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(54) Title: QUINOLONE NEUROPEPTIDE S RECEPTOR ANTAGONISTS

(57) Abstract: The present invention is directed to quinolone compounds which are antagonists of neuropeptide S receptors, and which are useful in the treatment or prevention of neurological and psychiatric disorders and diseases in which the neuropeptide S receptor is involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the neuropeptide S receptor is involved.

TITLE OF THE INVENTION

QUINOLONE NEUROPEPTIDE S RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

5 Neuropeptide S (NPS) is an endogenous brain protein, which is believed to affect arousal, wakefulness, propensity for movement, asthma and some allergic responses, stress associated with several anxiety disorders and other physiological functions. Neuropeptide S is the endogenous ligand for the Neuropeptide S receptor (NPSR), which has also been referred to as TGR23 and vasopressin receptor-related receptor 1 (VRR1). The Neuropeptide S receptor is expressed in certain regions of the brain known to be involved in anxiety (e. g., the amygdala, thalamus and hypothalamic regions) and administration of NPS to rodents can cause increased locomotion and anxiolytic effects.

 Neuropeptide S receptors are found in the mammalian brain and may have numerous implications in pathologies such as depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; eating disorders such as anorexia, bulimia, cachexia, dysregulated appetite control; obesity; addictive feeding behaviors; binge/purge feeding behaviors; cardiovascular diseases; diabetes; appetite, taste, eating or drinking disorders; emesis, vomiting, nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome/disease; basophile adenoma; prolactinoma; hyperprolactinemia; hypophysis tumour/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric dyskinesia; gastric ulcers; Froehlich's syndrome; adrenoypophysis disease; hypophysis disease; adrenoypophysis hypofunction; adrenoypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic- adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; vigilance; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardinal infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex

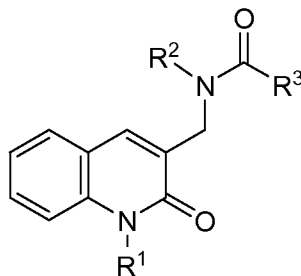
regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet lag syndrome; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration; epilepsy; seizure disorders and other diseases related to general neuropeptide S system dysfunction.

10 SUMMARY OF THE INVENTION

The present invention is directed to quinolone compounds which are antagonists of the neuropeptide S receptor, and which are useful in the treatment or prevention of neurological and psychiatric disorders and diseases in which neuropeptide S receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the neuropeptide S receptor is involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

wherein:

R¹ is hydrogen or C₁₋₆alkyl, which is unsubstituted or substituted with -O-C₁₋₆alkyl;

25 R² is -C₀₋₆alkyl, which is substituted with one or more substituents selected from R⁴,

wherein R⁴ is selected from the group consisting of:

- (1) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R¹³,

- (2) -C₃₋₈cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R¹³, or where the cycloalkyl may be fused to a phenyl, where the phenyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- 5 (3) -C₃₋₈cycloalkoxyl, where the cycloalkoxyl is unsubstituted or substituted with one or more substituents selected from R¹³, or where the cycloalkyl may be fused to a phenyl, where the phenyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- (4) -phenyl or -naphthyl, where the phenyl or naphthyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- 10 (5) -heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R¹³,
- (6) -NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are independently selected from the group consisting of:
- 15 (a) hydrogen,
- (b) C₁₋₆alkyl, which is unsubstituted or substituted with R¹³,
- (c) C₃₋₆alkenyl, which is unsubstituted or substituted with R¹³,
- (d) C₃₋₆alkynyl, which is unsubstituted or substituted with R¹³,
- (e) C₃₋₆cycloalkyl which is unsubstituted or substituted with R¹³,
- 20 (f) phenyl, which is unsubstituted or substituted with R¹³, and
- (g) heterocycle, which is unsubstituted or substituted with R¹³;

R³ is selected from the group consisting of:

- (1) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- 25 (2) -C₃₋₆cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- (3) -phenyl or -naphthyl, where the phenyl or naphthyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- 30 (4) -heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R¹³,
- (5) -NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are independently selected from the group consisting of:
- 35 (a) hydrogen,
- (b) C₁₋₆alkyl, which is unsubstituted or substituted with R¹³,

- (c) C₃₋₆alkenyl, which is unsubstituted or substituted with R¹³,
 (d) C₃₋₆alkynyl, which is unsubstituted or substituted with R¹³,
 (e) C₃₋₆cycloalkyl which is unsubstituted or substituted with R¹³,
 (f) phenyl, which is unsubstituted or substituted with R¹³, and
 5 (g) heterocycle, which is unsubstituted or substituted with R¹³;

R¹³ is selected from the group consisting of:

- (1) halogen,
 (2) hydroxyl,
 10 (3) -(C=O)_m-O_n-C₁₋₆alkyl, where m is 0 or 1, n is 0 or 1 (wherein if m is 0 or n is 0, a bond is present) and where the alkyl is unsubstituted or substituted with one or more substituents selected from R¹⁴,
 (4) -O_n-(C₁₋₃)perfluoroalkyl,
 (5) -(C=O)_m-O_n-C₃₋₆cycloalkyl, where the cycloalkyl is unsubstituted or substituted
 15 with one or more substituents selected from R¹⁴,
 (6) -(C=O)_m-C₂₋₄alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R¹⁴,
 (7) -(C=O)_m-C₂₋₄alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R¹⁴,
 20 (8) -(C=O)_m-O_n-phenyl or -(C=O)_m-O_n-naphthyl, where the phenyl or naphthyl is unsubstituted or substituted with one or more substituents selected from R¹⁴,
 (9) -(C=O)_m-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R¹⁴,
 (10) -(C=O)_m-NR¹⁵R¹⁶, where R¹⁵ and R¹⁶ are independently selected from
 25 hydrogen and -C₁₋₆alkyl, which is unsubstituted or substituted with phenyl,
 (11) -S(O)₂-NR¹⁵R¹⁶,
 (12) -S(O)_q-R¹², where q is 0, 1 or 2 and where R¹² is -C₁₋₆alkyl, which is unsubstituted or substituted with phenyl;
 (13) -CO₂H,
 30 (14) -CN, and
 (15) -NO₂;

R¹⁴ is selected from the group consisting of:

- (1) hydroxyl,
 35 (2) halogen,

- (3) C₁₋₆alkyl,
- (4) -C₃₋₆cycloalkyl,
- (5) -O-C₁₋₆alkyl,
- (6) -O(C=O)-C₁₋₆alkyl,
- 5 (7) -NH-C₁₋₆alkyl,
- (8) phenyl,
- (9) heterocycle,
- (10) -CO₂H, and
- (11) -CN;

10 or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds wherein R¹ is hydrogen or methyl. An embodiment of the present invention includes compounds wherein R¹ is hydrogen. An embodiment of the present invention includes compounds wherein R¹ is methyl.

15 An embodiment of the present invention includes compounds wherein R² is selected from the group consisting of:

- (1) tetralone,
- (2) -CH₂-cyclohexyl, where the cyclohexyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- 20 (3) -CH₂-morpholinyl, where the morpholinyl is unsubstituted or substituted with one or more substituents selected from R¹³, and
- (4) -CH₂-CH-(phenyl)heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R¹³.

25 An embodiment of the present invention includes compounds wherein R³ is selected from the group consisting of:

- (1) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from -C₃₋₆cycloalkyl and phenyl, where the cycloalkyl and phenyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of:
 - 30 (a) halogen,
 - (b) hydroxyl,
 - (c) C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or naphthyl, and

- (d) -O-C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl;
- (2) -C₃₋₆cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from -C₁₋₆alkyl and phenyl, where the alkyl and phenyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of:
- 5 (a) halogen,
(b) hydroxyl,
(c) C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or naphthyl, and
10 (d) -O-C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl;
- (3) -phenyl, which is unsubstituted or substituted with one or more substituents selected from the group consisting of:
- 15 (a) halogen,
(b) hydroxyl,
(c) C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or naphthyl, and
20 (d) -O-C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl.

An embodiment of the present invention includes compounds wherein R³ is selected from the group consisting of: cyclohexyl, cyclopentyl, sec-butyl, neo-pentyl and phenyl. An embodiment of the present invention includes compounds wherein R³ is cyclohexyl.

25 Specific embodiments of the present invention include a compound which is selected from the group consisting of the subject compounds of the Examples herein or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers,
30 diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to

comprehend all such isomeric forms of these compounds. Formula I shows the structure of the class of compounds without specific stereochemistry.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As appreciated by those of skill in the art, halogen or halo as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C₁₋₆, as in C₁₋₆alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C₁₋₈alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents. The term "heterocycle" as used herein includes both unsaturated and saturated heterocyclic moieties, wherein the unsaturated heterocyclic moieties (i.e. "heteroaryl") include benzoimidazolyl, benzimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzothiazolyl, benzotriazolyl, benzothiophenyl, benzoxazepin, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, dihydroindolyl, indolazinyll, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyll, quinolyl, quinoxalinyll, tetrahydroquinoxalinyll, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and N-oxides thereof, and wherein the saturated heterocyclic moieties include azetidinyll, 1,4-dioxanyll, hexahydroazepinyll, piperazinyll, piperidinyll, pyridin-2-onyll, pyrrolidinyll, morpholinyl, tetrahydrofuranyl, thiomorpholinyl, and tetrahydrothienyl, and N-oxides thereof.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particular embodiments include the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particular embodiments include the citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual enantiomers or diastereomers thereof.

The subject compounds are useful in a method of antagonizing neuropeptide S receptor activity in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as antagonists of neuropeptide S receptor activity. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention. The present invention is directed to a compound of the present invention or a pharmaceutically acceptable salt thereof for use in medicine. The present

invention is further directed to a use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing neuropeptide S receptor activity or treating the disorders and diseases noted herein in humans and animals.

5 The subject treated in the present methods is generally a mammal, such as a human being, male or female. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. It is recognized that one skilled in the art may affect the neurological and psychiatric disorders by treating a patient presently afflicted with the disorders or by prophylactically
10 treating a patient afflicted with the disorders with an effective amount of the compound of the present invention. As used herein, the terms "treatment" and "treating" refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not
15 necessarily indicate a total elimination of all disorder symptoms, as well as the prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder. The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need thereof.

20 The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier,
25 as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically
30 acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

