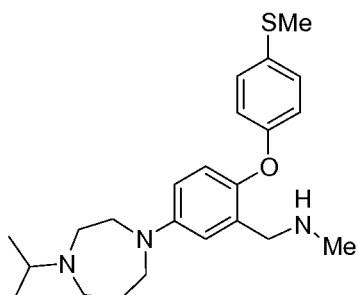
MS (ESI): mass calcd. for $C_{21}H_{25}Cl_2N_3O_2$, 421.13; m/z found, 422.3
 [M+H]⁺. ¹H NMR (CDCl₃): 7.41 (d, J = 2.6, 1H), 7.37 (d, J = 8.8, 1H), 7.20 (dd,
 20 J = 8.6, 2.6, 1H), 7.09 (d, J = 2.8, 1H), 6.90 (d, J = 8.6, 1H), 6.84 (dd, J = 8.8,
 2.8, 1H), 3.75 (s, 2H), 3.71-3.68 (m, 2H), 3.40 (s, 2H), 2.87-2.84 (m, 2H), 2.82-
 2.75 (m, 1H), 2.45 (s, 3H), 1.11 (d, J = 6.5, 6H).



Example 51: Methyl-[2-(4-methylsulfonyl-phenoxy)-5-(4-morpholin-4-yl-piperidin-1-yl)-benzyl]-amine.

MS (ESI): mass calcd. for $C_{24}H_{33}N_3O_2S$, 427.23; m/z found, 428.4

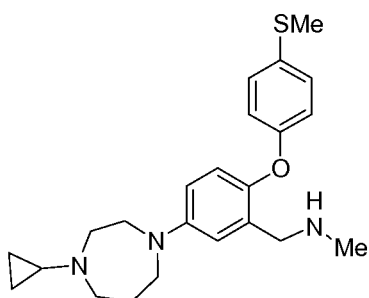
- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.23 (d, J = 8.8, 2H), 7.02 (d, J = 2.3, 1H), 6.84 (d, J = 8.8, 2H), 6.83-6.81 (m, 2H), 3.80 (s, 2H), 3.76-3.72 (m, 4H), 3.70-3.65 (m, 2H), 2.70 (td, J = 12.1, 2.1, 2H), 2.60-2.56 (m, 4H), 2.46 (s, 6H), 2.33-2.26 (m, 1H), 1.97-1.91 (m, 2H), 1.69-1.58 (m, 2H).



- 10 Example 52: [5-(4-isopropyl-[1,4]diazepan-1-yl)-2-(4-methylsulfonyl-phenoxy)-benzyl]-methyl-amine.

MS (ESI): mass calcd. for $C_{23}H_{33}N_3OS$, 399.23; m/z found, 400.4

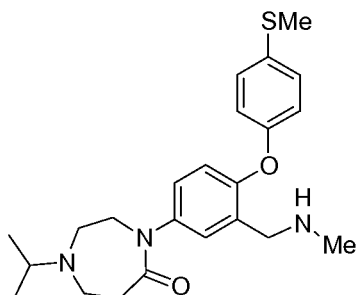
- 15 $[M+H]^+$. 1H NMR (MeOD): 7.37 (s, 1H), 7.32 (d, J = 8.6, 2H), 7.17-7.12 (m, 1H), 7.00 (d, J = 8.7, 2H), 6.92 (d, J = 9.0, 1H), 4.25 (s, 2H), 4.02-3.96 (m, 2H), 3.78-3.65 (m, 4H), 3.64-3.52 (m, 2H), 3.36-3.32 (m, 1H), 2.77 (s, 3H), 2.47 (s, 3H), 2.46-2.38 (m, 2H), 1.43 (d, J = 6.5, 6H).



Example 53: [5-(4-Cyclopropyl-[1,4]diazepan-1-yl)-2-(4-methylsulfonyl-phenoxy)-benzyl]-methyl-amine.

MS (ESI): mass calcd. for $C_{23}H_{31}N_3O_5$, 397.22; m/z found, 398.3 $[M+H]^+$.

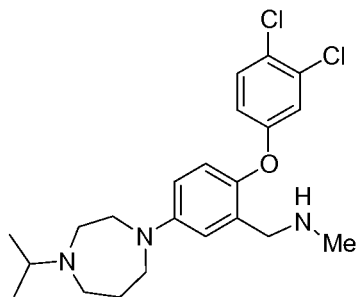
1H NMR ($CDCl_3$): 7.23 (d, J = 8.8, 2H), 6.90 (d, J = 2.9, 1H), 6.85 (d, J = 8.8, 2H), 6.82 (d, J = 9.0, 1H), 6.62 (dd, J = 9.0, 3.0, 1H), 4.06 (s, 2H), 3.65-3.60 (m, 2H), 3.42 (t, J = 6.2, 2H), 3.36-3.27 (m, 2H), 3.23-3.14 (m, 2H), 2.62 (s, 3H), 2.46 (s, 3H), 2.30-2.23 (m, 1H), 2.22-2.14 (m, 2H), 1.03-0.93 (m, 2H), 0.74-0.68 (m, 2H).



10 Example 54: 1-Isopropyl-4-[3-methylaminomethyl-4-(4-methylsulfonyl-phenoxy)-phenyl]-[1,4]diazepan-5-one.

MS (ESI): mass calcd. for $C_{23}H_{31}N_3O_2S$, 413.21; m/z found, 414.4

$[M+H]^+$. 1H NMR ($CDCl_3$): 7.35-7.30 (m, 1H), 7.28-7.24 (m, 2H), 7.08-7.03 (m, 1H), 7.00-6.96 (m, 1H), 6.94-6.91 (m, 1H), 6.85 (t, J = 8.2, 1H), 3.84-3.80 (m, 2H), 3.78 (d, J = 4.0, 2H), 2.99-2.91 (m, 1H), 2.85-2.76 (m, 6H), 2.45 (s, 3H), 2.00-1.90 (m, 3H), 1.06 (d, J = 6.6, 6H).

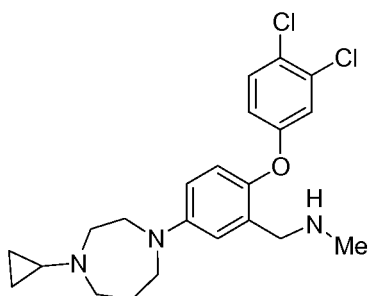


20 Example 55: [2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-[1,4]diazepan-1-yl)-benzyl]-methyl-amine.

MS (ESI): mass calcd. for $C_{22}H_{29}Cl_2N_3O$, 421.17; m/z found, 422.2

$[M+H]^+$. 1H NMR ($CDCl_3$): 7.30 (d, J = 8.9, 1H), 6.95 (d, J = 2.8, 1H), 6.82 (d, J = 8.9, 1H), 6.74 (dd, J = 8.9, 2.9, 1H), 6.73-6.71 (m, 1H), 6.58 (dd, J = 8.9, 3.1, 1H), 3.62 (s, 2H), 3.58-3.54 (m, 2H), 3.52 (t, J = 6.2, 2H), 3.03-2.95 (m, 1H),

2.83-2.80 (m, 2H), 2.66-2.62 (m, 2H), 2.41 (s, 3H), 2.00-1.94 (m, 2H), 1.04 (d, J = 6.6, 6H).

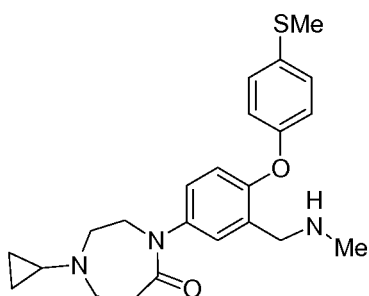


Example 56: [5-(4-Cyclopropyl-[1,4]diazepan-1-yl)-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine.

5

MS (ESI): mass calcd. for $C_{22}H_{27}Cl_2N_3O$, 419.15; m/z found, 420.8 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.30 (d, J = 8.9, 1H), 6.95 (d, J = 2.8, 1H), 6.83 (d, J = 8.9, 1H), 6.74 (dd, J = 8.9, 2.8, 1H), 6.72 (d, J = 3.1, 1H), 6.78 (dd, J = 8.9, 1H), 3.61 (s, 2H), 3.54-3.47 (m, 4H), 2.96-2.92 (m, 2H), 2.82-2.78 (m, 2H), 2.41 (s, 3H), 1.98-1.92 (m, 2H), 1.87-1.82 (m, 2H), 0.49-0.44 (m, 2H), 0.43-0.38 (m, 2H).

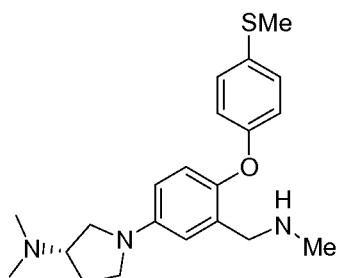
10



Example 57: 1-Cyclopropyl-4-[3-methylaminomethyl-4-(4-methylsulfonylphenoxy)phenyl]-[1,4]diazepan-5-one.

15

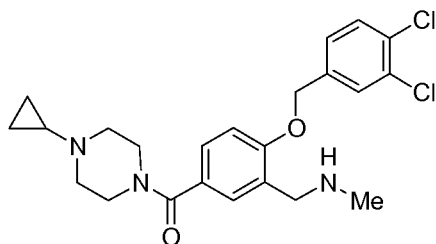
MS (ESI): mass calcd. for $C_{23}H_{29}N_3O_2S$, 411.20; m/z found, 412.8 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.27-7.24 (m, 3H), 7.05 (dd, J = 8.6, 2.6, 1H), 6.92 (d, J = 8.8, 2H), 6.83 (d, J = 8.6, 1H), 3.79-3.75 (m, 4H), 2.94-2.90 (m, 4H), 2.81-2.77 (m, 2H), 2.48 (s, 3H), 2.46 (s, 3H), 1.80-1.76 (m, 1H), 0.56-0.51 (m, 2H), 0.47-0.43 (m, 2H).



Example 58: (S)-Dimethyl-{1-[3-methylaminomethyl-4-(4-methylsulfonylphenoxy)-phenyl]-pyrrolidin-3-yl}-amine.

MS (ESI): mass calcd. for $C_{21}H_{29}N_3OS$, 371.20; m/z found, 372.7

- 5 $[M+H]^+$. 1H NMR ($CDCl_3$): 7.21 (d, $J = 8.9$, 2H), 6.86 (d, $J = 8.7$, 1H), 6.81 (d, $J = 8.8$, 2H), 6.57 (d, $J = 2.9$, 1H), 6.43 (dd, $J = 8.8$, 3.0, 1H), 3.66 (s, 2H), 3.53-3.48 (m, 1H), 3.45 (td, $J = 9.0$, 2.1, 1H), 3.37-3.30 (m, 1H), 3.17 (t, $J = 8.4$, 1H), 2.88-2.80 (m, 1H), 2.45 (s, 3H), 2.40 (s, 3H), 2.32 (s, 6H), 2.25-2.19 (m, 1H), 1.97-1.88 (m, 1H).



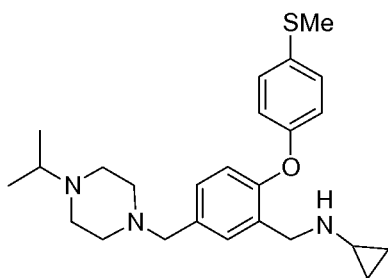
10

Example 59: (4-Cyclopropyl-piperazin-1-yl)-[4-(3,4-dichlorobenzoyloxy)-3-methylaminomethyl-phenyl]-methanone.

Step A: [5-Bromo-2-(3,4-dichlorobenzoyloxy)-benzyl]-methyl-carbamic acid tert-butyl ester. A mixture of (5-bromo-2-hydroxy-benzyl)-methyl-carbamic acid tert-butyl ester (1.0 g, 3.2 mmol), K_2CO_3 (655 mg, 4.74 mmol), and 4-bromomethyl-1,2-dichloro-benzene (1.14 g, 4.74 mmol) in CH_3CN (6.3 mL) was heated at 90 °C overnight. The mixture was then cooled to rt, diluted with EtOAc and water, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification by

15
20 FCC (EtOAc/hexanes) gave the desired product (1.49 g, 99%). 1H NMR ($CDCl_3$, mixture of rotamers): 7.49 (d, $J = 1.9$, 1H), 7.46 (d, $J = 7.8$, 1H), 7.31 (dd, $J = 8.7$, 2.0, 1H), 7.28-7.22 (m, 2H), 6.73 (d, $J = 8.6$, 1H), 5.00 (s, 2H), 4.52-4.38 (m, 2H), 2.90-2.80 (m, 3H), 1.52-1.39 (m, 9H).

Step B. The title compound was prepared in an analogous fashion to Example 1, Steps D-E. MS (ESI): mass calcd. for C₂₃H₂₇Cl₂N₃O₂, 447.15; m/z found, 448.3 [M+H]⁺. ¹H NMR (CDCl₃): 7.51 (d, J = 1.8, 1H), 7.45 (d, J = 8.2, 1H), 7.36 (d, J = 2.0, 1H), 7.29 (dd, J = 8.3, 2.1, 1H), 7.24 (dd, J = 8.3, 1.9, 1H),
 5 6.85 (d, J = 8.4, 1H), 5.06 (s, 2H), 3.81 (s, 2H), 3.75-3.32 (m, 4H), 2.72-2.48 (m, 4H), 2.44 (s, 3H), 2.21 (br s, 1H), 1.64-1.58 (m, 1H), 0.47-0.43 (m, 2H), 0.42-0.39 (m, 2H).



Example 60: Cyclopropyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine.

Step A: 2-(5-Bromo-2-fluoro-phenyl)-[1,3]dioxolane. A mixture of 5-bromo-2-fluoro-benzaldehyde (24.92 g, 123.2 mmol), ethylene glycol (21.0 mL, 369.6 mmol), toluene (650 mL), and TsOH (2.49 g, 12.4 mmol) were heated at reflux under a N₂ atmosphere in a flask fitted with a Dean Stark trap and
 15 condenser. After 18 h, the mixture was cooled to rt, washed with a satd. aq. NaHCO₃ and brine, dried (MgSO₄), and concentrated. Purification by FCC (EtOAc/hexanes) gave the desired product (28.74 g, 95%) as an oil. ¹H NMR (CDCl₃): 7.68-7.63 (m, 1H), 7.45-7.39 (m, 1H), 6.98-6.91 (m, 1H), 6.05-6.00 (m, 1H), 4.12 (br s, 2H), 4.02 (br s, 2H).

Step B: 3-[1,3]Dioxolan-2-yl-4-fluoro-benzaldehyde. To a -78 °C solution of 2-(5-bromo-2-fluoro-phenyl)-[1,3]dioxolane (1.024 g, 4.047 mmol) in THF (40 mL) was added 2.5 M *n*-BuLi (1.80 mL, 4.45 mmol). After 20 min, the reaction was quenched with DMF (1.60 mL). After stirring for 1 h, the mixture was diluted with DCM, washed with a satd. aq. NaHCO₃, dried (MgSO₄), and
 25 concentrated. Purification by FCC (EtOAc/hexanes) gave the desired product (406.5 mg, 87%) as a white solid. ¹H NMR (acetone-d₆): 10.05 (s, 1H), 8.17-8.09 (m, 1H), 8.06-7.97 (m, 1H), 7.43-7.33 (m, 1H), 6.10-6.04 (m, 1H), 4.19-4.11 (m, 2H), 4.08-4.00 (m, 2H).

Step C: 1-(3-[1,3] Dioxolan-2-yl-4-fluoro-benzyl)-4-isopropyl-piperazine.

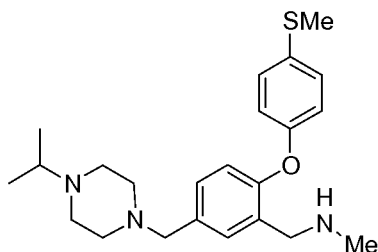
The title compound was prepared in an analogous fashion to Example 1, Step B, using NaBH(OAc)₃ instead of NaBH₄ (770.8 mg, 85%). MS (ESI): mass calcd. for C₁₇H₂₅FN₂O₂, 308.19; m/z found, 309.4 [M+H]⁺. ¹H NMR (CDCl₃):
5 7.45 (dd, J = 6.9, 1H), 7.34-7.30 (m, 1H), 7.03-6.98 (m, 1H), 6.06 (s, 1H), 4.18-4.15 (m, 2H), 4.06-4.03 (m, 2H), 3.47 (s, 2H), 2.68-2.38 (m, 9H), 1.04 (d, J = 6.5, 6H).

Step D: 2-Fluoro-5-(4-isopropyl-piperazin-1-ylmethyl)-benzaldehyde. A mixture of 1-(3-[1,3] dioxolan-2-yl-4-fluoro-benzyl)-4-isopropyl-piperazine
10 (695.2 mg, 2.25 mmol) and 6 N HCl (25 mL) was stirred at rt for 50 min, then was diluted with DCM (250 mL), and quenched slowly with 1 N NaOH. The organic layer was separated, dried (Na₂SO₄), and concentrated to give the desired product (573.5 mg, 96%). MS (ESI): mass calcd. for C₁₅H₂₁FN₂O, 264.16; m/z found, 265.3 [M+H]⁺. ¹H NMR (MeOD): 10.29 (s, 1H), 7.82-7.81
15 (m, 1H), 7.68-7.66 (m, 1H), 7.58-7.56 (m, 1H), 7.31-7.28 (m, 1H), 7.26-7.04 (m, 1H), 7.03-7.01 (t, J = 8.4, 1H), 3.55 (s, 1H), 3.50 (s, 1H), 2.64-2.40 (br m, 9H), 1.07-1.06 (m, 6H).

Step E: 5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzaldehyde. A mixture of 2-fluoro-5-(4-isopropyl-piperazin-1-ylmethyl)-benzaldehyde (513.7 mg, 1.943 mmol), 4-methylsulfanyl-phenol
20 (326.8 mg, 2.138 mmol), and K₂CO₃ (845.2 mg, 5.829 mmol) in DMF (9.0 mL) was heated at 90 °C for 3 days. After cooling to rt, the mixture was diluted with Et₂O, washed with 1 N NaOH and brine, dried (Na₂SO₄), and concentrated. Purification by FCC followed by reverse phase chromatography gave the
25 desired product (804.5 mg, >100%). MS (ESI): mass calcd. for C₂₂H₂₈N₂O₂S, 384.19; m/z found, 385.3 [M+H]⁺.

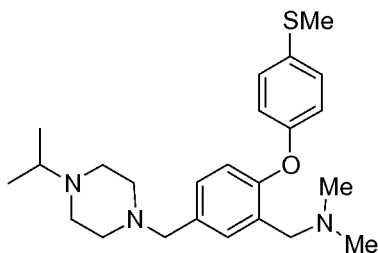
Step F. The title compound was prepared in an analogous fashion to Example 1, Step B, using NaB(OAc)₃H, to give the desired product. MS (ESI): mass calcd. for C₂₅H₃₅N₃OS, 425.25; m/z found, 426.4 [M+H]⁺. ¹H NMR
30 (MeOD): 7.42-7.40 (m, 1H), 7.29 (d, J = 8.8, 2H), 7.23 (dd, J = 8.3, 2.1, 1H), 6.92 (d, J = 8.8, 2H), 6.84 (d, J = 8.3, 1H), 4.88 (s, 2H), 3.83 (s, 2H), 3.53 (s, 2H), 2.68-2.49 (m, 8H), 2.46 (s, 3H), 2.15-2.09 (m, 1H), 1.08 (d, J = 6.5, 6H), 0.46-0.42 (m, 2H), 0.38-0.34 (m, 2H).

The compounds in Examples 61-65 were prepared by a sequence similar to that described in Example 60.



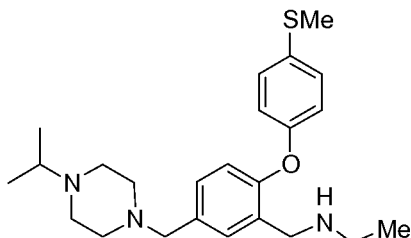
5 Example 61: [5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfonylphenoxy)-benzyl]-methyl-amine.

MS (ESI): mass calcd. for $C_{23}H_{33}N_3OS$, 399.23; m/z found, 400.40
 [M+H]⁺. ¹H NMR (MeOD): 7.40-7.38 (m, 1H), 7.30-7.28 (m, 2H), 7.24-7.22 (m, 1H), 6.93-6.91 (m, 2H), 6.82 (d, J = 8.0, 1H), 3.73 (s, 2H), 3.53 (s, 2H), 2.66-
 10 2.50 (m, 9H), 2.45 (s, 3H), 2.36 (s, 3H), 1.08 (d, J = 6.5, 6H).



15 Example 62: [5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfonylphenoxy)-benzyl]-dimethyl-amine.

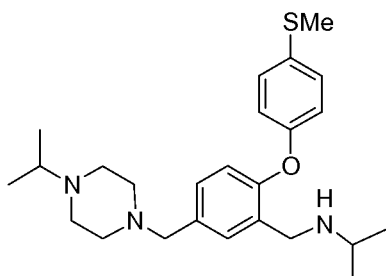
¹H NMR (MeOD): 7.41 (d, J = 2.0, 1H), 7.29-7.26 (m, 2H), 7.26-7.24 (m, 1H), 6.90-6.88 (m, 2H), 6.83 (d, J = 8.5, 1H), 3.54 (s, 4H), 2.74-2.48 (br m, 9H),
 2.45 (s, 3H), 2.27 (s, 6H), 1.08 (d, J = 6.5, 6H).