 The utility of the compounds in accordance with the present invention as Neuropeptide S receptor agonists and/or antagonists may be readily determined without undue
35 experimentation by methodology well known in the art, including the "FLIPR Ca²⁺ Flux Assay" (Hodder et al., J Biomol Screen., 9(5):417-26, 2004). In a typical experiment the Neuropeptide S

receptor agonistic and antagonistic activity of the compounds of the present invention were determined in accordance with the following experimental method. For intracellular calcium measurements, Chinese hamster ovary (CHO) cells expressing the human Neuropeptide S receptor A gene (NPSr A) (T. Laitinen et al., Science 304:300, 2004), are grown in Dulbecco's Modification of Eagle's Medium (DMEM) containing 4 mM L-glutamine, 0.5 g/ml G418, 100 uM non-essential amino acids (glycine, L-alanine, L-asparagine, L-aspartic acid, L-glutamic acid, L-proline, and L-serine), 1 mM sodium pyruvate, 25 mM Hepes, pH 7.4, 100 U/ml penicillin, 100 ug/ml streptomycin and 10 % fetal bovine serum (FBS). The cells are seeded at 15,000 cells / well into black 384-well clear bottom sterile plates coated with poly-D-lysine (BectonDickinson Labware). DMEM is from MediaTech Inc., FBS is from Hyclone Inc., and the remaining reagents were from GIBCO-Invitrogen Corp. The seeded plates are incubated for 24 hours at 37°C and 5% CO₂. Human Neuropeptide S (Y-L. Xu et al., Neuron 43:487, 2004) as the agonist is prepared as a 400 nM stock solution in assay buffer pH 7.4 (HBSS containing 20 mM Hepes , 250uM probenecid, 0.1% (w/v) bovine serum albumin fraction V (BSA) and 800 uM TR40 (Zhang et al., J Biomol Screening 8:571-77, 2003)). Test compounds for the first addition are prepared as 10 mM stock solutions in DMSO, then are serially titrated in DMSO, diluted into assay buffer and transferred into 384-well plates, giving 5x compound concentrations from 50 uM in assay buffer plus 0.1% BSA, 800 uM TR40, and 2.5% DMSO. Human Neuropeptide S is used as a positive control at a 5x concentration of 100 nM. After 24 hours of growth, cells are washed 3 times with 100 ul wash buffer (assay buffer without TR40 or BSA), leaving 30ul each time. Then 10 ul of 4x dye loading buffer is added, resulting in a 40ul volume of assay buffer plus 2.5 uM Fluo-4 AM ester, 0.02 % pluronic acid, 0.1 % BSA and 800 uM TR40. Cells are incubated in dye loading buffer for 60 min (37° C, 5% CO₂). After 60 minutes, plates are transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), where 10ul of the 5x compound plate are added to the 40 ul existing volume. Fluorescence is measured for each well at 1 second intervals for 1 minute then 6 second intervals for 3 minutes; and each fluorescence peak maximum is compared to the fluorescence peak maximum induced by 20nM (EC₁₀₀) human Neuropeptide S. For each tested compound, an EC₅₀ value (the effective concentration of compound needed to produce 50 % of the NPS control response) is determined. After the initial 4 minute FLIPR read, 16.67 ul of 4x NPS agonist is immediately added to the 50 ul existing well volume, giving a final concentration of NPS at its EC₈₀ of 3nM. Fluorescence is measured for each well at 1 second intervals for 1 minute then 6 second intervals for 3 minutes; and each fluorescence peak maximum is compared to the fluorescence peak maximum induced by 3 nM NPS with 0.5% DMSO in assay buffer in place of test compound. For each tested antagonist, IC₅₀ value (the concentration of compound needed to inhibit 50 % of the agonist response) is determined. The intrinsic Neuropeptide S receptor

agonist and antagonist activity of a compound which may be used in the present invention may be determined by these assays.

One skilled in the art can appreciate that the potentiator activity of test compounds can also be determined by similar experimental methods by adding Neuropeptide S at its EC₂₀ concentration of 0.05 nM in the second addition, and determining if compounds sensitized the cells to NPS by measuring any increase in the FLIPR response.

In particular, the compounds of the following examples had activity in agonizing and/or antagonizing the human Neuropeptide S receptor in the aforementioned assays, generally with an IC₅₀ of less than about 10 uM. Many of compounds within the present invention had activity in agonizing and/or antagonizing the human Neuropeptide S receptor in the aforementioned assays with an IC₅₀ of less than about 100 nM. Additional data is provided herein. Such a result is indicative of the intrinsic activity of the compounds in use as agonists and/or antagonists of human Neuropeptide S receptor. The present invention also includes compounds within the generic scope of the invention which possess activity as agonists of the Neuropeptide S receptor

The Neuropeptide S receptor has been implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species. The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with neuropeptide S receptors, including one or more of the following conditions or diseases: sleep disorders, sleep disturbances, including enhancing sleep quality, improving sleep quality, increasing sleep efficiency, augmenting sleep maintenance; increasing the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; improving sleep initiation; decreasing sleep latency or onset (the time it takes to fall asleep); decreasing difficulties in falling asleep; increasing sleep continuity; decreasing the number of awakenings during sleep; decreasing intermittent wakings during sleep; decreasing nocturnal arousals; decreasing the time spent awake following the initial onset of sleep; increasing the total amount of sleep; reducing the fragmentation of sleep; altering the timing, frequency or duration of REM sleep bouts; altering the timing, frequency or duration of slow wave (i.e. stages 3 or 4) sleep bouts; increasing the amount and percentage of stage 2 sleep; promoting slow wave sleep; enhancing EEG-delta activity during sleep; decreasing nocturnal arousals, especially early morning awakenings; increasing daytime alertness; reducing daytime drowsiness; treating or reducing excessive daytime sleepiness; increasing satisfaction with the intensity of sleep; increasing sleep maintenance; idiopathic insomnia; sleep problems; insomnia, hypersomnia, idiopathic hypersomnia, repeatability hypersomnia, intrinsic hypersomnia, narcolepsy, interrupted sleep, sleep apnea, wakefulness,

nocturnal myoclonus, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dyssomnias, night terror, insomnias associated with depression, emotional/mood disorders, Alzheimer's disease or cognitive impairment, as well as sleep walking and enuresis, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with

5 circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules, conditions due to drugs which cause reductions in REM sleep as a side effect; fibromyalgia; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep; conditions which result from a diminished quality of sleep; increasing learning;

10 augmenting memory; increasing retention of memory; eating disorders associated with excessive food intake and complications associated therewith, compulsive eating disorders, obesity (due to any cause, whether genetic or environmental), obesity-related disorders including overeating and bulimia nervosa, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer,

15 osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting

20 energy expenditure as a percentage of total fat-free mass, e.g. children with acute lymphoblastic leukemia, metabolic syndrome, also known as syndrome X, insulin resistance syndrome, reproductive hormone abnormalities, sexual and reproductive dysfunction, such as impaired fertility, infertility, hypogonadism in males and hirsutism in females, fetal defects associated with maternal obesity, gastrointestinal motility disorders, intestinal motility dyskinesias, obesity-

25 related gastro-esophageal reflux, hypothalamic diseases, hypophysis diseases, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), breathlessness, cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, kidney cancer, increased anesthetic risk, reducing the risk of secondary outcomes of

30 obesity, such as reducing the risk of left ventricular hypertrophy; diseases or disorders where abnormal oscillatory activity occurs in the brain, including depression, migraine, neuropathic pain, Parkinson's disease, psychosis and schizophrenia, as well as diseases or disorders where there is abnormal coupling of activity, particularly through the thalamus; enhancing cognitive function, including cognitive dysfunctions that comprise deficits in all types of attention,

35 learning and memory functions occurring transiently or chronically in the normal, healthy, young, adult or aging population, and also occurring transiently or chronically in psychiatric,

neurologic, cardiovascular and immune disorders; enhancing memory; increasing memory retention; increasing immune response; increasing immune function; hot flashes; night sweats; extending life span; schizophrenia; muscle-related disorders that are controlled by the excitation/relaxation rhythms imposed by the neural system such as cardiac rhythm and other disorders of the cardiovascular system; conditions related to proliferation of cells such as vasodilation or vasoconstriction and blood pressure; cancer; cardiac arrhythmia; hypertension; congestive heart failure; conditions of the genital/urinary system; disorders of sexual function and fertility; adequacy of renal function; responsiveness to anesthetics; mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder, mood disorders due to a general medical condition, and substance-induced mood disorders; anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage; Huntington's Chorea; amyotrophic lateral sclerosis; multiple sclerosis; ocular damage; retinopathy; cognitive disorders; idiopathic and drug-induced Parkinson's disease; muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, seizure disorders, absence seizures, complex partial and generalized seizures; Lennox-Gastaut syndrome; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnesic disorders or age related cognitive decline; schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced psychotic disorder; dissociative disorders including multiple personality syndromes and psychogenic amnesias; substance-related disorders, substance use, substance abuse, substance seeking, substance reinstatement, all types of psychological and physical addictions and addictive behaviors, reward-related behaviors (including substance-induced delirium, persisting dementia, persisting amnesic disorder, psychotic disorder or anxiety disorder; tolerance, addictive feeding, dependence, withdrawal or relapse from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, morphine,

nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), chronic fatigue syndrome, fatigue, including Parkinson's fatigue, multiple sclerosis fatigue, fatigue caused by a sleep disorder or a circadian rhythm disorder, medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor), Gilles de la Tourette's syndrome, epilepsy, and dyskinesias [including tremor (such as rest tremor, essential tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), restless leg syndrome and dystonia (including generalised dystonia such as idiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxysmal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia); attention deficit/hyperactivity disorder (ADHD); conduct disorder; migraine (including migraine headache); headache; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; emesis, nausea, vomiting; gastric dyskinesia; gastric ulcers; Kallman's syndrome (anosmia); conditions associated with visceral pain such as irritable bowel syndrome, and angina; eating disorders; urinary incontinence; substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.); psychosis; schizophrenia; anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder); mood disorders (including depression, mania, bipolar disorders); trigeminal neuralgia; hearing loss; tinnitus; neuronal damage including ocular damage; retinopathy; macular degeneration of the eye; emesis; brain edema; pain, including acute and chronic pain states, severe pain, intractable pain, inflammatory pain, neuropathic pain, post-traumatic pain, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, neuropathic pain, post-traumatic pain, trigeminal neuralgia, migraine and migraine headache.

Thus, in specific embodiments the present invention provides methods for:
enhancing the quality of sleep; augmenting sleep maintenance; increasing REM sleep; increasing
stage 2 sleep; decreasing fragmentation of sleep patterns; treating insomnia and all types of sleep
disorders; treating or controlling sleep disturbances associated with diseases such as neurological
5 disorders including neuropathic pain and restless leg syndrome; treating or controlling addiction
disorders; treating or controlling psychoactive substance use and abuse; enhancing cognition;
increasing memory retention; treating or controlling obesity; treating or controlling diabetes and
appetite, taste, eating, or drinking disorders; treating or controlling hypothalamic diseases;
treating or controlling depression; treating, controlling, ameliorating or reducing the risk of
10 epilepsy, including absence epilepsy; treating or controlling pain, including neuropathic pain;
treating or controlling Parkinson's disease; treating or controlling psychosis; treating or
controlling dysthymic, mood, psychotic and anxiety disorders; treating or controlling depression,
including major depression and major dpression disorder; treating or controlling bipolar
disorder; or treating, controlling, ameliorating or reducing the risk of schizophrenia, in a
15 mammalian patient in need thereof which comprises administering to the patient a
therapeutically effective amount of a compound of the present invention.

The subject compounds are further useful in a method for the prevention,
treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions
noted herein. The dosage of active ingredient in the compositions of this invention may be
20 varied, however, it is necessary that the amount of the active ingredient be such that a suitable
dosage form is obtained. The active ingredient may be administered to patients (animals and
human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy.
The selected dosage depends upon the desired therapeutic effect, on the route of administration,
and on the duration of the treatment. The dose will vary from patient to patient depending upon
25 the nature and severity of disease, the patient's weight, special diets then being followed by a
patient, concurrent medication, and other factors which those skilled in the art will recognize.
Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered
to the patient, e.g., humans and elderly humans, to obtain effective antagonism of neuropeptide S
receptors. The dosage range will generally be about 0.5 mg to 1.0 g. per patient per day which
30 may be administered in single or multiple doses. In one embodiment, the dosage range will be
about 0.5 mg to 500 mg per patient per day; in another embodiment about 0.5 mg to 200 mg per
patient per day; and in yet another embodiment about 5 mg to 50 mg per patient per day.
Pharmaceutical compositions of the present invention may be provided in a solid dosage
formulation such as comprising about 0.5 mg to 500 mg active ingredient, or comprising about 1
35 mg to 250 mg active ingredient. The pharmaceutical composition may be provided in a solid
dosage formulation comprising about 1 mg, 5 mg, 10 mg, 25 mg, 30 mg, 50 mg, 80 mg, 100 mg,

200 mg or 250 mg active ingredient. For oral administration, the compositions may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, such as 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

5 The compounds may be administered on a regimen of 1 to 4 times per day, such as once or twice per day. The compounds may be administered before bedtime. For example, the compounds may be administered about 1Hour prior to bedtime, about 30 minutes prior to bedtime or immediately before bedtime.

The compounds of the present invention may be used in combination with one or
10 more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of the present invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a
15 compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention is contemplated. However, the combination therapy may also includes therapies in which the compound of the present invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in
20 combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the present invention. The above combinations include combinations of a compound of the present invention not only with
25 one other active compound, but also with two or more other active compounds.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor,
30 contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is contemplated. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a
35 compound of the present invention.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, such as about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used. In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered in combination with other compounds which are known in the art to be useful for enhancing sleep quality and preventing and treating sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, antihistamines, benzodiazepines, barbiturates, cyclopyrrolones, GABA agonists, 5HT-2 antagonists including 5HT-2A antagonists and 5HT-2A/2C antagonists, histamine antagonists including histamine H3 antagonists, histamine H3 inverse agonists, imidazopyridines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, other neuropeptide S antagonists, orexin agonists, prokineticin agonists and antagonists, pyrazolopyrimidines, T-type calcium channel antagonists, triazolopyridines, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, armodafinil, APD-125, bentazepam, benzocetamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capromorelin, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, conazepam, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, EMD-281014, eplivanserin, estazolam, eszopiclone, ethchlorynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, gaboxadol, glutethimide, halazepam, hydroxyzine, ibutamoren, imipramine, indiplon, lithium, lorazepam, lormetazepam, LY-156735, maprotiline, MDL-100907, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, methyprylon, midaflur, midazolam, modafinil, nefazodone, NGD-2-73, nisobamate, nitrazepam, nortriptyline, ornortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, ramelteon, reclazepam, roletamide, secobarbital, sertraline, suproclone, TAK-375, temazepam, thioridazine, tiagabine, tracazolate, tranlycypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam,

venlafaxine, zaleplon, zolazepam, zopiclone, zolpidem, and salts thereof, and combinations thereof, and the like, or the compound of the present invention may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with other compounds which are known in the art, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: insulin sensitizers including (i) PPAR γ antagonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone; rosiglitazone; troglitazone; tularik; BRL49653; CLX-0921; 5-BTZD), GW-0207, LG-100641, and LY-300512, and the like); (iii) biguanides such as metformin and phenformin; (b) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (73-7) (insulintropin); and GLP-1 (7-36)-NH₂); (c) sulfonylureas, such as acetohexamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide; (d) α -glucosidase inhibitors, such as acarbose, adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like; (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (atorvastatin, itavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, rosuvastatin, simvastatin, and other statins), (ii) bile acid absorbers/sequestrants, such as cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid[®]; LoCholest[®], and the like, (ii) nicotiny alcohol, nicotinic acid or a salt thereof, (iii) proliferator-activater receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (iv) inhibitors of cholesterol absorption such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and the like, and (acyl CoA:cholesterol acyltransferase (ACAT)) inhibitors such as avasimibe, and melinamide, (v) anti-oxidants, such as probucol, (vi) vitamin E, and (vii) thyromimetics; (f) PPAR α agonists such as beclofibrate, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil; and other fibric acid derivatives, such as Atromid[®], Lipid[®] and Tricor[®], and the like, and PPAR α agonists as described in WO 97/36579; (g) PPAR δ agonists, such as those disclosed in WO97/28149; (h) PPAR α/δ agonists, such as muraglitazar, and the compounds disclosed in US 6,414,002; (i) anti-obesity agents, such as (1) growth hormone secretagogues, growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429, and L-163,255, and such as those disclosed in U.S. Patent Nos. 5,536,716, and 6,358,951, U.S. Patent Application Nos. 2002/049196 and 2002/022637, and PCT Application Nos. WO 01/56592 and WO 02/32888; (2) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (3) cannabinoid receptor ligands, such as cannabinoid CB₁ receptor antagonists or inverse agonists, such as rimonabant,

taranabant, AMT-251, and SR-14778 and SR 141716A (Sanofi Synthelabo), SLV-319 (Solvay), BAY 65-2520 (Bayer) and those disclosed in U.S. Patent Nos. 5,532,237, 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,624,941, 6,028,084, PCT Application Nos. WO 96/33159, WO 98/33765, WO98/43636, WO98/43635, WO 01/09120, WO98/31227, WO98/41519, 5 WO98/37061, WO00/10967, WO00/10968, WO97/29079, WO99/02499, WO 01/58869, WO 01/64632, WO 01/64633, WO 01/64634, W002/076949, WO 03/007887, WO 04/048317, and WO 05/000809; (4) anti-obesity serotonergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (5) β 3-adrenoreceptor agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL- 10 35135A, CGP12177A, BTA-243, Trecadrine, Zeneca D7114, SR 59119A; (6) pancreatic lipase inhibitors, such as orlistat (Xenical®), Triton WR1339, RHC80267, lipstatin, tetrahydrolipstatin, teasaponin, diethylumbelliferyl phosphate, and those disclosed in PCT Application No. WO 01/77094; (7) neuropeptide Y1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY- 357897, CP-671906, GI-264879A, and those disclosed in U.S. Patent No. 6,001,836, and PCT 15 Patent Publication Nos. WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (8) neuropeptide Y5 antagonists, such as GW- 569180A, GW-594884A, GW-587081X, GW-548118X, FR226928, FR 240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104, and those disclosed in U.S. Patent Nos. 6,057,335; 6,043,246; 6,140,354; 6,166,038; 20 6,180,653; 6,191,160; 6,313,298; 6,335,345; 6,337,332; 6,326,375; 6,329,395; 6,340,683; 6,388,077; 6,462,053; 6,649,624; and 6,723,847, European Patent Nos. EP-01010691, and EP- 01044970; and PCT International Patent Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/24768; WO 98/25907; WO 98/25908; WO 98/27063, WO 98/47505; WO 98/40356; WO 99/15516; WO 99/27965; WO 00/64880, WO 25 00/68197, WO 00/69849, WO 01/09120, WO 01/14376; WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 0248152, and WO 02/49648; WO 02/094825; WO 03/014083; WO 03/10191; WO 03/092889; WO 04/002986; and WO 04/031175; (9) melanin-concentrating hormone (MCH) receptor antagonists, such as those 30 disclosed in WO 01/21577 and WO 01/21169; (10) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda), and those disclosed in PCT Patent Application Nos. WO 01/82925, WO 01/87834, WO 02/051809, WO 02/06245, WO 02/076929, WO 02/076947, WO 02/04433, WO 02/51809, WO 02/083134, WO 02/094799, WO 03/004027; (11) melanin-concentrating hormone 2 receptor (MCH2R) agonist/antagonists; (12) orexin 35 receptor antagonists, such as SB-334867-A, and those disclosed in patent publications herein; (13) serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline; (14)

melanocortin agonists, such as Melanotan II; (15) Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, and ME-10145 (Melacure), CHIR86036 (Chiron); PT-141, and PT-14 (Palatin); (16) 5HT-2 agonists; (17) 5HT2C (serotonin receptor 2C) agonists, such as BVT933, DPCA37215, WAY161503, R-1065, and those disclosed in U.S. Patent No. 3,914,250, and PCT Application Nos. WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457; (18) galanin antagonists; (19) CCK agonists; (20) CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623 and SR14613, and those disclosed in U.S. Patent No. 5,739,106; (21) GLP-1 agonists; (22) corticotropin-releasing hormone agonists; (23) histamine receptor-3 (H3) modulators; (24) histamine receptor-3 (H3) antagonists/inverse agonists, such as hioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and O-[3-(1H-imidazol-4-yl)propanol]-carbamates; (25) β -hydroxy steroid dehydrogenase-1 inhibitors (β -HSD-1); (26) PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; (27) phosphodiesterase-3B (PDE3B) inhibitors; (28) NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (29) ghrelin receptor antagonists, such as those disclosed in PCT Application Nos. WO 01/87335, and WO 02/08250; (30) leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (31) leptin derivatives; (32) BRS3 (bombesin receptor subtype 3) agonists such as [D-Phe⁶,beta-Ala¹¹,Phe¹³,Nle¹⁴]Bn(6-14) and [D-Phe⁶,Phe¹³]Bn(6-13)propylamide, and those compounds disclosed in Pept. Sci. 2002 Aug; 8(8): 461-75); (33) CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer); (34) CNTF derivatives, such as axokine (Regeneron); (35) monoamine reuptake inhibitors, such as sibutramine; (36) UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid; (37) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS); (38) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (39) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (40) DGAT2 (diacylglycerol acyltransferase 2) inhibitors; (41) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (42) glucocorticoid antagonists; (43) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (44) dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, sitagliptin; and the compounds disclosed in US 6,699,871, WO 03/004498; WO 03/004496; EP 1 258 476; WO 02/083128; WO 02/062764; WO 03/000250; WO 03/002530; WO 03/002531; WO 03/002553; WO 03/002593; WO 03/000180;

and WO 03/000181; (46) dicarboxylate transporter inhibitors; (47) glucose transporter inhibitors; (48) phosphate transporter inhibitors; (49) Metformin (Glucophage®); (50) Topiramate (Topimax®); (50) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM-43073D, BIM-43004C (Olitvak, D.A. et al., Dig. Dis. Sci. 44(3):643-48 (1999)); (51) 5 Neuropeptide Y2 (NPY2) receptor agonists such as NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (52) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP), and other Y4 agonists such as 1229U91; (54) cyclooxygenase-2 inhibitors such as etoricoxib, celecoxib, valdecoxib, parecoxib, lumiracoxib, BMS347070, tiracoxib or JTE522, ABT963, CS502 and GW406381; (55) Neuropeptide Y1 10 (NPY1) antagonists such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A; (56) Opioid antagonists such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, naltrexone; (57) 11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors such as BVT 3498, BVT 2733, and those disclosed in WO 01/90091, WO 01/90090, WO 01/90092, US 6,730,690 and US 2004-0133011; (58) aminorex; (59) ampechloral; (60) 15 amphetamine; (61) benzphetamine; (62) chlorphentermine; (63) clobenzorex; (64) cloforex; (65) clominorex; (66) clortermine; (67) cyclexedrine; (68) dextroamphetamine; (69) diphemethoxidine, (70) N-ethylamphetamine; (71) fenbutrazate; (72) fenisorex; (73) fenproporex; (74) fludorex; (75) fluminorex; (76) furfurylmethylamphetamine; (77) levamfetamine; (78) levophacetoperane; (79) mefenorex; (80) metamfepramone; (81) 20 methamphetamine; (82) norpseudoephedrine; (83) pentorex; (84) phendimetrazine; (85) phenmetrazine; (86) picilorex; (87) phytopharm 57; and (88) zonisamide., (89) neuromedin U and analogs or derivatives thereof, (90) oxyntomodulin and analogs or derivatives thereof, and (91) Neurokinin-1 receptor antagonists (NK-1 antagonists) such as the compounds disclosed in: U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 25 5,496,833, and 5,637,699.

In another embodiment, the subject compound may be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine 30 oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; 35 amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranlycypromine

and selegiline; moclobemide; venlafaxine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

5 In another embodiment, the subject compound may be employed in combination with anti-Alzheimer's agents; beta-secretase inhibitors; gamma-secretase inhibitors; growth hormone secretagogues; recombinant growth hormone; HMG-CoA reductase inhibitors; NSAID's including ibuprofen; vitamin E; anti-amyloid antibodies; CB-1 receptor antagonists or
10 CB-1 receptor inverse agonists; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, and tacrine; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H₃ antagonists; AMPA agonists; PDE IV inhibitors; GABA_A inverse agonists; or neuronal nicotinic agonists.

 In another embodiment, the subject compound may be employed in combination
15 with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, buspirone, butabarbital, butalbital, capuride,
20 carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam,
25 maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranlycypromaine, trazodone,
30 triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

 In another embodiment, the subject compound may be employed in combination
35 with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or

lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole.

In another embodiment, the subject compound may be employed in combination with acetophenazine, alentemol, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene or trifluoperazine.

In another embodiment, the subject compound may be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone.