20 Example 63: Ethyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfonylphenoxy)-benzyl]-amine.

MS (ESI): mass calcd. for $C_{24}H_{35}N_3OS$, 413.25; m/z found, 414.4
 [M+H]⁺. ¹H NMR (MeOD): 7.42-7.39 (m, 1H), 7.30 (d, J = 8.8, 2H), 7.24 (dd, J

= 8.3, 2.1, 1H), 6.92 (d, J = 8.8, 2H), 6.84 (d, J = 8.3, 1H), 4.91 (s, 3H), 3.78 (s, 2H), 3.54 (s, 2H), 2.68-2.48 (m, 9H), 2.46 (s, 3H), 1.12-1.06 (m, 9H).



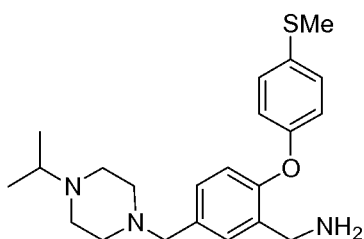
Example 64: Isopropyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine.

5

MS (ESI): mass calcd. for C₂₅H₃₇N₃OS, 427.27; m/z found, 428.4

[M+H]⁺. ¹H NMR (MeOD): 7.44 (d, J = 2.0, 1H), 7.29 (d, J = 8.7, 2H), 7.23 (dd, J = 8.3, 2.1, 1H), 6.91 (d, J = 8.9, 2H), 6.84 (d, J = 8.3, 1H), 4.90 (s, 3H), 3.77 (s, 2H), 3.53 (s, 2H), 2.80-2.73 (m, 1H), 2.72-2.47 (m, 7H), 2.45 (s, 3H), 1.08

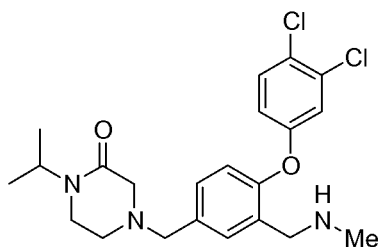
10 (d, J = 6.5, 6H), 1.05 (d, J = 6.3, 6H).



Example 65: 5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzylamine.

MS (ESI): mass calcd. for C₂₂H₃₁N₃OS, 385.22; m/z found, 386.4

15 [M+H]⁺. ¹H NMR (MeOD): 7.43-7.39 (m, 1H), 7.27 (d, J = 8.8, 2H), 7.20 (dd, J = 8.3, 2.0, 1H), 6.91 (d, J = 8.8, 2H), 6.80 (d, J = 8.2, 1H), 4.95-4.86 (m, 2H), 3.80 (s, 2H), 3.52 (s, 2H), 2.74-2.47 (m, 7H), 2.45 (s, 3H), 1.08 (d, J = 6.5, 6H).



Example 66: 4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-1-isopropyl-piperazin-2-one.

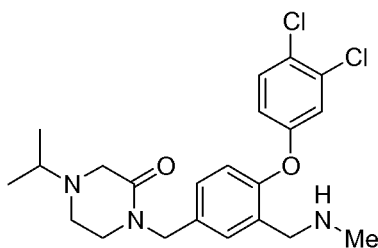
20

Step A: [2-(3,4-Dichloro-phenoxy)-5-formyl-benzyl]-methyl-carbamic acid tert-butyl ester. The title compound was prepared from [5-bromo-2-(3,4-dichloro-phenoxy) benzyl] methyl carbamic acid tert-butyl ester (Example 1, Steps A-C) in analogous fashion to Example 60, Step B.

5 Step B: [2-(3,4-Dichloro-phenoxy)-5-(3-oxo-piperazin-1-ylmethyl)-benzyl]-methyl-carbamic acid tert-butyl ester. The title compound was prepared in analogous fashion to Example 60, Step C.

Step C: [2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-3-oxo-piperazin-1-ylmethyl)-benzyl]-methyl-carbamic acid tert-butyl ester. To a solution of [2-(3,4-dichloro-phenoxy)-5-(3-oxo-piperazin-1-ylmethyl)-benzyl]-methyl-carbamic acid tert-butyl ester 79 mg, 0.16 mmol) in DMF (3.2 mL) at 0 °C was added NaH (90%, 7.6 mg). After 30 min, 2-bromopropane (15 μ L, 0.16 mmol) was added and the reaction was allowed to come to rt and stir overnight. The mixture was quenched with satd. aq. NaHCO₃ and extracted with DCM. The combined
10 organic layers were dried (Na₂SO₄) and concentrated. The crude product was purified by FCC to provide the title compound (35 mg, 41%). MS (ESI): mass calcd. for C₂₇H₃₅Cl₂N₃O₄, 535.20; m/z found, 536.2 [M+H].

Step D. The title compound was prepared in an analogous fashion to Example 1, Step E. MS (ESI): mass calcd. for C₂₂H₂₇Cl₂N₃O₂, 435.15; m/z
20 found, 436.1 [M+H]⁺.



Example 67: 1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-4-isopropyl-piperazin-2-one.

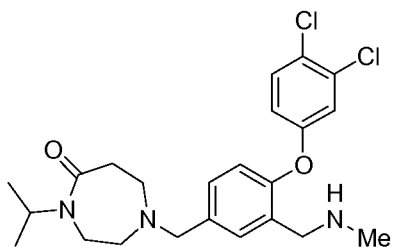
25 Step A: [2-(3,4-Dichloro-phenoxy)-5-hydroxymethyl-benzyl]-methyl-carbamic acid tert-butyl ester. To a solution of [2-(3,4-dichloro-phenoxy)-5-formyl-benzyl]-methyl-carbamic acid tert-butyl ester (816 mg, 1.98 mmol) in MeOH (40 mL), was added NaBH₄ (75 mg, 1.98 mmol). After 24 h, the mixture was treated with 1 N NaOH, was stirred an additional 1 h, and then partially concentrated. The resulting aqueous mixture was extracted with DCM and the

combined organic layers were dried (Na_2SO_4) and concentrated. The crude material was carried forward without further purification (784 mg, 96%). MS (ESI): mass calcd. for $\text{C}_{20}\text{H}_{23}\text{Cl}_2\text{NO}_4$, 411.10; m/z found, 434.7 $[\text{M}+\text{Na}]^+$.

Step B: [5-Chloromethyl-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester. To a solution of 2-(3,4-dichloro-phenoxy)-5-hydroxymethyl-benzyl]-methyl-carbamic acid tert-butyl ester (248 mg, 0.61 mmol) in DCM was added K_2CO_3 (250 mg, 1.80 mmol). The mixture was cooled to 0 °C and SOCl_2 (85 μL , 1.2 mmol) was added. After 2 h, the solids were filtered off and the filtrate was concentrated. Purification by FCC gave the
5
10 desired product (241 mg, 93%). MS (ESI): mass calcd. for $\text{C}_{20}\text{H}_{22}\text{Cl}_3\text{NO}_3$, 429.07; m/z found, 330.6 $[\text{M}+\text{H}-\text{Boc}]^+$.

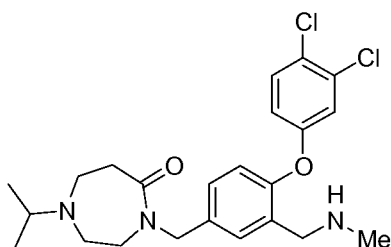
Step C: [2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-2-oxo-piperazin-1-ylmethyl)-benzyl]-methyl-carbamic acid tert-butyl ester. To a solution of 4-isopropyl-piperazin-2-one (32 mg, 0.22 mmol) in DMF (2.2 mL) at 0 °C was
15 added NaH (90%, 11 mg). After 30 min, a solution of [5-chloromethyl-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester (96 mg, 0.22 mmol) in DMF (2.2 mL) was added and the reaction was allowed to come to rt and stir overnight. The mixture was quenched with satd. aq. NaHCO_3 and extracted with DCM. The combined organic layers were dried (Na_2SO_4) and
20 concentrated. The crude product was purified by FCC to provide the desired product (94 mg, 79%). MS (ESI): mass calcd. for $\text{C}_{27}\text{H}_{35}\text{Cl}_2\text{N}_3\text{O}_4$, 535.20; m/z found, 536.2 $[\text{M}+\text{H}]$.

Step D. The title compound was prepared in an analogous fashion to Example 1, Step E. MS (ESI): mass calcd. for $\text{C}_{22}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_2$, 435.15; m/z
25 found, 436.1 $[\text{M}+\text{H}]$.



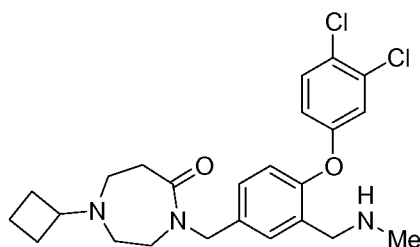
Example 68: 1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-4-isopropyl-[1,4]diazepan-5-one.

MS (ESI): mass calcd. for $C_{23}H_{29}Cl_2N_3O_2$, 449.16; m/z found, 450.1
 [M+H]⁺.



Example 69: 4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-1-
 5 isopropyl-[1,4]diazepan-5-one.

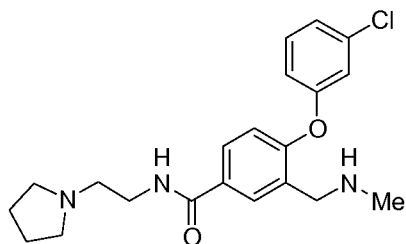
MS (ESI): mass calcd. for $C_{23}H_{29}Cl_2N_3O_2$, 449.16; m/z found, 450.2
 [M+H]⁺.



Example 70: 1-Cyclobutyl-4-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-
 10 benzyl]-[1,4]diazepan-5-one.

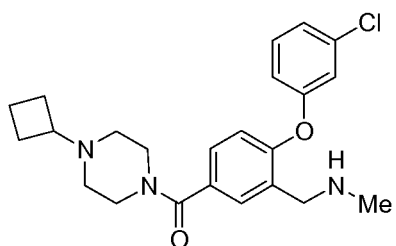
MS (ESI): mass calcd. for $C_{24}H_{29}Cl_2N_3O_2$, 461.16; m/z found, 462.1
 [M+H]⁺.

The compounds in Examples 71-88 were prepared using methods
 15 analogous to those described in the preceding examples.