In another embodiment, the subject compound may be employed in combination with a nicotine agonist or a nicotine receptor partial agonist such as varenicline, opioid antagonists (e.g., naltrexone (including naltrexone depot), antabuse, and nalmefene), dopaminergic agents (e.g., apomorphine), ADD/ADHD agents (e.g., methylphenidate hydrochloride (e.g., Ritalin® and Concerta®), atomoxetine (e.g., Strattera®), a monoamine oxidase inhibitor (MAOI), amphetamines (e.g., Adderall®)) and anti-obesity agents, such as apo-B/MTP inhibitors, 11Beta-hydroxy steroid dehydrogenase-1 (11Beta-HSD type 1) inhibitors, peptide YY3-36 or analogs thereof, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β 3 adrenergic receptor agonists, dopamine receptor agonists, melanocyte-stimulating hormone receptor analogs, 5-HT2c receptor agonists, melanin concentrating hormone receptor antagonists, leptin, leptin analogs, leptin receptor agonists, galanin receptor antagonists, lipase inhibitors, bombesin receptor agonists, neuropeptide-Y receptor antagonists (e.g., NPY Y5 receptor antagonists), thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor antagonists, other neuropeptide S receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary

neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists, and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination
5 with an anorectic agent such as aminorex, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclohexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levopropylpropylamine, mazindol, mefenorex,
10 metamfetramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; selective serotonin reuptake inhibitor (SSRI); halogenated amphetamine derivatives, including chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination
15 with an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing
20 antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the subject compound may be administered with a pain reliever; a potentiator such as caffeine, an H₂-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine,
25 phenylpropanolamine, pseudoephedrine, oxymetazoline, ephedrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a diuretic; and a sedating or non-sedating antihistamine.

The compounds of the present invention may be administered by oral, parenteral
30 (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-
35 blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients.

5 In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition"
10 is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

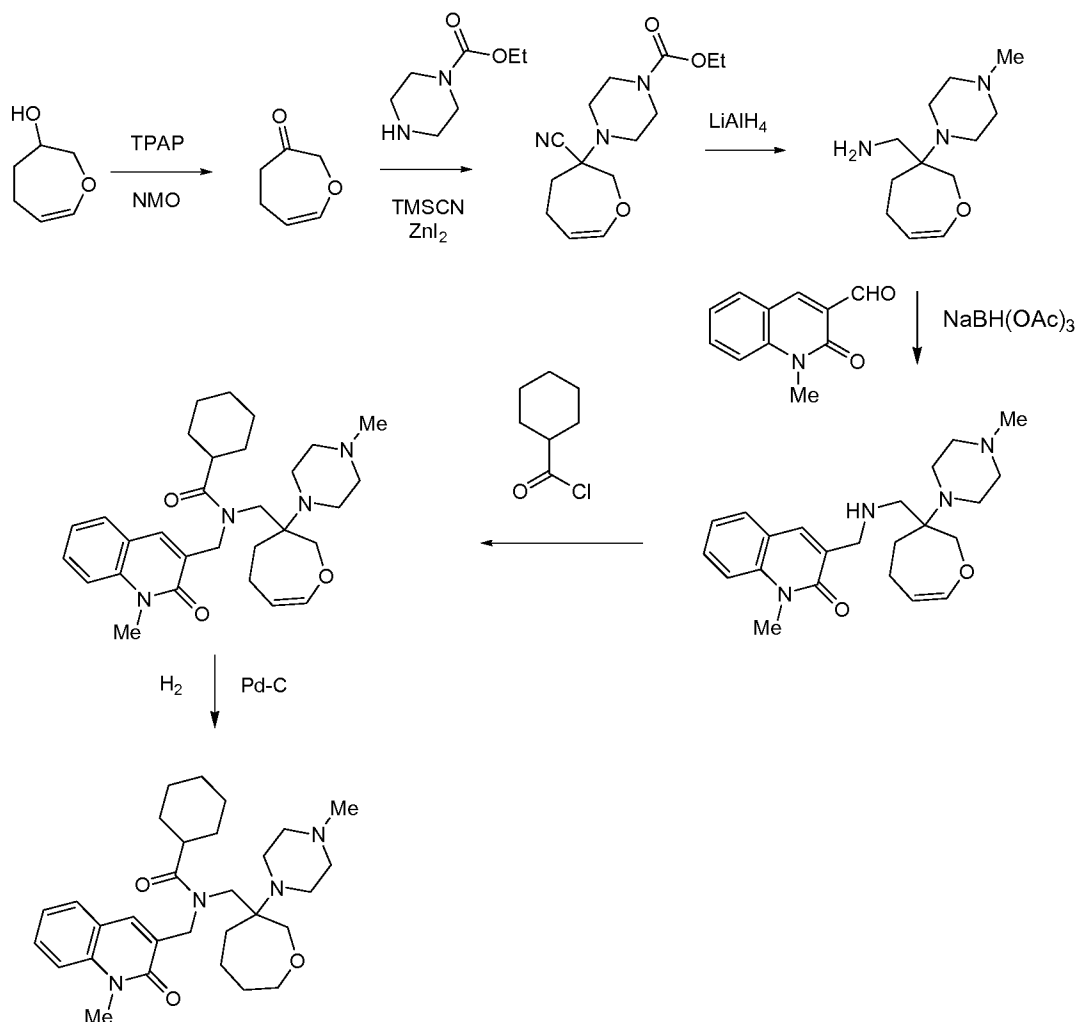
Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such
15 compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium
20 carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action
25 over a longer period. Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the
30 manufacture of aqueous suspensions. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Pharmaceutical compositions of the present compounds may be
35 in the form of a sterile injectable aqueous or oleagenous suspension. The compounds of the present invention may also be administered in the form of suppositories for rectal administration.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention may be employed. The compounds of the present invention may also be formulated for administered by inhalation. The compounds of the present invention may also be administered by a transdermal patch by methods known in the art.

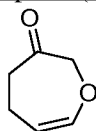
5 Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein. The following abbreviations are used herein: Me: methyl; Et: ethyl; i-Pr: isopropyl; t-Bu: *tert*-butyl; Ar: aryl; Ph: phenyl; Bn: benzyl; Ac: acetyl; THF: tetrahydrofuran; DEAD: diethylazodicarboxylate; DIPEA: N,N-diisopropylethylamine;
10 NMM: N-methylmorpholine; DMAP: 4-dimthylaminopyridine; DMSO: dimethylsulfoxide; EDC: N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide; HOBT: hydroxybenzotriazole hydrate; Boc: *tert*-butyloxy carbonyl; TEA: triethylamine; DCM: dichloromethane; DCE: dichloroethane; BSA: bovine serum albumin; TFA: trifluoroacetic acid; DMF: N,N-dimethylformamide; MTBE: methyl *tert*-butyl ether; SOCl₂: thionyl chloride; CDI: carbonyl
15 diimidazole; PyClu: 1-(chloro-1-pyrrolidinylmethylene)-pyrrolidinium hexafluorophosphate; dba: dibenzylideneacetone; S-Phos: 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; dppf: 1,1'-bis-(diphenylphosphino)ferrocene; rt: room temperature; HPLC: high performance liquid chromatography. The compounds of the present invention can be prepared in a variety of fashions.

20 In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following
25 examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

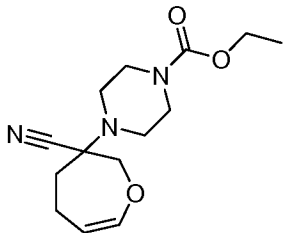
EXAMPLE 1



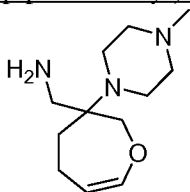
4,5-Dihydrooxepin-3(2H)-one



- To a solution of 2,3,4,5-tetrahydrooxepin-3-ol (308 mg, 2.70 mmole, J. Org. Chem. 2001, 66, 3201-3205) in CH₂Cl₂ (10 ml) was added 500 mg 5A sieves, NMO (379 mg, 3.24 mmole), then TPAP (47.4 mg, 0.135 mmole) at RT. After 72 hr the mixture was filtered through a pad of silica gel washing with dichloromethane and concentrated to a light yellow oil (220 mg, 73%). Used in the next step without purification.

Ethyl 4-(3-cyano-2,3,4,5-tetrahydrooxepin-3-yl)piperazine-1-carboxylate

4,5-Dihydrooxepin-3(2*H*)-one (220 mg, 1.962 mmole) and zinc iodide (31 mg, 0.097 mmole) were combined neat. To this was added TMSCN (0.28 ml, 2.089 mmole) slowly (cooling with cold water bath). After 1 hr a solution of 1-ethoxycarbonylpiperazine (0.32 ml, 2.195 mmole) in MeOH (10 ml) was added then the mixture was heated to reflux. After 16 hr the mixture was cooled to RT and concentrated. Flash column chromatography (25% EtOAc/hexanes) gave the title compound as a clear oil (320 mg, 58%). ¹H-NMR (CDCl₃, 500 MHz) 6.32 (d, J = 6.34 Hz, 1 H), 4.80 (m, 1 H), 4.31 (d, J = 12.94 Hz, 1 H), 4.15 (m, 3 H), 3.55 (bs, 4 H), 2.64 (bs, 4 H), 2.30 (bs, 3 H), 2.16 (m, 1 H), 1.27 (t, J = 7.08 Hz, 3 H).

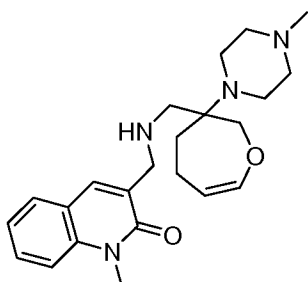
1-[3-(4-Methylpiperazin-1-yl)-2,3,4,5-tetrahydrooxepin-3-yl]methanamine

15

To a solution of ethyl 4-(3-cyano-2,3,4,5-tetrahydrooxepin-3-yl)piperazine-1-carboxylate (320 mg, 1.146 mmole) in dry THF (5 ml) was added LAH (1.75 ml, 3.50 mmole) at 0 °C. After 30 min the mixture was warmed to RT. After 16 hr the mixture was cooled to 0 °C and slowly quenched with 2M NaOH until gas evolution had ceased and a fine white precipitate formed. Anhydrous Na₂SO₄ was added and the mixture stirred for 15 min. The slurry was filtered through a pad of Celite washing with THF. The filtrate was concentrated to give the title compound as a clear oil (250 mg, 97%) which was used in the next step without purification. ¹H-NMR (CDCl₃, 500 MHz) d 6.23 (d, J = 6.83 Hz, 1 H), 4.60 (m, 1 H), 4.11 (dd AB, J = 12.46 and 58.83 Hz, 2 H), 2.77 (s, 2 H), 2.70 (m, 4 H), 2.43 (m, 4 H), 2.27 (s, 3 H), 2.13 (m, 4 H).

25

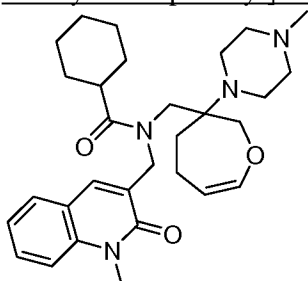
1-Methyl-3-[(3-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydrooxepin-3-yl)methyl]amino)methyl]quinolin-2(1*H*)-one



To a solution of 1-[3-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydrooxepin-3-yl]methanamine (250 mg, 1.109 mmole) in 1,2-dichloroethane (4 ml) was added AcOH (290 μ L, 5.07 mmole) then 1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (190 mg, 1.015 mmole). After 20 min sodium triacetoxyborohydride (323 mg, 1.522 mmole) was added. After 16 hr the mixture was diluted with 1M aqueous NaOH and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (MgSO_4), filtered, and concentrated. Flash column chromatography (gradient, 0-10% MeOH/ CH_2Cl_2) gave the title compound as a pale yellow oil (279 mg, 69%).

¹H-NMR (CDCl_3 , 500 MHz) δ 7.70 (s, 1 H), 7.56 (m, 2 H), 7.35 (d, J = 8.30 Hz, 1 H), 7.25 (m, 1 H), 6.24 (d, J = 6.6 Hz, 1 H), 4.59 (m, 1 H), 4.25 (dd AB, J = 12.94 and 44.19 Hz, 2 H), 3.80 (m, 2 H), 3.74 (s, 3 H), 2.71-2.61 (m, 6 H), 2.44 (m, 4 H), 2.28 (s, 3 H), 2.21-2.06 (m, 4 H), 1.51 (m, 1 H).

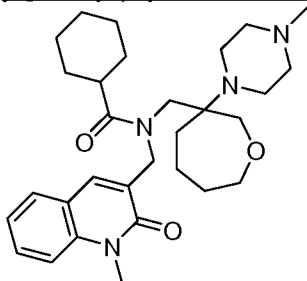
N-[1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-*N*-{3-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydrooxepin-3-yl)methyl}cyclohexanecarboxamide



To a solution of 1-methyl-3-[(3-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydrooxepin-3-yl)methyl]amino)methyl]quinolin-2(1*H*)-one (100 mg, 0.252 mmole) in CH_2Cl_2 (1.5 ml) was added TEA (0.053 ml, 0.378 mmole) then cyclohexanecarbonyl chloride (0.044 ml, 0.328 mmole). After 2 hr the mixture was concentrated. The crude material was purified by preparative reversed-phase HPLC (30x150mm Waters Sunfire, 5- 50% CH_3CN /water containing 0.1% TFA over 20 min at 50 mL/min). Fractions containing the product were pooled and concentrated. The residue was taken up in MeOH then passed through Dowex 1x2-400 ion exchange resin (prewashed with 1M NaOH, H_2O , MeOH) washing with MeOH. The filtrate was

concentrated to give the title compound as a white solid (89 mg, 70%). ¹H-NMR (CDCl₃, 500 MHz) d 7.58 (t, J = 8.30 Hz, 1 H), 7.52 (d, J = 7.57 Hz, 1 H), 7.39 (d, J = 8.30 Hz, 1 H), 7.25 (m, 1 H), 7.22 (s, 1 H), 6.21 (d, J = 6.34 Hz, 1 H), 5.24 (d, J = 19.77 Hz, 1 H), 4.60 (m, 2 H), 4.44 (d, J = 13.19 Hz, 1 H), 4.24 (d, J = 14.16 Hz, 1 H), 4.05 (d, J = 13.18 Hz, 1 H), 3.78 (s, 3 H), 3.07 (d, J = 14.16 Hz, 1 H), 2.74 (m, 1 H), 2.62 (m, 2 H), 2.45-2.21 (m, 6 H), 2.26 (s, 3 H), 2.16-2.05 (m, 2 H), 1.82-1.48 (m, 9 H), 1.25-1.06 (m, 3 H). HRMS (M+H)⁺ calculated 507.3330, found 507.3329.

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-*N*-{[3-(4-methylpiperazin-1-yl)oxepan-3-yl]methyl}cyclohexanecarboxamide



N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-*N*-{[3-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydrooxepin-3-yl]methyl}cyclohexanecarboxamide (59 mg, 0.116 mmole) was hydrogenated at atmospheric pressure (H₂ balloon) with 10% Pd/C (13 mg, 0.012 mmole) in EtOH at RT. After 16 hr the mixture was filtered through a pad of Celite washing with EtOH and concentrated to an off-white solid (57 mg, 96%). ¹H-NMR (CDCl₃, 500 MHz) d 7.58 (t, J = 7.08 Hz, 1 H), 7.52 (d, J = 6.59 Hz, 1 H), 7.39 (d, J = 8.30 Hz, 1 H), 7.25 (m, 1 H), 7.21 (s, 1 H), 5.34 (d, J = 19.78 Hz, 1 H), 4.58 (d, J = 19.78 Hz, 1 H), 4.31 (d, J = 14.41 Hz, 1 H), 4.01 (m, 1 H), 3.88 (dd AB, J = 13.91 and 74.95 Hz, 1 H), 3.78 (s, 3 H), 3.37 (m, 1 H), 2.91 (d, J = 14.65 Hz, 1 H), 2.80-2.26 (m, 12 H), 1.84-1.06 (m, 17 H). HRMS (M+H)⁺ calculated 509.3486, found 509.3491.

The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, as described in the foregoing Reaction Schemes and Examples. The requisite amine, acid chloride, and aldehyde starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

Name	MS <i>m/z</i> (M+H)
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N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{4-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl}cyclohexanecarboxamide	495.3349
N-({4-[4-(1-methylethyl)piperazin-1-yl]tetrahydro-2H-pyran-4-yl)methyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	523.36857
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{4-(4-phenylpiperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl}cyclohexanecarboxamide	557.34958
N-{{4-(4-benzylpiperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	571.36666
N-({4-[4-(2-hydroxyethyl)piperazin-1-yl]tetrahydro-2H-pyran-4-yl)methyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	525.34616
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(4-piperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl]cyclohexanecarboxamide	481.317
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-({4-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]tetrahydro-2H-pyran-4-yl)methyl}cyclohexanecarboxamide	563.3187
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}cyclohexanecarboxamide	495.3324
N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	481.3167

4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl}methyl}cyclohexanecarboxamide	511.3288
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl}methyl}-N~2~-(2,2,2-trifluoroethyl)-L-valinamide	566.3287
N-[3-methoxy-2-methyl-2-(4-methylpiperazin-1-yl)propyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	483.3334
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl}methyl}cyclohexanecarboxamide	
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl}methyl}cyclohexanecarboxamide	
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3-piperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl]cyclohexanecarboxamide	481.3174
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl}methyl}cycloheptanecarboxamide	509.3487
2-ethyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl}methyl}butanamide	483.3333
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl}methyl}-2-propylpentanamide	511.3645

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}cyclopentanecarboxamide	481.3172
2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}acetamide	495.3327
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydrofuran-3-yl]methyl}cyclohexanecarboxamide	481.3169
N- {[3-(4-methyl-1,4-diazepan-1-yl)tetrahydro-2H-pyran-3-yl]methyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	509.3492
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(2-phenylpiperidin-1-yl)ethyl]cyclohexanecarboxamide	486.3114
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(2-phenylpyrrolidin-1-yl)ethyl]cyclohexanecarboxamide	472.2959
N- {2-[benzyl(methyl)amino]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	446.2802
N-[(1-methyl-2-oxo-5-phenyl-1,2-dihydropyridin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}cyclohexanecarboxamide	521.3491
(1S,4R)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}bicyclo[2.2.1]heptane-2-carboxamide	507.3334

3-methoxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} cyclohexanecarboxamide	525.3446
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}-4-(trifluoromethyl)cyclohexanecarboxamide	563.3207
2-methyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} cyclohexanecarboxamide	509.3497
. 4-(1-methylethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} cyclohexanecarboxamide	537.3807
. 4-tert-butyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} cyclohexanecarboxamide	551.397
2-cyclohexyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} acetamide	509.3498
. 4-methyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} pentanamide	483.3334
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} benzamide	489.2872
3-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl} propanamide	509.3499

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}-2-phenylacetamide	503.3026
2-cycloheptyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}acetamide	523.3654
3,3-difluoro-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}cyclopentanecarboxamide	517.2988
. 4,4-difluoro-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl]methyl}cyclohexanecarboxamide	531.315
N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-benzothiophene-2-carboxamide	528.26
N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-3-phenylpropanamide	500.32
(1R,2R,4R)-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]bicyclo[2.2.1]hept-5-ene-2-carboxamide	488.32
(1S,2S)-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-2-phenylcyclopropanecarboxamide	512.32
N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclopropanecarboxamide	436.28

3-methyl-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]butanamide	452.32
3-cyclopentyl-1- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]urea	479.33
N-[(1-morpholin-4-ylcyclohexyl)methyl]-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	466.308
N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-ylcyclohexyl)methyl]cyclohexanecarboxamide	464.3285
N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	479.337
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	493.3522
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclobutyl]methyl}cyclohexanecarboxamide	465.3212
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclopentyl]methyl}cyclohexanecarboxamide	479.3367
(1R,2R,4R)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclopentyl]methyl}bicyclo[2.2.1]hept-5-ene-2-carboxamide	489.3218

2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclopentyl]methyl}acetamide	479.337
2-(1-hydroxycyclopentyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}acetamide	509.3487
cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	509.3497
4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	523.366
cis-4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	523.364
trans-4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	523.3638
N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	497.6
N- {[1-(2-methoxyethyl)-2-oxo-1,2-dihydroquinolin-3-yl]methyl}-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	537.6
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-ylcycloheptyl)methyl]cyclohexanecarboxamide	494.54

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-ylcyclopentyl)methyl]cyclohexanecarboxamide	466.3048
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-ylcyclohexyl)methyl]cyclohexanecarboxamide	478.3428
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-ylcyclohexyl)methyl]cyclohexanecarboxamide	480.3217
cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-ylcyclohexyl)methyl]cyclohexanecarboxamide	494.54
cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-ylcyclohexyl)methyl]cyclohexanecarboxamide	496.51
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-ylcyclopentyl)methyl]cyclohexanecarboxamide	464.3269
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-ylcycloheptyl)methyl]cyclohexanecarboxamide	494.3373
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl]methyl}cyclohexanecarboxamide	493.3533

The following compounds were prepared using the foregoing methodology, but substituting commercially supplied amines for 1-[3-(4-Methylpiperazin-1-yl)-2,3,4,5-tetrahydrooxepin-3-yl]methanamine, as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

Name	MS <i>m/z</i> (M+H)
N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)benzamide	465.24
3-methyl-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)butanamide	445.27
3-tert-butyl-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(2-phenyl-2-piperidin-1-ylethyl)urea	460.28
2-methyl-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	422.2
N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-2-phenyl-N-(2-phenyl-2-piperidin-1-ylethyl)acetamide	479.26
N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	408.18

N-[1-(2-methylphenyl)piperidin-4-yl]-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	457.27
3-methyl-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1,2,3,4-tetrahydronaphthalen-1-yl)butanamide	388.22
N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)thiophene-2-carboxamide	471.2
3-(2-chlorophenyl)-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(1,2,3,4-tetrahydronaphthalen-1-yl)urea	457.16
3-(2-methoxyphenyl)-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(1,2,3,4-tetrahydronaphthalen-1-yl)urea	453.21
3-cyclopentyl-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(2-phenyl-2-piperidin-1-ylethyl)urea	472.28
3-cyclohexyl-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(2-phenyl-2-piperidin-1-ylethyl)urea	486.3
2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-1-yl)-2-phenylethyl]acetamide	501.3203
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-1-yl)-2-phenylethyl]cyclohexanecarboxamide	501.3204

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide	486.3108
2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-1-yl)ethyl]acetamide	425.2921
2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)acetamide	486.3108
cis-4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide	516.3221
2-(1-hydroxycyclopentyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)acetamide	524.2908
cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide	502.3064
N-(1-benzylpiperidin-3-yl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	472.2934
N-[2-(3,4-dihydroisoquinolin-2(1H)-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	458.2802
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-{4-[2-(4-methylphenyl)ethyl]piperidin-1-yl}ethyl)cyclohexanecarboxamide	528.3585

N-[2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	518.3014
N-[2-(2,3-dihydro-1H-indol-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	444.44
N-[2-(4-benzylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	501.53
N-[2-(4-benzylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	501.52
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[3-(2-methylphenyl)pyrrolidin-1-yl]ethyl}cyclohexanecarboxamide	486.3111
N-{2-[2-(1H-indol-2-yl)piperidin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	525.3222
. 1-tert-butyl 2-methyl (2S,4S)-4-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}pyrrolidine-1,2-dicarboxylate	526.2931
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(2-phenyl-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)ethyl]cyclohexanecarboxamide	536.3021
benzyl 3-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino]-2-phenylpiperidine-1-carboxylate	592.3192

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-piperidin-1-yl-2-pyridin-3-ylethyl)cyclohexanecarboxamide	487.306
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[2-(phenoxymethyl)morpholin-4-yl]ethyl}cyclohexanecarboxamide	518.3015
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-1-yl)ethyl]cyclohexanecarboxamide	425.2909
N-[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	410.2799
N-[2-(dimethylamino)-1-methylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	384.264
benzyl {2-[(tert-butoxycarbonyl)amino]ethyl}{2-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}ethyl}carbamate	619.3487
N-{2-[4-(2,3-dihydro-1H-inden-2-yl)piperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	527.3382
tert-butyl [(3R,4R)-1-benzyl-4-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino]pyrrolidin-3-yl]carbamate	573.3432
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[4-(phenylcarbonyl)piperazin-1-yl]ethyl}cyclohexanecarboxamide	515.3062