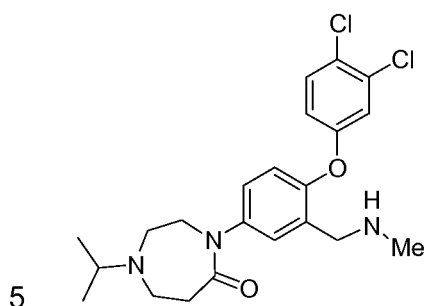
Example 71: 4-(3-Chloro-phenoxy)-3-methylaminomethyl-N-(2-pyrrolidin-1-yl-
 ethyl)-benzamide.

MS (ESI): m/z found, 388.7 [M+H]⁺.



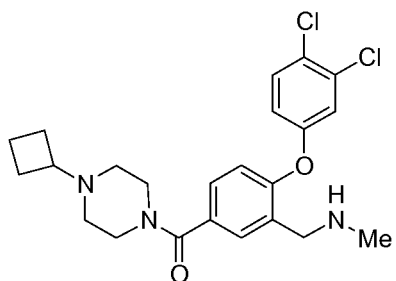
Example 72: [4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclobutyl-piperazin-1-yl)-methanone.

MS (ESI): m/z found, 414.8 [M+H]⁺.



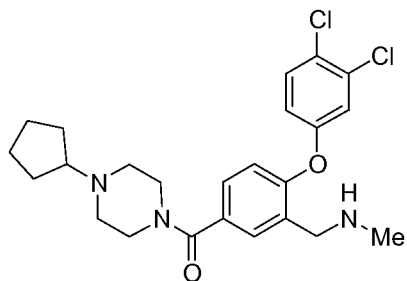
Example 73: 4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-1-isopropyl-[1,4]diazepan-5-one.

MS (ESI): m/z found, 436.8 [M+H]⁺.



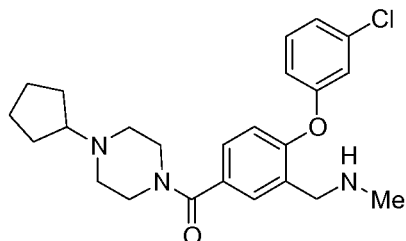
10 Example 74: (4-Cyclobutyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone.

MS (ESI): m/z found, 448.2 [M+H]⁺.



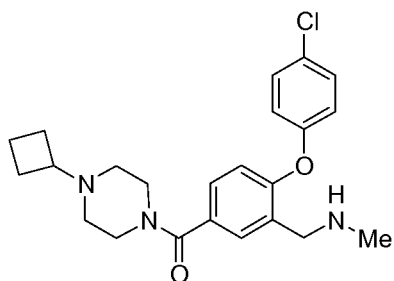
Example 75: (4-Cyclopentyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone.

MS (ESI): m/z found, 462.3 [M+H]⁺.



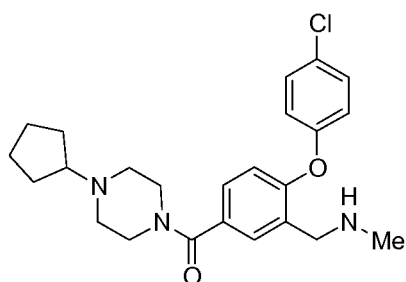
5 Example 76: [4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-[4-cyclobutyl-piperazin-1-yl]-methanone.

MS (ESI): m/z found, 428.4 [M+H]⁺.



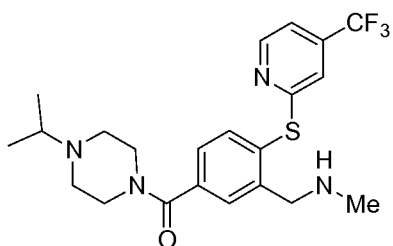
10 Example 77: [4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-[4-cyclobutyl-piperazin-1-yl]-methanone.

MS (ESI): m/z found, 414.3 [M+H]⁺.

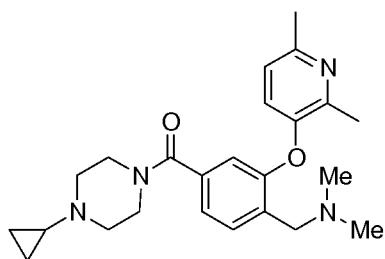


Example 78: [4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-[4-cyclopentyl-piperazin-1-yl]-methanone.

15 MS (ESI): m/z found, 428.4 [M+H]⁺.

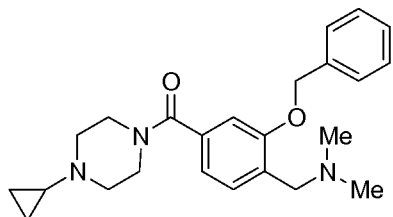


Example 79: (4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-trifluoromethyl-pyridin-2-ylsulfanyl)-phenyl]-methanone.



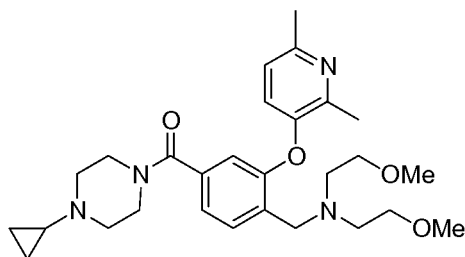
5 Example 80: (4-Cyclopropyl-piperazin-1-yl)-[4-dimethylaminomethyl-3-(2,6-dimethyl-pyridin-3-yloxy)-phenyl]-methanone.

MS (ESI): m/z found, 409.3 [M+H]⁺.



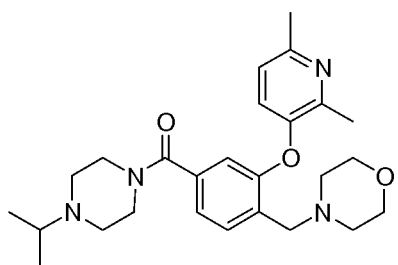
10 Example 81: (3-Benzoyloxy-4-dimethylaminomethyl-phenyl)-(4-cyclopropyl-piperazin-1-yl)-methanone.

MS (ESI): m/z found, 394.3 [M+H]⁺.



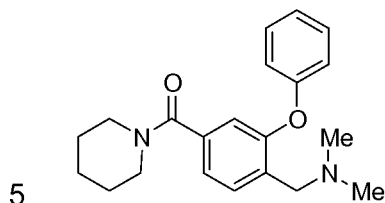
15 Example 82: [4-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-3-(2,6-dimethyl-pyridin-3-yloxy)-phenyl]-[4-(4-cyclopropyl-piperazin-1-yl)-methanone.

MS (ESI): m/z found, 497.3 [M+H]⁺.



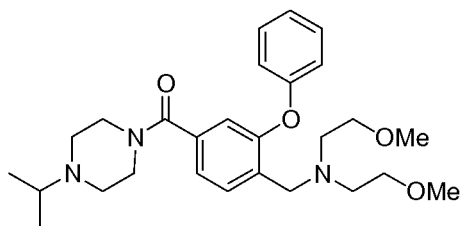
Example 83: [3-(2,6-Dimethyl-pyridin-3-yloxy)-4-morpholin-4-ylmethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone.

MS (ESI): m/z found, 453.3 [M+H]⁺.



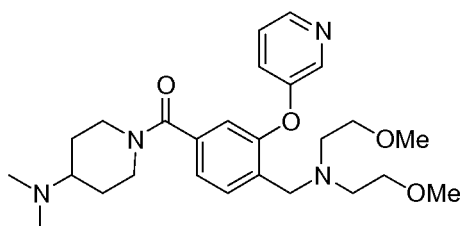
Example 84: (4-Dimethylaminomethyl-3-phenoxy-phenyl)-piperidin-1-yl-methanone.

MS (ESI): m/z found, 339.2 [M+H]⁺.



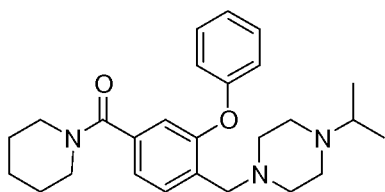
10 Example 85: (4-[[Bis-(2-methoxy-ethyl)-amino]-methyl]-3-phenoxy-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone.

MS (ESI): m/z found, 470.3 [M+H]⁺.



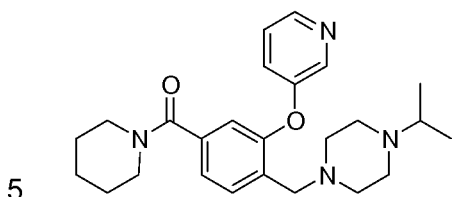
15 Example 86: [4-[[Bis-(2-methoxy-ethyl)-amino]-methyl]-3-(pyridin-3-yloxy)-phenyl]-(4-dimethylamino-piperidin-1-yl)-methanone.

MS (ESI): m/z found, 471.3 [M+H]⁺.



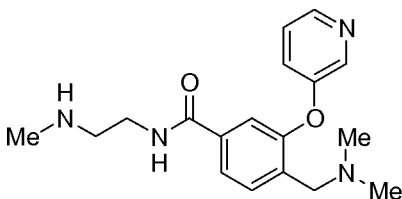
Example 87: [4-(4-Isopropyl-piperazin-1-ylmethyl)-3-phenoxy-phenyl]-piperidin-1-yl-methanone.

MS (ESI): m/z found, 422.3 [M+H]⁺.



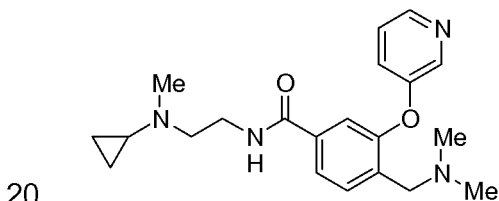
Example 88: [4-(4-Isopropyl-piperazin-1-ylmethyl)-3-(pyridin-3-yloxy)-phenyl]-piperidin-1-yl-methanone.

MS (ESI): m/z found, 423.3 [M+H]⁺.



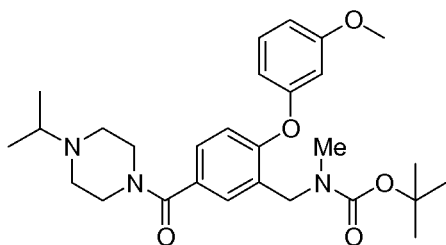
10 Example 89: 4-Dimethylaminomethyl-N-(2-methylamino-ethyl)-3-(pyridin-3-yloxy)-benzamide.

To a solution of {2-[4-dimethylaminomethyl-3-(pyridin-3-yloxy)-benzoylamino]-ethyl}-methyl-carbamic acid tert-butylester (250 mg, 0.58 mmol) in CH₂Cl₂ (3 mL) was added trifluoroacetic acid (1 mL). The reaction was allowed to stir at rt for 16 h and then concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (50 mL), washed with 1 M NaOH (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. FCC purification (MeOH/CH₂Cl₂) provided the desired product (0.13g, 68%) as a yellow oil. MS (ESI): m/z found, 329.2 [M+H]⁺.



Example 90: N-[2-(Cyclopropyl-methyl-amino)-ethyl]-4-dimethylaminomethyl-3-(pyridin-3-yloxy)-benzamide.

To a solution of 4-dimethylaminomethyl-N-(2-methylamino-ethyl)-3-(pyridin-3-yloxy)-benzamide (0.090g, 0.274 mmol) in a 1:1 mixture of
5 THF:MeOH (4 mL) was added [(1-ethoxycyclopropyl)-oxy]trimethylsilane (0.28 mL, 1.37 mmol), AcOH (0.08 mL, 1.37 mmol), and NaCNBH₃ (0.088g, 1.37 mmol). The reaction mixture was heated to 50° C for 24 h, cooled to rt and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (15 mL), washed with sat. NaHCO₃ (5 mL), dried (Na₂SO₄), and concentrated.
10 HPLC purification under basic conditions yielded the desired product (0.036g, 38%). MS (ESI): m/z found, 369.2 [M+H]⁺.



Example 91: [5-(4-Isopropyl-piperazine-1-carbonyl)-2-(3-methoxy-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester.

15 The title compound was prepared using methods analogous to those described in the preceding examples.

Biological Methods:

20 Compounds were tested as the free base, hydrochloride salt, TFA salt, or citric acid salt forms.

H₃ receptor binding

Binding of compounds to the cloned human and rat H₃ receptors, stably expressed in SK-N-MC cells, was performed as described by Barbier, A.J. et al. (Br. J. Pharmacol. 2004, 143(5), 649-661). Data for compounds tested in this
25 assay are presented in Table 1.

Rat brain SERT

A rat brain without cerebellum (Zivic Laboratories, Inc.—Pittsburgh, PA) was homogenized in a 52.6 mM Tris pH 8/126.4 mM NaCl/5.26 mM KCl mixture and centrifuged at 1,000 rpm for 5 min. The supernatant was removed

and re-centrifuged at 15,000 rpm for 30 min. Pellets were re-homogenized in a 52.6 mM Tris pH8/126.4 mM NaCl/5.26 mM KCl mixture. Membranes were incubated with 0.6 nM [³H]-Citalopram plus/minus test compounds for 60 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.

5 Nonspecific binding was defined in the presence of 100 μM fluoxetine. IC₅₀ values were determined by a single site curve-fitting program (GraphPad, San Diego, CA) and converted to K_i values based on a [³H]-Citalopram K_d of 0.6 nM and a ligand concentration of 0.6 nM. Data for compounds tested in this assay

10 are presented in Table 1. NT = not tested.

Table 1.

Ex.	Human H₃ K_i (nM)	Rat SERT K_i (nM)		Ex.	Human H₃ K_i (nM)	Rat SERT K_i (nM)
1	2.4	4.9		47	20	2
2	29	4.0		48	5500	0.4
3	2.2	1.8		49	400	2
4	4.3	5.8		50	150	7
5	23	9.3		51	28	2
6	1.1	18		52	8	1
7	1.1	8.2		53	28	6
8	0.8	90		54	3	0.5
9	1	160		55	27	10
10	33	260		56	25	16
11	14	113		57	37	4
12	8	230		58	300	6
13	15	102		59	70	4
14	37	16		60	2	3
15	22	2000		61	2	0.8
16	21	4.2		62	21	1
17	1.5	1500		63	0.9	6
18	11	9.7		64	0.5	7
19	14	40		65	4	18

20	59	190		66	2500	6
21	32	19		67	6	4
22	18	21		68	6300	7
23	50	3		69	110	4
24	31	130		70	19	5
25	7	0.9		71	6	2
26	100	3		72	4	65
27	48	0.8		73	7.7	12
28	150	NT		74	4	9
29	170	10000		75	20	11
30	3	4000		76	2	28
31	10	1000		77	2.4	10
32	26	6000		78	3.4	8.1
33	2	10000		79	28	3150
34	3	10000		80	140	500
35	7	10000		81	67	8000
36	4	28		82	200	NT
37	1	2		83	21	NT
38	4	130		84	4500	NT
39	15	17		85	12	NT
40	7	0.1		86	200	NT
41	210	0.4		87	280	NT
42	6	0.3		88	220	NT
43	110	0.7		89	1900	NT
44	160	0.5		90	45	NT
45	76	1		91	58	NT
46	49	4				

Human SERT

Homogenized HEK293 (Human Embryonic Kidney) membranes expressing the human SERT were incubated with ³H-citalopram (SERT) at rt
5 for 1 h in 50 mM Tris, 120 mM NaCl, 5 mM KCl (pH 7.4). Nonspecific binding

was determined in the presence of 10 μ M fluoxetine for the SERT. The membranes were washed and the radioactivity was counted as above. Calculations for K_i at the SERT were based on a K_d value for 3 H-citalopram and a ligand concentration of 3.1 nM. Data for compounds tested in this assay are presented in Table 2.

Table 2.

Ex.	Human SERT K_i (nM)		Ex.	Human SERT K_i (nM)
1	6.3		13	363
2	5.0		14	37
3	5.9		16	11
4	8.1		17	2000
5	6.8		18	23
6	28		73	16
7	24		75	15
9	420		77	39
11	155		78	24
12	380			

Cyclic AMP accumulation

Sublines of SK-N-MC cells were created that expressed a reporter construct and the human H_3 receptor. The reporter gene (β -galactosidase) is under the control of multiple cyclic AMP responsive elements. In 96-well plates, histamine was added directly to the cell media followed 5 min later by an addition of forskolin (5 μ M final concentration). When appropriate, antagonists were added 10 min prior to agonist addition. After a 6-h incubation at 37 $^{\circ}$ C, the media was aspirated and the cells washed with 200 μ L of phosphate-buffered saline followed by a second aspiration. Cells were lysed with 25 μ L 0.1 x assay buffer (10 mM Na-phosphate, pH 8, 0.2 mM $MgSO_4$, 0.01 mM $MnCl_2$) and incubated at rt for 10 min. Cells were then incubated for 10 min with 100 μ L of 1 x assay buffer containing 0.5% Triton and 40 mM β -mercaptoethanol. Color was developed using 25 μ L of 1 mg/mL substrate

solution (chlorophenolred β -D galactopyranoside; Roche Molecular Biochemicals, Indianapolis, IN). Color was quantitated on a microplate reader at absorbance 570 nm. The pA_2 values were calculated by Schild regression analysis of the pEC_{50} values and are presented for compounds tested in Table

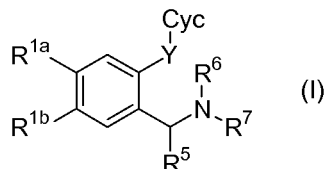
5 3.

Table 3.

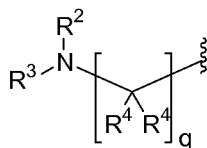
Ex.	pA_2		Ex.	pA_2
1	8.14		31	8.8
3	8.57		33	9.5
4	8.12		34	8.9
5	8.11		35	8.6
6	8.61		36	8.2
7	8.64		54	8.7
30	9.1		73	8.35

What is claimed is:

1. A compound of Formula (I):



- 5 wherein



one of R^{1a} and R^{1b} is

R² and R³ are each independently selected from the group consisting of: -H; a -C₁₋₆alkyl group unsubstituted or substituted with -OH, -OC₁₋₄alkyl, -NH₂, -N(R^a)R^b, or -F; -CO₂C₁₋₄alkyl; and a monocyclic cycloalkyl group

- 10 unsubstituted or substituted with -C₁₋₄alkyl, -OH, halo, or -CF₃;

where R^a and R^b are each independently -H, -C₁₋₆alkyl, or monocyclic cycloalkyl, or R^a and R^b taken together with their nitrogen of attachment form a monocyclic heterocycloalkyl group; provided that R² and R³ are not both H;

- 15 or, alternatively,

R² and R³ taken together with the nitrogen to which they are attached form a saturated monocyclic heterocycloalkyl group unsubstituted or substituted on a carbon ring member with one, two, or three R^d moieties and substituted on a nitrogen ring member with an R^e moiety;

- 20 where each R^d moiety is independently selected from the group consisting of: -C₁₋₆alkyl; -C₁₋₄alkyl-OH; halo; -OH; -OC₁₋₆alkyl; ipso-substituted -OC₂₋₃alkylO-; -CN; -NO₂; -N(R^g)R^h; -C(O)N(R^g)R^h; -N(R^g)SO₂C₁₋₆alkyl; -C(O)C₁₋₆alkyl; -S(O)₀₋₂-C₁₋₆alkyl; -SO₂N(R^g)R^h; -SCF₃; -CF₃; -OCF₃; -CO₂H; and -CO₂C₁₋₆alkyl;

- 25 where R^g and R^h are each independently -H or -C₁₋₆alkyl, or R^g and R^h taken together with their nitrogen of attachment form a monocyclic heterocycloalkyl group; and

where R^e is selected from the group consisting of: -H; a -C₁₋₆alkyl or
 -C(O)C₁₋₆alkyl group unsubstituted or substituted with halo, -CN, -OH,
 -OC₁₋₄alkyl, or -CF₃; -C(O)CF₃; -S(O)₀₋₂-C₁₋₆alkyl; -CO₂C₁₋₆alkyl; and a
 phenyl, monocyclic carbon-linked heteroaryl, monocyclic cycloalkyl, or
 5 monocyclic carbon-linked heterocycloalkyl group, each unsubstituted or
 substituted with -C₁₋₄alkyl, halo, -CN, -OH, -OC₁₋₄alkyl, or -CF₃;

q is 0 or 1;

each R⁴ is independently -H or methyl, or both R⁴ substituents taken together
 form a carbonyl;

10 Y is -O-, -OCH₂-, -S-, -SO-, or -SO₂-;

R⁵ is -H or -C₁₋₆alkyl;

R⁶ is -H; or -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, monocyclic cycloalkyl, or
 -C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with -C₁₋₄
 4alkyl, -OH, -OC₁₋₄alkyl, halo, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN,
 15 -CO₂H, or -CO₂C₁₋₄alkyl;

R⁷ is -H; or -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, monocyclic cycloalkyl, or
 -C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with -C₁₋₄
 4alkyl, -OH, -OC₁₋₄alkyl, halo, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN,
 -CO₂H, or -CO₂C₁₋₄alkyl;

20 or R⁶ and R⁷ taken together with their nitrogen of attachment form a saturated
 monocyclic heterocycloalkyl group unsubstituted or substituted with -C₁₋₄
 4alkyl, -OC₁₋₄alkyl, or halo; and

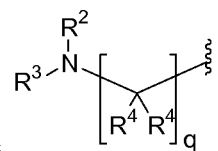
Cyc is a phenyl or monocyclic carbon-linked heteroaryl group, unsubstituted or
 substituted with one, two, or three R^k moieties;

25 where each R^k moiety is independently selected from the group consisting
 of: -C₁₋₆alkyl, -CHF₂, -CF₃, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -OH, -OC₁₋₆alkyl,
 -OCHF₂, -OCF₃, -OC₃₋₆alkenyl, -OC₃₋₆alkynyl, -CN, -NO₂, -N(R^l)R^m,
 -N(R^l)C(O)R^m, -N(R^l)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -S(O)₀₋₂-C₁₋₆alkyl,
 -C(O)N(R^l)R^m, -SO₂N(R^l)R^m, -SCF₃, halo, -CO₂H, and -CO₂C₁₋₆alkyl; or
 30 two R^k moieties on adjacent carbon atoms of attachment together are
 -OC₁₋₄alkyleneO- to form a cyclic ring which is unsubstituted or
 substituted with one or two fluoro substituents;

where R^l and R^m are each independently -H or -C₁₋₆alkyl;

provided that when both R⁴ substituents taken together form a carbonyl, then R² and R³ taken together are not diazepanyl; or a pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, or a pharmaceutically active metabolite thereof.