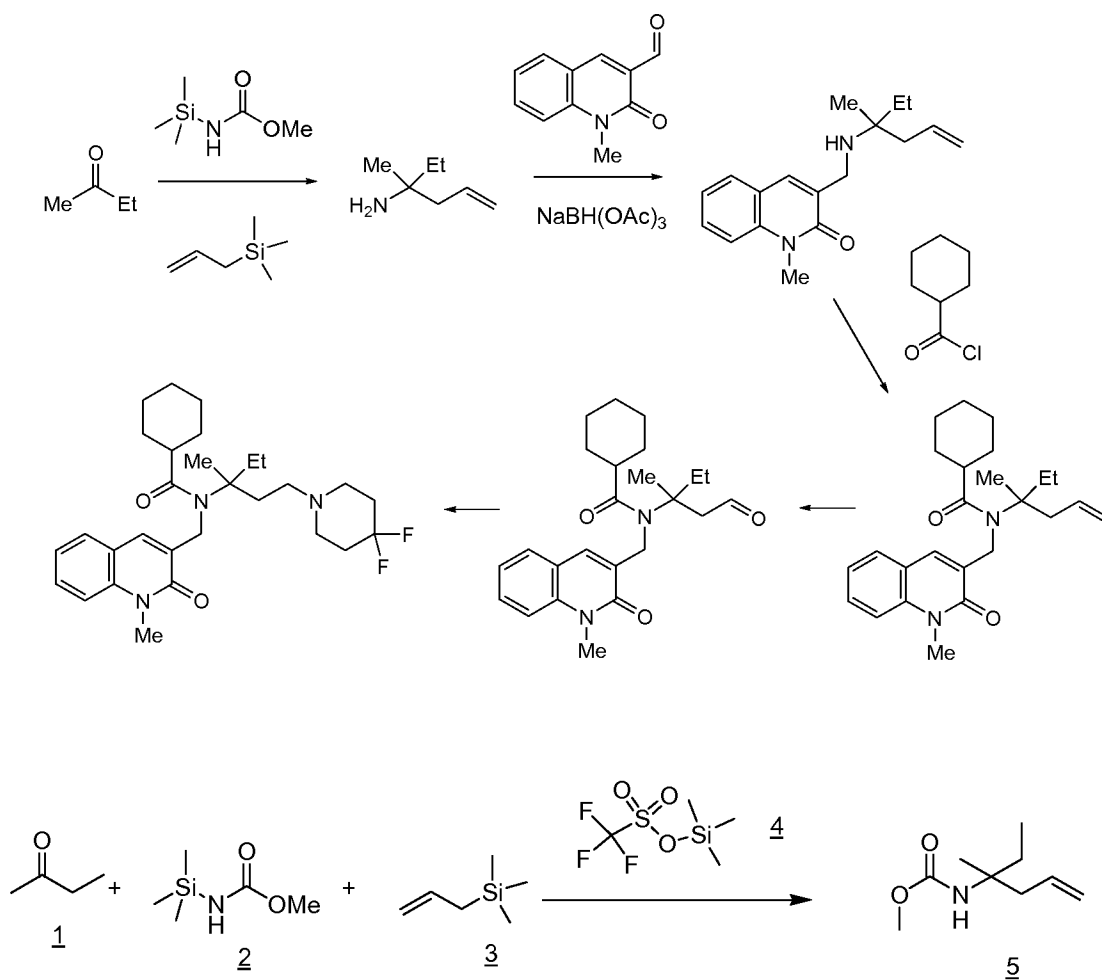
N-{2-[3-(1,3-benzoxazol-2-yl)piperidin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	527.3034
N-[2-(4-benzylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	501.3227
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(2S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]cyclohexanecarboxamide	435.3001
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1S,2R)-2-phenylcyclopentyl]cyclohexanecarboxamide	443.2691
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3R,4R)-1-methyl-3-phenylpiperidin-4-yl]cyclohexanecarboxamide	472.2954
N-[2-(3,3-dimethylpiperidin-2-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	438.3115
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1S,2S)-2-phenylcyclopentyl]cyclohexanecarboxamide	443.269
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenylcyclopentyl)cyclohexanecarboxamide	443.2696
N-[3-(diethylamino)-1,1-dimethylpropyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	440.3266

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1S,9aR)-octahydro-2H-quinolizin-1-ylmethyl]cyclohexanecarboxamide	450.3111
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1-methyl-3-pyrrolidin-1-ylpropyl)cyclohexanecarboxamide	424.2954
N-(1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	440.2903
N-(1,1-dimethyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	454.3058
N-(1,1-dimethyl-3-pyrrolidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	438.311
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(3-phenylpyrrolidin-1-yl)ethyl]cyclohexanecarboxamide	472.2954
N-[2-(dimethylamino)-2-pyridin-2-ylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	447.2752
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[4-(1-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl}cyclohexanecarboxamide	507.3687
tert-butyl {[1-(2-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)ethyl]piperidin-3-yl)methyl} carbamate	539.3584

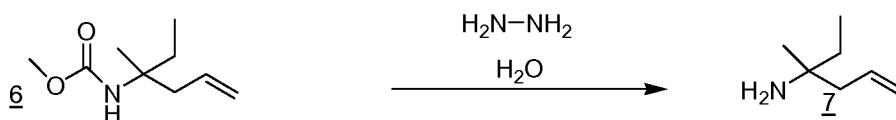
tert-butyl 1-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate	544.3173
N-[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	410.2798
N- {[1-(1-methylethyl)pyrrolidin-2-yl]methyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	424.2955
N- {[1-(1-methylethyl)pyrrolidin-2-yl]methyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	424.2955
N-[(3S)-1-benzylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	458.43
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-piperazin-1-ylethyl)cyclohexanecarboxamide	511.53
N-[(3R)-1-benzylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	458.44
N-(1,1-dimethyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	452.49
tert-butyl 4-(3-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-3-methylbutyl)piperazine-1-carboxylate	553.52

tert-butyl 4-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)ethyl)piperidine-1-carboxylate	510.44
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-piperidin-4-ylethyl)cyclohexanecarboxamide	410.29

EXAMPLE 2



To an oven dried flask at 0C was added anhydrous CH₂Cl₂ (200mL) followed by 4 (8.66 g, 39 mmol). After 5 minutes, a mixture of 1(28.1 g, 390 mmol) and 2 (57.4 g, 390 mmol) in 50 mL anhydrous CH₂Cl₂ was added to the reaction. Next a solution of allyltrimethylsilane 3 (44.5 g, in 50ml CH₂Cl₂) was added to the reaction. The solution was stirred and warmed to ambient temperature overnight. The reaction was quenched with NH₃ saturated CHCl₃ (20 mL) and concentrated in vacuo to give an oil. Flash chromatography (silica, 5-10% EtOAc/hexanes over 20 min) provided 5 (26 g, 39% yield) as a clear oil.

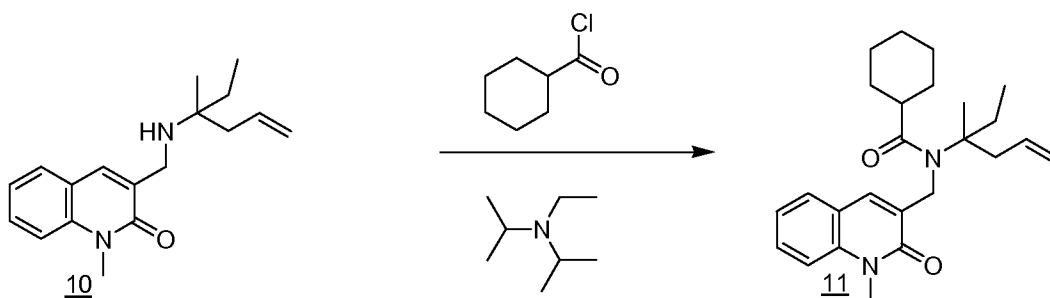


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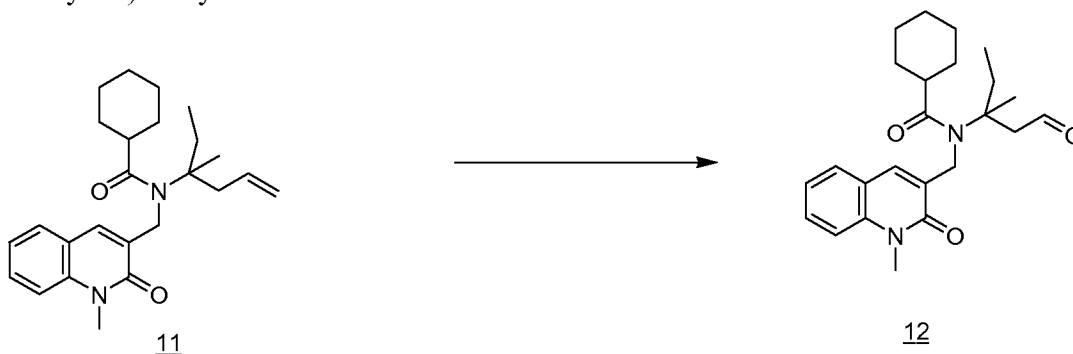
To 6 (9.2 g, 53.7 mmol) in ethylene glycol (270 ml) was added hydrazine hydrate(10.42 ml, 215 mmol) and potassium hydroxide (36.2 g, 645 mmol). The reaction was heated to reflux and stirred overnight. The reaction was cooled to room temperature and then diluted with sat. NaHCO₃, extracted with CH₂Cl₂ 3 times. The organics were combined, dried over Na₂SO₄ and concentrated in vacuo to provide a clear oil. Flash chromatography (silica, 12g column, 0-8% MeOH/NH₃ sat'd CHCl₃) provided 7 (3.5g, 57.5% yield) as a clear oil.



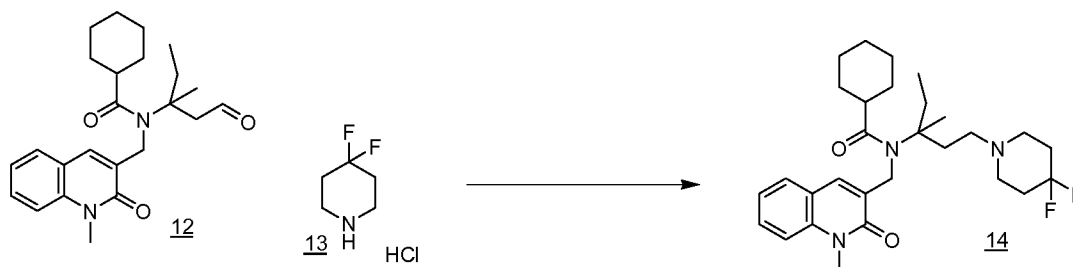
A mixture of 8 (900 mg, 4.81 mmol) and 9 (560 mg, 4.95 mmol) in dichloroethane (24 mL) was stirred at room temperature for 45 minutes. Next sodium triacetoxyborohydride (3.06 g, 14.42 mmol) and acetic acid (1.65 ml, 28.8 mmol) were added. After 1 hour, the reaction was complete. The reaction was quenched with sat. NaHCO₃, extracted with CH₂Cl₂ 3 times. The organics were combined, dried over Na₂SO₄ and concentrated in vacuo to yield a yellow oil. Flash chromatography (silica, 0-5% MeOH/ NH₃ saturated CH₃Cl) provided 10 (350 mg, 25% yield) as a yellow solid.



To 10 (300 mg, 1.055 mmol) in dichloroethane (10 ml) was added cyclohexane carbonyl chloride (1.4 ml, 10.55 mmol) and diisopropylethylamine (2.7 ml, 15.82 mmol). The reaction was stirred overnight. Next the reaction was quenched with MeOH and diluted with CH₂Cl₂, washed with sat. NaHCO₃, dried over Na₂SO₄ and concentrated in vacuo to give an orange oil. Flash chromatography (silica, 8 g col, 2-35% EtOAc/hexanes) provided 11 (284 mg, 68% yield) as a yellow foam.



To a mixture of 11 (284 mg, 0.72 mmol) in t-BuOH (1.8 mL) and THF (0.6 mL) at room temperature was added N-methylmorpholine N-oxide (337 mg, 1.44 mmol) followed by osmium tetroxide (0.027 mL, 0.022 mmol). The mixture was stirred at room temperature overnight. The reaction was then diluted with phosphate buffer (pH 7, 5 mL). Sodium periodate (693 mg, 3.24 mmol) was then added and the cloudy solution was stirred vigorously for 2 hours. Next it was diluted with water and extracted three times with ethyl acetate. The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give 12 as a yellow solid (251 mg, 88%).



N-(1-ethyl-1-methyl-3-(4,4-difluoro-piperidin-1-yl)propyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide

5 To 12 (125 mg, 0.315 mmol) and 13 (54.6 mg, 0.347 mmol) in dichloroethane (2 ml) was added sodium triacetoxyborohydride (100 mg, 0.473 mmol), acetic acid (0.054 ml, 0.946 mmol) and sodium acetate (51.7 mg, 0.63 mmol). The reaction was stirred at room temperature for one hour. Next the reaction was diluted with sat. NaHCO₃ and extracted with CH₂Cl₂ 3 times. The combined organics were dried over Na₂SO₄, filtered, and concentrated in vacuo to give an oil. Acidic reversed phase chromatography provided 14 as a foamy solid (66 mg, 41.7% yield). ¹H NMR (500 MHz, CD₃OD) 7.60 (t, 1H), 7.56 (d, 1H, J = 8 Hz), 7.42 (d, 1H, J = 8 Hz), 7.29 (d, 1H, J = 8 Hz), 4.50 (m, 2H), 3.79 (s, 3H), 3.49 (s, 3H), 2.55 (m, 4H), 2.44 (m, 1H), 2.19 (m, 2H), 1.89 (m, 12H), 1.20 (s, 4H), 0.87 (m, 3H). HRMS (ES, M+1) calc'd 502.3240, found 502.3239.

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The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

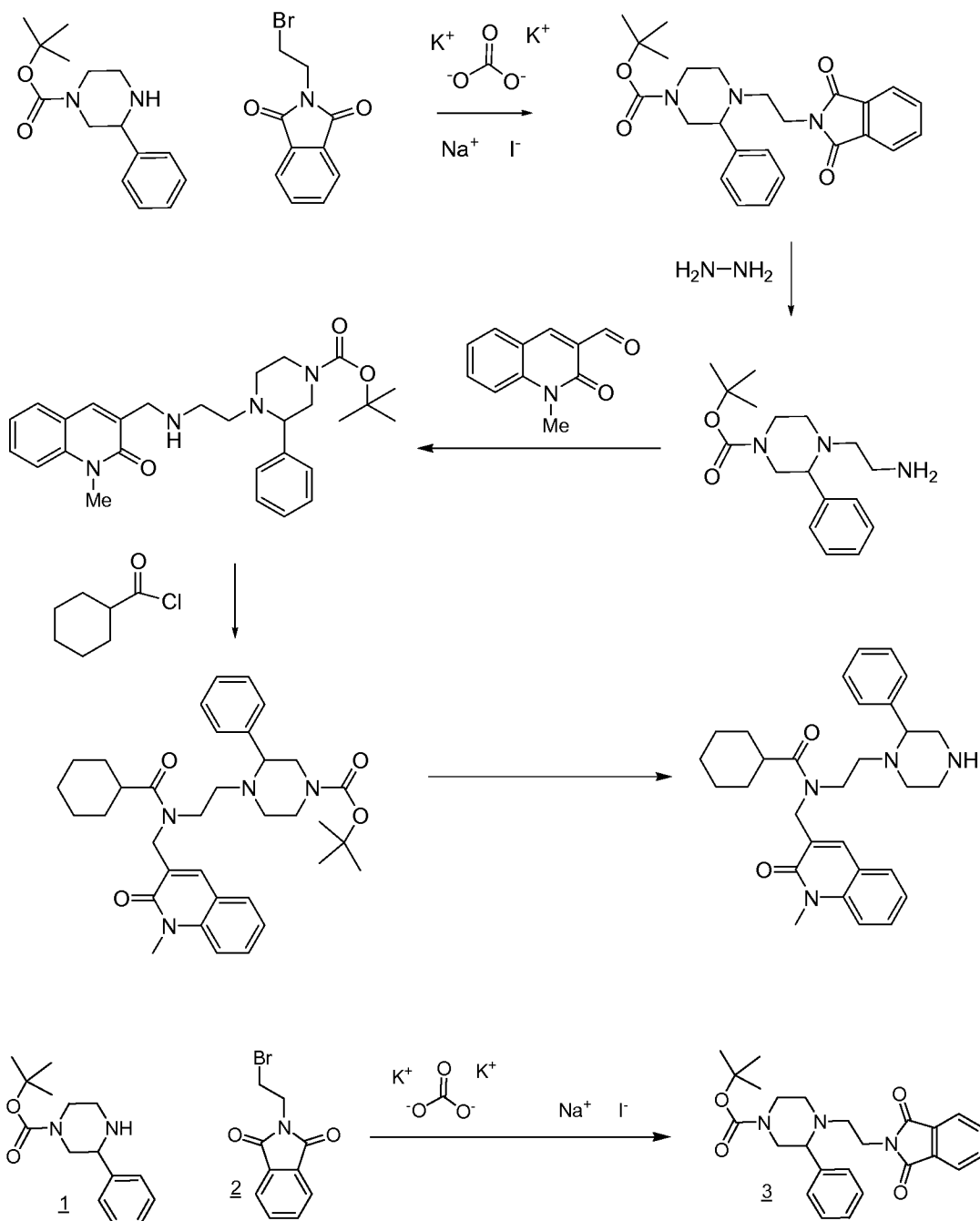
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Name	MS <i>m/z</i> (M+H)
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]tetrahydro-2H-pyran-4-carboxamide	468.3231
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-4,4-difluoro-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	502.325

N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	468.3228
N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	468.3229
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]tetrahydro-2H-pyran-3-carboxamide	468.3221
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]tetrahydro-2H-pyran-2-carboxamide	468.322
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-2-(tetrahydrofuran-3-yl)acetamide	468.3222
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-2-(1-hydroxycyclopentyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]acetamide	482.3378
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	466.4
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	466.4
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	466.4

N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	468.4
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]cyclohexanecarboxamide	470.3
N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]cyclohexanecarboxamide	472.3

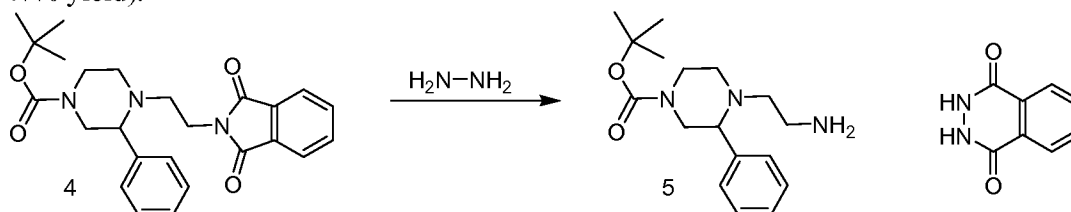
EXAMPLE 3



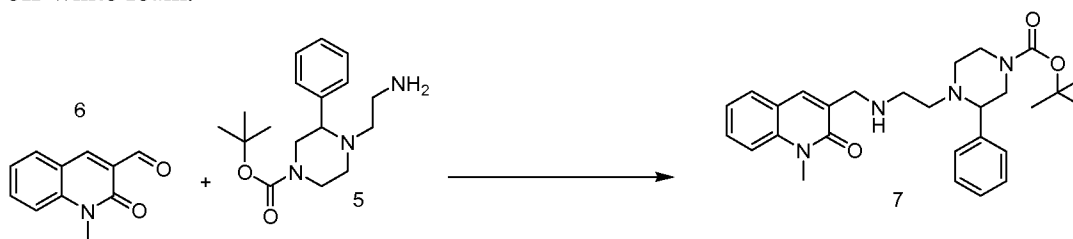
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To a solution of potassium carbonate (1.59g, 11.5 mmol) and sodium iodide (37 mg, .247 mmol) in DMF (15 mL) with stirring was added 1 (1.017 g, 3.88 mmol) and 2 (1.107 g, 4.36 mmol). The reaction was heated to 50 C overnight. Next the reaction was cooled to room temperature, partitioned with EtOAc and H₂O, washed with H₂O and brine. The organics were

dried over Na₂SO₄ (anhydrous), decanted, concentrated and dried to yield clear oil. Flash chromatography [silica, 120 g column, 0-100 % EtOAc/hexane] provided a white foam (810 mg, 47% yield).



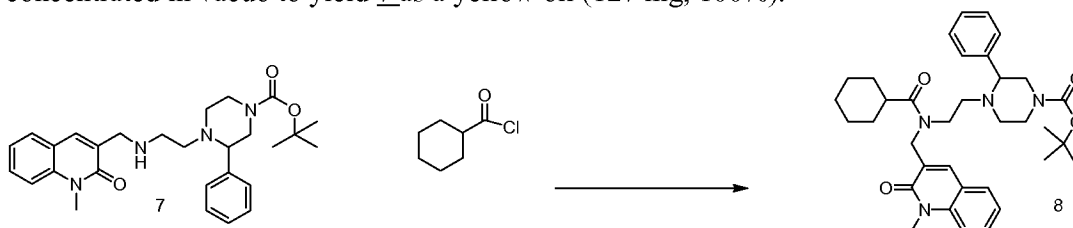
5 To a solution of 4 (790 mg, 1.814 mmol) in EtOH (10 ml) was added hydrazine monohydrate (200 uL, 3.25 mmol). The reaction was heated to 80 C. After 5 hours, added additional hydrazine (100 uL, 1.6 mmol) and continued heating for 24 hours. The reaction was cooled and filtered. The filtrate was concentrated and dried to yield 5 (792 mg, 140% yield) an off-white foam.



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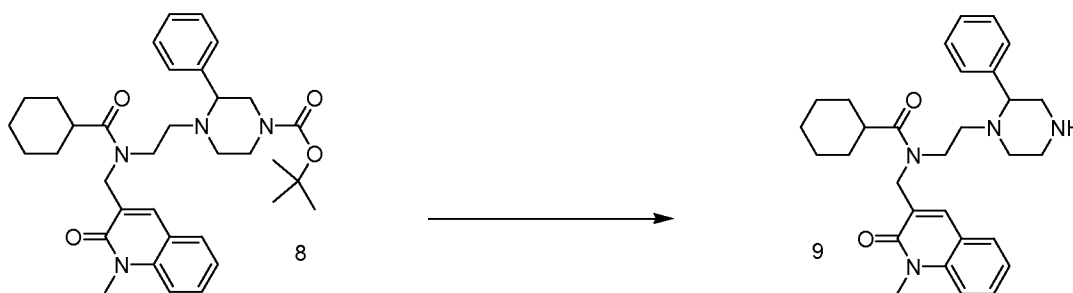
A mixture of 6 (50 mg, 0.267 mmol) and 5 (82 mg, 0.267 mmol) in dichloroethane (2 mL) was stirred at room temperature for 45 minutes. Next sodium triacetoxyborohydride (170 mg, 0.801 mmol) and acetic acid (0.092 ml, 1.6 mmol) were added. After 24 hours the reaction was complete. The reaction was quenched with sat. NaHCO₃, extracted with CH₂Cl₂ three times. The organics were combined, dried over Na₂SO₄ and concentrated in vacuo to yield 7 as a yellow oil (127 mg, 100%).

15



20

To 7 (127 mg, 0.267 mmol) in dichloroethane (1 ml) was added cyclohexane carbonyl chloride (.054 ml, 0.401 mmol) and diisopropylethylamine (0.233ml, 1.335 mmol). The reaction was stirred overnight. Next the reaction was quenched with MeOH and diluted with CH₂Cl₂, washed with sat. NaHCO₃, dried over Na₂SO₄ and concentrated in vacuo to give an oil. Basic reversed phase chromatography provided 8 (60 mg, 68%) as a foam.