5



2. A compound as defined in claim 1, wherein R^{1b} is

3. A compound as defined in claim 1, wherein R² and R³ are each independently -H; or methyl, ethyl, propyl, isopropyl, sec-butyl, 2-methylpropyl, cyclopropyl, cyclobutyl, or cyclopentyl, each unsubstituted or substituted as previously described.

4. A compound as defined in claim 1, wherein R² and R³ are each independently -H, methyl, ethyl, propyl, isopropyl, sec-butyl, 2-hydroxyethyl, 2-methoxyethyl, 2-methylaminoethyl, 2-dimethylaminoethyl, 2-(cyclopropylmethyl-amino)-ethyl, 2-pyrrolidin-1-yl-ethyl, 2-hydroxy-2-methylpropyl, 3-dimethylaminopropyl, cyclopropyl, cyclobutyl, or cyclopentyl.

5. A compound as defined in claim 1, wherein R² and R³ are each independently -H, methyl, cyclopropyl, dimethylaminoethyl, or dimethylaminopropyl.

6. A compound as defined in claim 1, wherein R^a and R^b are each independently -H, methyl, or cyclopropyl, or R^a and R^b taken together form pyrrolidinyl.

7. A compound as defined in claim 1, wherein R² and R³ taken together with the nitrogen to which they are attached form azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-1λ⁶-thiomorpholin-4-yl, homopiperidinyl, diazepanyl, piperazinonyl, or diazapanonyl, each unsubstituted or substituted as previously described.

8. A compound as defined in claim 1, wherein R² and R³ taken together with the nitrogen to which they are attached form azetidiny, 3,3-difluoroazetidiny, pyrrolidiny, 2-methylpyrrolidiny, 3-hydroxypyrrolidiny, 3,3-dimethylaminopyrrolidiny, 2,5-dimethylpyrrolidiny, 2-trifluoromethylpyrrolidiny, 2-hydroxymethylpyrrolidiny, 3,3-difluoropyrrolidiny, piperidiny, 3,3-difluoropiperidiny, 4-fluoropiperidiny, 3,3-difluoropiperidiny, 4,4-difluoropiperidiny, 3-trifluoromethylpiperidiny, 4-trifluoromethylpiperidiny, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, 4-cyanopiperidiny, 4-carboethoxypiperidiny, 3-hydroxypiperidiny, 4-hydroxypiperidiny, 2-hydroxymethylpiperidiny, 3-hydroxymethylpiperidiny, 4-hydroxymethylpiperidiny, 3-hydroxyethylpiperidiny, 4-hydroxyethylpiperidiny, 4-dimethylaminopiperidiny, 4-morpholin-4-yl-piperidin-1-yl, morpholinyl, 2-methylmorpholin-4-yl, 3-methylmorpholin-4-yl, 2,6-dimethylmorpholin-4-yl, 3-hydroxymethylmorpholin-4-yl, 2-hydroxymethylmorpholin-4-yl, piperazinyl, 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl, 4-(2-fluoroethyl)-piperazin-1-yl, 4-isopropyl-piperazin-1-yl, 4-cyclopropyl-piperazin-1-yl, 4-cyclobutyl-piperazin-1-yl, 4-cyclopentyl-piperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(2-methoxyethyl)-piperazin-1-yl, 4-(tert-butoxycarbonyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-(2-hydroxyphenyl)piperazinyl, 4-(4-trifluoromethyl-phenyl)-piperazin-1-yl, 4-thiazol-2-yl-piperazin-1-yl, 4-(2-thiophenyl)piperazinyl, 4-pyridin-4-yl-piperazin-1-yl, 4-acetyl-piperazin-1-yl, 4-isobutyryl-piperazin-1-yl, 4-piperazin-2-onyl, 1-isopropyl-4-piperazin-2-onyl, 4-isopropyl-1-piperazin-2-onyl, 1-cyclopropyl-4-piperazin-2-onyl, thiomorpholinyl, 1,1-dioxo-1λ⁶-thiomorpholin-4-yl, 4-isopropyl-[1,4]diazepan-1-yl, 4-cyclopropyl-[1,4]diazepan-1-yl, 1-cyclobutyl-4-diazepan-5-onyl, 4-isopropyl-1-diazepan-5-onyl, 1-isopropyl-4-diazepan-5-onyl, or 1-cyclopropyl-4-diazepan-5-onyl.

9. A compound as defined in claim 1, wherein R² and R³ taken together with the nitrogen to which they are attached form pyrrolidiny, 3,3-dimethylaminopyrrolidiny, piperidiny, 4-fluoropiperidiny, 4-dimethylaminopiperidiny, 4-morpholin-4-yl-piperidin-1-yl, morpholinyl, thiomorpholinyl, piperazinyl, 4-methyl-piperazin-1-yl, 4-isopropyl-piperazin-1-yl,

4-(2-fluoroethyl)-piperazin-1-yl, 4-cyclopropyl-piperazin-1-yl, 4-cyclobutyl-piperazin-1-yl, 4-cyclopentyl-piperazin-1-yl, 4-pyridin-4-yl-piperazin-1-yl, 4-piperazin-2-onyl, 1-isopropyl-4-piperazin-2-onyl, 4-isopropyl-[1,4]diazepan-1-yl, or 1-isopropyl-4-diazepan-5-onyl.

5

10. A compound as defined in claim 1, wherein each R^d moiety is independently selected from the group consisting of: methyl, ethyl, isopropyl, hydroxyethyl, fluoro, methoxy, dimethylamino, piperidinyl, morpholinyl, acetyl, trifluoromethyl, -CO₂H, and -CO₂-methyl.

10

11. A compound as defined in claim 1, wherein R^g and R^h are each independently -H, methyl, ethyl, or isopropyl, or R^g and R^h taken together with their nitrogen of attachment form pyrrolidinyl, piperidinyl, morpholinyl, or thiomorpholinyl.

15

12. A compound as defined in claim 1, wherein R^e is selected from the group consisting of: -H, methyl, ethyl, isopropyl, 2-fluoroethyl, hydroxyethyl, methoxypropyl, acetyl, tert-butoxycarbonyl, phenyl, 4-pyridyl, cyclopropyl, cyclobutyl, cyclopentyl, and piperidinyl.

20

13. A compound as defined in claim 1, wherein R^e is selected from the group consisting of: -H, isopropyl, and cyclopropyl.

14. A compound as defined in claim 1, wherein q is 1 and both R⁴ substituents taken together form a carbonyl.

25

15. A compound as defined in claim 1, wherein q is 0.

16. A compound as defined in claim 1, wherein q is 1 and each R⁴ is -H.

30

17. A compound as defined in claim 1, wherein Y is -O- or -S-.

18. A compound as defined in claim 1, wherein Cyc is a phenyl or pyridyl group unsubstituted or substituted with one, two, or three R^k moieties.
19. A compound as defined in claim 1, wherein Cyc is a thiophenyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, or pyrazinyl group unsubstituted or substituted with one, two, or three R^k moieties.
20. A compound as defined in claim 1, wherein Cyc is phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-2-methylphenyl, 4-hydroxy-3-fluorophenyl, 3,4-dihydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 3-ethynylphenyl, 4-ethynylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3-iodophenyl, 4-iodophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-fluoro-3-chlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl, 4-fluoro-3-methylphenyl, 3-chloro-4-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-chloro-4-difluoromethoxyphenyl, 4-chloro-3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 4-difluoromethoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-acetylphenyl, 4-acetylphenyl, 3-nitrophenyl, 4-nitrophenyl, 4-aminophenyl, 4-dimethylaminophenyl, 4-carbamoylphenyl, 4-methanesulfanylphenyl, 4-methanesulfinylphenyl, 4-methanesulfonylphenyl, 4-trifluoromethanesulfanylphenyl, 3-methyl-4-methylsulfanylphenyl, benzo[1,3]dioxol-4-yl, benzo[1,3]dioxol-5-yl, thiophen-2-yl, thiophen-3-yl, oxazol-5-yl, thiazol-5-yl, thiazol-2-yl, 2H-pyrazol-3-yl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 4-trifluoromethyl-pyridin-2-yl, 2,6-dimethyl-pyridin-3-yl, 6-methyl-pyridin-3-yl, 2-chloro-5-pyridinyl, 2-dimethylamino-5-pyridinyl, 6-methoxy-

pyridin-3-yl, 6-methylsulfanyl-pyridin-3-yl, 2-hydroxy-5-pyridinyl, 6-bromo-pyridin-3-yl, or pyrazin-2-yl.

21. A compound as defined in claim 1, wherein Cyc is phenyl, 3-
5 methoxyphenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-2-fluorophenyl, 4-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 4-trifluoromethylphenyl, 4-methanesulfanylphenyl, 3-methyl-4-methanesulfanylphenyl, 2-pyridinyl, 3-pyridinyl, or 6-methyl-3-pyridinyl.
- 10 22. A compound as defined in claim 1, wherein each R^k moiety is independently selected from the group consisting of: methyl, methoxy, fluoro, chloro, trifluoromethyl, methanesulfanyl, trifluoromethanesulfanyl, cyano, and trifluoromethoxy.
- 15 23. A compound as defined in claim 1, wherein R^l and R^m are each independently -H or methyl.
24. A compound as defined in claim 1, wherein R⁵ is -H or methyl.
- 20 25. A compound as defined in claim 1, wherein R⁵ is -H.
26. A compound as defined in claim 1, wherein R⁶ is -H, methyl, ethyl, isopropyl, sec-butyl, cyclopropyl, cyclobutyl, or cyclopentyl, each unsubstituted or substituted as previously described.
- 25 27. A compound as defined in claim 1, wherein R⁶ is -H or methyl.
28. A compound as defined in claim 1, wherein R⁷ is -H, methyl, ethyl, propyl, isopropyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
30 cyclopropylmethyl, cyclobutylmethyl, or cyclopentylmethyl, each unsubstituted or substituted as previously described.

29. A compound as defined in claim 1, wherein R⁷ is methyl, ethyl, isopropyl, sec-butyl, cyclopropyl, cyclobutyl, or cyclopentyl.
30. A compound as defined in claim 1, wherein R⁷ is methyl, ethyl, isopropyl,
5 or cyclopropyl.
31. A compound as defined in claim 1, wherein R⁶ and R⁷ taken together with their nitrogen of attachment form azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, thiomorpholiny, 1,1-dioxo-1λ⁶-thiomorpholin-4-yl,
10 homopiperidiny, diazepany, or homomorpholiny, each unsubstituted or substituted as previously described.
32. A compound as defined in claim 1, wherein R⁶ and R⁷ taken together with their nitrogen of attachment form piperidiny, pyrrolidiny, morpholiny, 4-
15 isopropyl-piperazin-1-yl, or homomorpholiny.
33. A compound selected from the group consisting of:
[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone;
(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone;
(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(3-methyl-4-methylsulfanyl-phenoxy)-phenyl]-methanone;
(4-Cyclopropyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
(4-Isopropyl-piperazin-1-yl)-[4-(3-methoxy-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
[4-(4-Chloro-phenoxy)-3-cyclopropylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;

(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-methanone;

[4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-(3-methylaminomethyl-4-phenoxy-phenyl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[4-(3-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-trifluoromethyl-phenoxy)-phenyl]-methanone;

[3-Cyclopropylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(3-methyl-4-methylsulfanyl-phenoxy)-phenyl]-methanone;

[3-Cyclopropylaminomethyl-4-(pyridin-3-yloxy)-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;

[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[4-(4-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-methanone;

[4-(3-Chloro-4-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

[4-(4-Chloro-2-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

[3-Methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-(4-morpholin-4-yl-piperidin-1-yl)-methanone;

[4-(3-Chloro-2-fluoro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

(S)-3-Dimethylamino-pyrrolidin-1-yl]-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-methanone;

4-(3-Chloro-phenoxy)-N-(2-dimethylamino-ethyl)-3-methylaminomethyl-benzamide;

4-(3-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-methylaminomethyl-benzamide;

[4-(4-Chloro-phenylsulfanyl)-3-methylaminomethyl-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(pyridin-2-ylsulfanyl)-phenyl]-methanone;

[4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;

[4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;

[4-Cyclopropylaminomethyl-3-(pyridin-3-yloxy)-phenyl]-(3-dimethylamino-pyrrolidin-1-yl)-methanone;

(4-Isopropyl-piperazin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone;

(3-Dimethylamino-pyrrolidin-1-yl)-[4-piperidin-1-ylmethyl-3-(pyridin-3-yloxy)-phenyl]-methanone;

[3-(4-Chloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;

[3-(3,4-Dichloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;

[3-(3-Chloro-phenoxy)-4-methylaminomethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-[3-(3,4-dichloro-phenoxy)-4-methylaminomethyl-phenyl]-methanone

[5-(4-Isopropyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methylamine;

Methyl-[5-(4-methyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;

[5-(4-Cyclobutyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;

Methyl-[2-(4-methylsulfanyl-phenoxy)-5-(4-pyridin-4-yl-piperazin-1-yl)-benzyl]-amine;

[5-[4-(2-Fluoro-ethyl)-piperazin-1-yl]-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;

[5-(4-Cyclopropyl-piperazin-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine

[5-(4-Cyclopropyl-piperazin-1-yl)-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine;

[2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-piperazin-1-yl)-benzyl]-methyl-amine;

1-[3-Methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-piperazin-2-one;

4-Isopropyl-1-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-piperazin-2-one;

1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-4-isopropyl-piperazin-2-one;

Methyl-[2-(4-methylsulfanyl-phenoxy)-5-(4-morpholin-4-yl-piperidin-1-yl)-benzyl]-amine;

[5-(4-Isopropyl-[1,4]diazepan-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;

[5-(4-Cyclopropyl-[1,4]diazepan-1-yl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;

1-Isopropyl-4-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-[1,4]diazepan-5-one;

[2-(3,4-Dichloro-phenoxy)-5-(4-isopropyl-[1,4]diazepan-1-yl)-benzyl]-methyl-amine;

[5-(4-Cyclopropyl-[1,4]diazepan-1-yl)-2-(3,4-dichloro-phenoxy)-benzyl]-methyl-amine;

1-Cyclopropyl-4-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-[1,4]diazepan-5-one;

(S)-Dimethyl-{1-[3-methylaminomethyl-4-(4-methylsulfanyl-phenoxy)-phenyl]-pyrrolidin-3-yl}-amine;

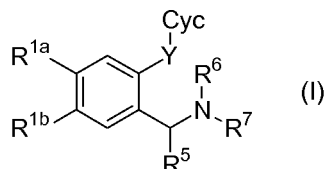
(4-Cyclopropyl-piperazin-1-yl)-[4-(3,4-dichloro-benzyloxy)-3-methylaminomethyl-phenyl]-methanone;
Cyclopropyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;
[5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-methyl-amine;
[5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-dimethyl-amine;
Ethyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;
Isopropyl-[5-(4-isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzyl]-amine;
5-(4-Isopropyl-piperazin-1-ylmethyl)-2-(4-methylsulfanyl-phenoxy)-benzylamine;
4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-1-isopropyl-piperazin-2-one;
1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-4-isopropyl-piperazin-2-one;
1-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-4-isopropyl-[1,4]diazepan-5-one;
4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-benzyl]-1-isopropyl-[1,4]diazepan-5-one;
1-Cyclobutyl-4-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-benzyl]-[1,4]diazepan-5-one;
4-(3-Chloro-phenoxy)-3-methylaminomethyl-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
[4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclobutyl-piperazin-1-yl)-methanone;
4-[4-(3,4-Dichloro-phenoxy)-3-methylaminomethyl-phenyl]-1-isopropyl-[1,4]diazepan-5-one;
(4-Cyclobutyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;
(4-Cyclopentyl-piperazin-1-yl)-[4-(3,4-dichloro-phenoxy)-3-methylaminomethyl-phenyl]-methanone;

[4-(3-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopentyl-piperazin-1-yl)-methanone;
[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclobutyl-piperazin-1-yl)-methanone;
[4-(4-Chloro-phenoxy)-3-methylaminomethyl-phenyl]-(4-cyclopentyl-piperazin-1-yl)-methanone;
(4-Isopropyl-piperazin-1-yl)-[3-methylaminomethyl-4-(4-trifluoromethyl-pyridin-2-ylsulfanyl)-phenyl]-methanone;
(4-Cyclopropyl-piperazin-1-yl)-[4-dimethylaminomethyl-3-(2,6-dimethyl-pyridin-3-yloxy)-phenyl]-methanone;
(3-Benzyloxy-4-dimethylaminomethyl-phenyl)-(4-cyclopropyl-piperazin-1-yl)-methanone;
[4-{{Bis-(2-methoxy-ethyl)-amino}-methyl}-3-(2,6-dimethyl-pyridin-3-yloxy)-phenyl]-(4-cyclopropyl-piperazin-1-yl)-methanone;
[3-(2,6-Dimethyl-pyridin-3-yloxy)-4-morpholin-4-ylmethyl-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone;
(4-Dimethylaminomethyl-3-phenoxy-phenyl)-piperidin-1-yl-methanone;
(4-{{Bis-(2-methoxy-ethyl)-amino}-methyl}-3-phenoxy-phenyl)-(4-isopropyl-piperazin-1-yl)-methanone;
[4-{{Bis-(2-methoxy-ethyl)-amino}-methyl}-3-(pyridin-3-yloxy)-phenyl]-(4-dimethylamino-piperidin-1-yl)-methanone;
[4-(4-Isopropyl-piperazin-1-ylmethyl)-3-phenoxy-phenyl]-piperidin-1-yl-methanone;
[4-(4-Isopropyl-piperazin-1-ylmethyl)-3-(pyridin-3-yloxy)-phenyl]-piperidin-1-yl-methanone;
4-Dimethylaminomethyl-N-(2-methylamino-ethyl)-3-(pyridin-3-yloxy)-benzamide;
N-[2-(Cyclopropyl-methyl-amino)-ethyl]-4-dimethylaminomethyl-3-(pyridin-3-yloxy)-benzamide; and
[5-(4-Isopropyl-piperazine-1-carbonyl)-2-(3-methoxy-phenoxy)-benzyl]-methyl-carbamic acid tert-butyl ester;
and pharmaceutically acceptable salts thereof.

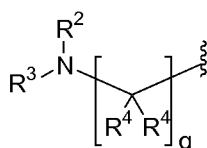
34. A compound or pharmaceutically acceptable salt according to claim 1.

35. A pharmaceutical composition for treating a disease, disorder, or medical condition mediated by histamine H₃ receptor and/or serotonin transporter activity, comprising:

- 5 (a) an effective amount of a compound of Formula (I):



wherein



one of R^{1a} and R^{1b} is

R² and R³ are each independently selected from the group consisting of: -H; a

- 10 -C₁₋₆alkyl group unsubstituted or substituted with -OH, -OC₁₋₄alkyl, -NH₂, -N(R^a)R^b, or -F; -CO₂C₁₋₄alkyl; and a monocyclic cycloalkyl group unsubstituted or substituted with -C₁₋₄alkyl, -OH, halo, or -CF₃;

where R^a and R^b are each independently -H, -C₁₋₆alkyl, or monocyclic cycloalkyl, or R^a and R^b taken together with their nitrogen of attachment

- 15 form a monocyclic heterocycloalkyl group;

provided that R² and R³ are not both H;

or, alternatively,

R² and R³ taken together with the nitrogen to which they are attached form a

saturated monocyclic heterocycloalkyl group unsubstituted or substituted on

- 20 a carbon ring member with one, two, or three R^d moieties and substituted on a nitrogen ring member with an R^e moiety;

where each R^d moiety is independently selected from the group consisting

of: -C₁₋₆alkyl; -C₁₋₄alkyl-OH; halo; -OH; -OC₁₋₆alkyl; ipso-substituted -OC₂₋₃alkylO-; -CN; -NO₂; -N(R^g)R^h; -C(O)N(R^g)R^h; -N(R^g)SO₂C₁₋₆alkyl; 25 -C(O)C₁₋₆alkyl; -S(O)₀₋₂-C₁₋₆alkyl; -SO₂N(R^g)R^h; -SCF₃; -CF₃; -OCF₃; -CO₂H; and -CO₂C₁₋₆alkyl;

where R^g and R^h are each independently -H or -C₁₋₆alkyl, or R^g and R^h taken together with their nitrogen of attachment form a monocyclic heterocycloalkyl group; and

where R^e is selected from the group consisting of: -H; a -C₁₋₆alkyl or
 5 -C(O)C₁₋₆alkyl group unsubstituted or substituted with halo, -CN, -OH, -OC₁₋₄alkyl, or -CF₃; -C(O)CF₃; -S(O)₀₋₂-C₁₋₆alkyl; -CO₂C₁₋₆alkyl; and a phenyl, monocyclic carbon-linked heteroaryl, monocyclic cycloalkyl, or monocyclic carbon-linked heterocycloalkyl group, each unsubstituted or substituted with -C₁₋₄alkyl, halo, -CN, -OH, -OC₁₋₄alkyl, or -CF₃;

10 q is 0 or 1;

each R⁴ is independently -H or methyl, or both R⁴ substituents taken together form a carbonyl;

Y is -O-, -OCH₂-, -S-, -SO-, or -SO₂-;

R⁵ is -H or -C₁₋₆alkyl;

15 R⁶ is -H; or -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, monocyclic cycloalkyl, or -C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with -C₁₋₄alkyl, -OH, -OC₁₋₄alkyl, halo, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN, -CO₂H, or -CO₂C₁₋₄alkyl;

R⁷ is -H; or -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, monocyclic cycloalkyl, or
 20 -C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with -C₁₋₄alkyl, -OH, -OC₁₋₄alkyl, halo, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN, -CO₂H, or -CO₂C₁₋₄alkyl;

or R⁶ and R⁷ taken together with their nitrogen of attachment form a saturated monocyclic heterocycloalkyl group unsubstituted or substituted with -C₁₋

25 ₄alkyl, -OC₁₋₄alkyl, or halo; and

Cyc is a phenyl or monocyclic carbon-linked heteroaryl group, unsubstituted or substituted with one, two, or three R^k moieties;

where each R^k moiety is independently selected from the group consisting
 of: -C₁₋₆alkyl, -CHF₂, -CF₃, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -OH, -OC₁₋₆alkyl,
 30 -OCHF₂, -OCF₃, -OC₃₋₆alkenyl, -OC₃₋₆alkynyl, -CN, -NO₂, -N(R^l)R^m,
 -N(R^l)C(O)R^m, -N(R^l)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -S(O)₀₋₂-C₁₋₆alkyl,
 -C(O)N(R^l)R^m, -SO₂N(R^l)R^m, -SCF₃, halo, -CO₂H, and -CO₂C₁₋₆alkyl; or two R^k moieties on adjacent carbon atoms of attachment together are

-OC₁₋₄alkyleneO- to form a cyclic ring which is unsubstituted or substituted with one or two fluoro substituents;

where R^l and R^m are each independently -H or -C₁₋₆alkyl;

provided that when both R⁴ substituents taken together form a carbonyl, then

5 R² and R³ taken together are not diazepanyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite thereof; and

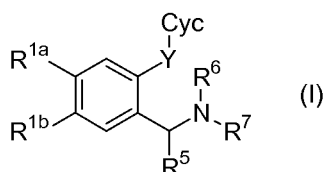
(b) a pharmaceutically acceptable excipient.

10 36. A pharmaceutical composition according to claim 35, further comprising: an active ingredient selected from the group consisting of H₁ receptor antagonists, H₂ receptor antagonists, H₃ receptor antagonists, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, noradrenergic reuptake inhibitors, non-selective serotonin re-uptake inhibitors,

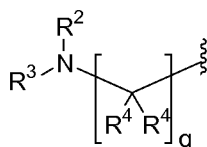
15 acetylcholinesterase inhibitors, and modafinil.

37. A method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by histamine H₃ receptor and/or serotonin transporter activity, comprising administering to the subject in

20 need of such treatment an effective amount of a compound of Formula (I):



wherein



one of R^{1a} and R^{1b} is and the other is -H;

R² and R³ are each independently selected from the group consisting of: -H; a

25 -C₁₋₆alkyl group unsubstituted or substituted with -OH, -OC₁₋₄alkyl, -NH₂, -N(R^a)R^b, or -F; -CO₂C₁₋₄alkyl; and a monocyclic cycloalkyl group unsubstituted or substituted with -C₁₋₄alkyl, -OH, halo, or -CF₃;

where R^a and R^b are each independently –H, –C₁₋₆alkyl, or monocyclic cycloalkyl, or R^a and R^b taken together with their nitrogen of attachment form a monocyclic heterocycloalkyl group; provided that R² and R³ are not both H;

5 or, alternatively,

R² and R³ taken together with the nitrogen to which they are attached form a saturated monocyclic heterocycloalkyl group unsubstituted or substituted on a carbon ring member with one, two, or three R^d moieties and substituted on a nitrogen ring member with an R^e moiety;

10 where each R^d moiety is independently selected from the group consisting of: –C₁₋₆alkyl; –C₁₋₄alkyl-OH; halo; –OH; –OC₁₋₆alkyl; ipso-substituted –OC₂₋₃alkylO–; –CN; –NO₂; –N(R^g)R^h; –C(O)N(R^g)R^h; –N(R^g)SO₂C₁₋₆alkyl; –C(O)C₁₋₆alkyl; –S(O)₀₋₂–C₁₋₆alkyl; –SO₂N(R^g)R^h; –SCF₃; –CF₃; –OCF₃; –CO₂H; and –CO₂C₁₋₆alkyl;

15 where R^g and R^h are each independently –H or –C₁₋₆alkyl, or R^g and R^h taken together with their nitrogen of attachment form a monocyclic heterocycloalkyl group; and

where R^e is selected from the group consisting of: –H; a –C₁₋₆alkyl or –C(O)C₁₋₆alkyl group unsubstituted or substituted with halo, –CN, –OH, 20 –OC₁₋₄alkyl, or –CF₃; –C(O)CF₃; –S(O)₀₋₂–C₁₋₆alkyl; –CO₂C₁₋₆alkyl; and a phenyl, monocyclic carbon-linked heteroaryl, monocyclic cycloalkyl, or monocyclic carbon-linked heterocycloalkyl group, each unsubstituted or substituted with –C₁₋₄alkyl, halo, –CN, –OH, –OC₁₋₄alkyl, or –CF₃;

q is 0 or 1;

25 each R⁴ is independently –H or methyl, or both R⁴ substituents taken together form a carbonyl;

Y is –O–, –OCH₂–, –S–, –SO–, or –SO₂–;

R⁵ is –H or –C₁₋₆alkyl;

30 R⁶ is –H; or –C₁₋₆alkyl, –C₃₋₆alkenyl, –C₃₋₆alkynyl, monocyclic cycloalkyl, or –C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with –C₁₋₄alkyl, –OH, –OC₁₋₄alkyl, halo, –NH₂, –NH(C₁₋₄alkyl), –N(C₁₋₄alkyl)₂, –CN, –CO₂H, or –CO₂C₁₋₄alkyl;

R⁷ is -H; or -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, monocyclic cycloalkyl, or -C₁₋₆alkyl-(monocyclic cycloalkyl), each unsubstituted or substituted with -C₁₋₄alkyl, -OH, -OC₁₋₄alkyl, halo, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CN, -CO₂H, or -CO₂C₁₋₄alkyl;

5 or R⁶ and R⁷ taken together with their nitrogen of attachment form a saturated monocyclic heterocycloalkyl group unsubstituted or substituted with -C₁₋₄alkyl, -OC₁₋₄alkyl, or halo; and

Cyc is a phenyl or monocyclic carbon-linked heteroaryl group, unsubstituted or substituted with one, two, or three R^k moieties;

10 where each R^k moiety is independently selected from the group consisting of: -C₁₋₆alkyl, -CHF₂, -CF₃, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -OH, -OC₁₋₆alkyl, -OCHF₂, -OCF₃, -OC₃₋₆alkenyl, -OC₃₋₆alkynyl, -CN, -NO₂, -N(R^l)R^m, -N(R^l)C(O)R^m, -N(R^l)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -S(O)₀₋₂-C₁₋₆alkyl, -C(O)N(R^l)R^m, -SO₂N(R^l)R^m, -SCF₃, halo, -CO₂H, and -CO₂C₁₋₆alkyl; or
15 two R^k moieties on adjacent carbon atoms of attachment together are -OC₁₋₄alkyleneO- to form a cyclic ring which is unsubstituted or substituted with one or two fluoro substituents;

where R^l and R^m are each independently -H or -C₁₋₆alkyl;

provided that when both R⁴ substituents taken together form a carbonyl, then

20 R² and R³ taken together are not diazepanyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite thereof.

38. The method according to claim 37, wherein the disease, disorder, or
25 medical condition is selected from the group consisting of: cognitive disorders, sleep disorders, psychiatric disorders, and other disorders.

39. The method according to claim 37, wherein the disease, disorder, or
30 medical condition is selected from the group consisting of: dementia, Alzheimer's disease, cognitive dysfunction, mild cognitive impairment, pre-dementia, attention deficit hyperactivity disorders, attention-deficit disorders, and learning and memory disorders.

40. The method according to claim 37, wherein the disease, disorder, or medical condition is selected from the group consisting of: learning impairment, memory impairment, and memory loss.

5 41. The method according to claim 37, wherein the disease, disorder, or medical condition is selected from the group consisting of: insomnia, disturbed sleep, narcolepsy with or without associated cataplexy, cataplexy, disorders of sleep/wake homeostasis, idiopathic somnolence, excessive daytime sleepiness, circadian rhythm disorders, fatigue, lethargy, and jet lag.

10

42. The method according to claim 37, wherein the disease, disorder, or medical condition is selected from the group consisting of: sleep apnea, perimenopausal hormonal shifts, Parkinson's disease, multiple sclerosis, depression, chemotherapy, and shift work schedules.

15

43. The method according to claim 37, wherein the disease, disorder, or medical condition is selected from the group consisting of: schizophrenia, bipolar disorders, manic disorders, depression, obsessive-compulsive disorder, and post-traumatic stress disorder.

20

44. The method according to claim 37, wherein the disease, disorder, or medical condition is selected from the group consisting of: motion sickness, vertigo, epilepsy, migraine, neurogenic inflammation, eating disorders, obesity, and substance abuse disorders.

25

45. The method according to claim 37, wherein the disease, disorder, or medical condition is selected from the group consisting of: depression, disturbed sleep, fatigue, lethargy, cognitive impairment, memory impairment, memory loss, learning impairment, attention-deficit disorders, and eating
30 disorders.

46. A pharmaceutical composition according to claim 35, further comprising topiramate.

47. The method according to claim 37, wherein the disease, disorder, or medical condition is selected from the group consisting of: age-related cognitive decline, REM-behavioral disorder, benign postural vertigo, tinnitus, movement disorders, restless leg syndrome, eye-related disorders, macular degeneration, and retinitis pigmentosis.
- 5