N-{2-[2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide

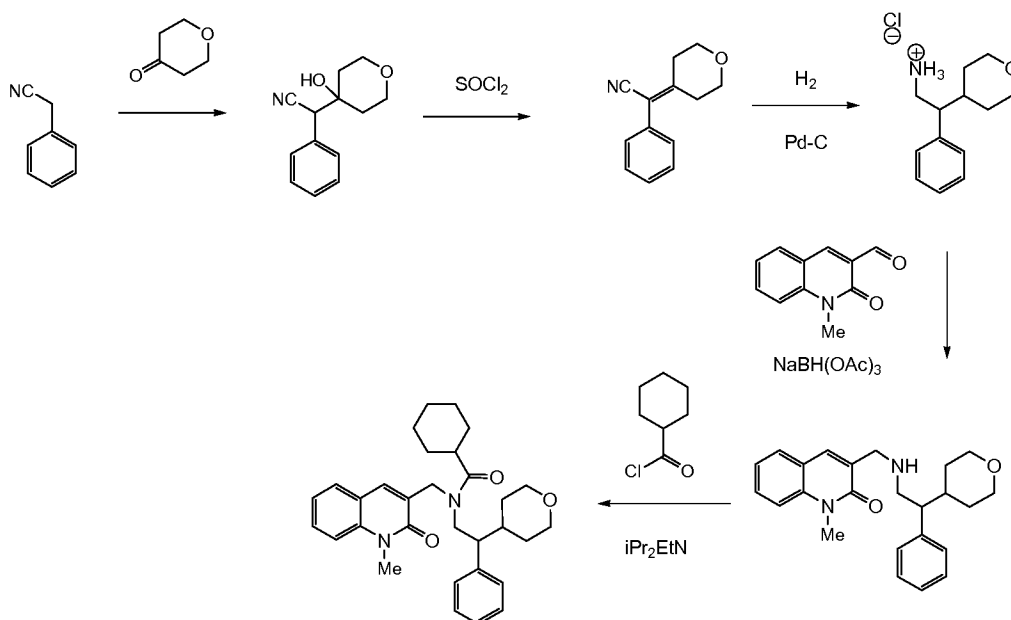
- 5 To 8 (60mg, 0.102 mmol) in CH₂Cl₂ (1 ml) was added TFA (.6 ml, 7.5 mmol). After 2 hours, the reaction was concentrated and azeotroped with toluene to give a yellow oil. Acidic reverse phase chromatography provided 9 (27 mg, 54% yield) as a foam. ¹H NMR (500 MHz, CD₃OD) d 7.58 (t, 1H, J = 8 Hz), 7.52 (m, 1H), 7.49 (d, 1H, J = 8 Hz), 7.39 (d, 1H, J = 8 Hz), 7.31 (m, 3H), 7.23 (m, 3H), 4.45 (m, 4H), 4.20 (d, 1H, J = 15 Hz), 3.75 (s, 3H), 3.55 (m, 2H), 3.44 (m, 1H), 3.37 (m, 1H), 3.22 (m, 3 H), 3.00(m, 4H), 2.71(m, 3H), 2.35 (m, 1H), 2.25 (m, 2H), 2.15(m, 2H), 1.5 (m, 3H).
- 10 HRMS (ES, M+1) calc'd 487.2995 found 487.3062.

- 15 The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

Name	MS <i>m/z</i> (M+H)
N-{2-[4-(cyclopropylmethyl)-2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	541.3532
N-{2-[4-(cyclopropylcarbonyl)-2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	555.3338

N-{2-[4-(cyclobutylmethyl)-2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	555.3687
N-[2-(4-benzyl-2-phenylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	577.3527

EXAMPLE 4



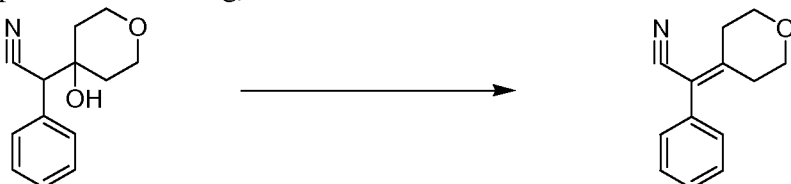
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(4-hydroxytetrahydro-2H-pyran-4-yl)(phenyl)acetonitrile

To benzyl cyanide (1.970 ml, 19.39 mmol) was added THF (100 ml) and the solution cooled to -78 °C. *n*-butyllithium (2.5 M in hexanes, 7.84 ml, 19.59 mmol) was added dropwise over 20 min via syringe pump and the solution stirred 30 min. Tetrahydro-4H-pyran-4-one (1.791 ml, 19.39 mmol) was added over 20 min via syringe pump and the solution stirred

for 3 hours. The reaction was quenched by addition of ice-cold satd. NH_4Cl and then partitioned between cold satd. NH_4Cl and CH_2Cl_2 . The aqueous portion was extracted 2x CH_2Cl_2 , dried (Na_2SO_4), and concentrated *in vacuo*. Took up material in CH_2Cl_2 and allowed to crystallize over the weekend. The crystals were washed with diethyl ether and used without further purification. 3.14 g, 81%.

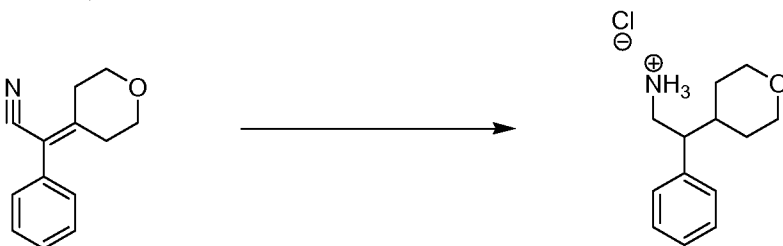
5



phenyl(tetrahydro-4H-pyran-4-ylidene)acetonitrile

(4-hydroxytetrahydro-2H-pyran-4-yl)(phenyl)acetonitrile (500 mg, 2.301 mmol) was dissolved in pyridine (10 ml). SOCl_2 (1.680 ml, 23.01 mmol) was added and the reaction was stirred for 25 minutes then concentrated *in vacuo*. The crude material was purified by silica gel chromatography on an Isco Companion (5 to 35% EA/hexanes over 20 min, 40 g silica column). The desired fractions were combined and concentrated *in vacuo*. 450 mg, 98%.

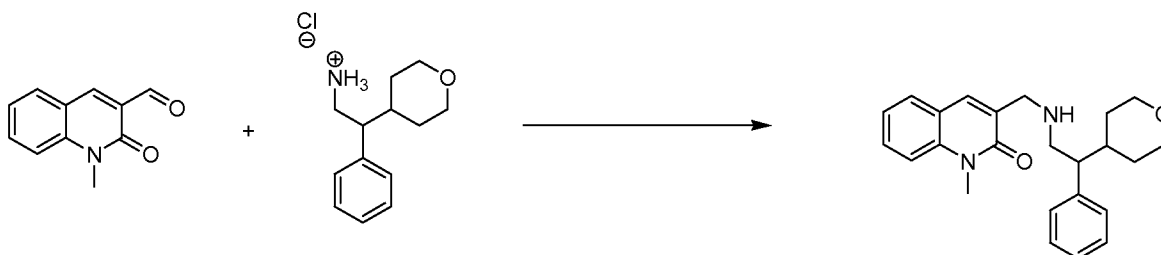
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15 2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethanaminium chloride

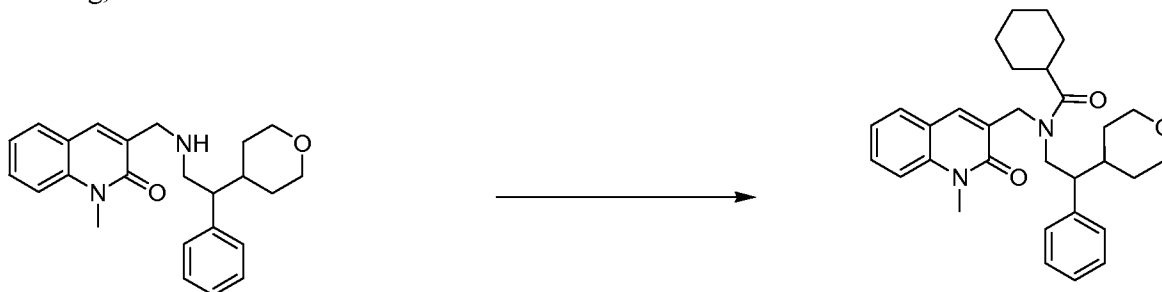
To phenyl(tetrahydro-4H-pyran-4-ylidene)acetonitrile (450 mg, 2.258 mmol) in ethanol (11 ml) was added HCl (12.1 M, 1.867 ml, 22.58 mmol) then 10% Pd/C (48.1 mg, 0.045 mmol) as a slurry in ethanol. The reaction mixture was put under H_2 balloon pressure for 21 hours. The reaction was filtered through a 0.45 μm syringe-tip filter, then concentrated *in vacuo*.

20 The product was used without further purification.



1-methyl-3-({[2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethyl]amino}methyl)quinolin-2(1H)-one

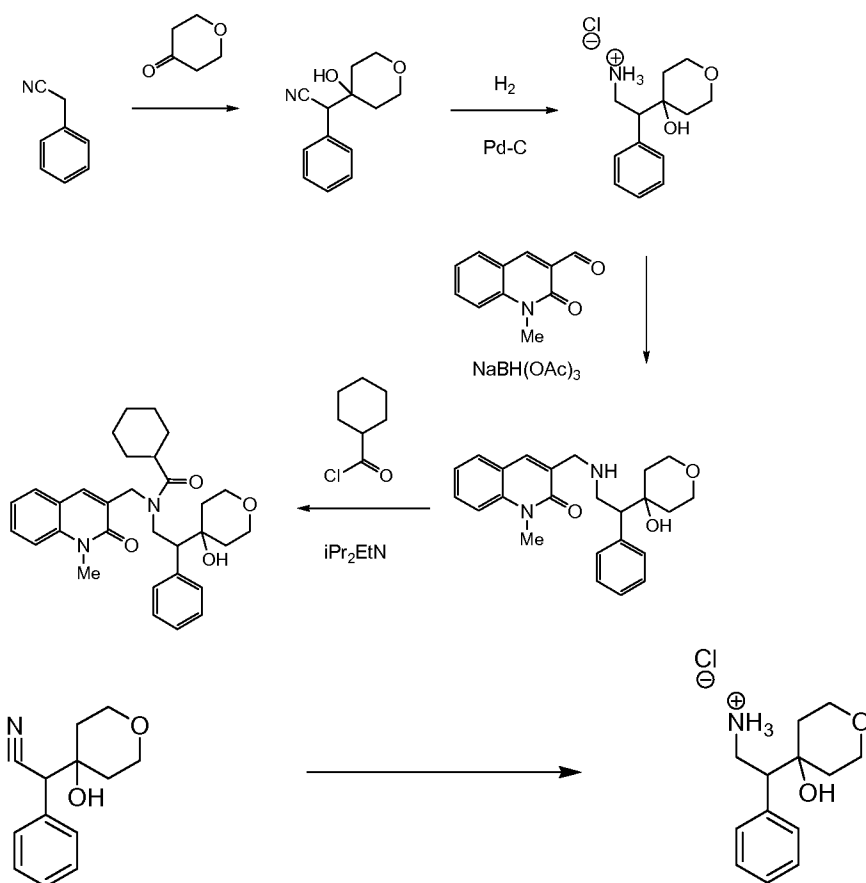
1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (35 mg, 0.187 mmol), sodium acetate (19.94 mg, 0.243 mmol), and 2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethanaminium chloride (45.2 mg, 0.187 mmol) were combined in 1,2 dichloroethane (2 ml). Acetic acid (0.021 ml, 0.374 mmol) and sodium triacetoxyborohydride (119 mg, 0.561 mmol) were added and the reaction stirred for 20 hours. The mixture was partitioned between CH₂Cl₂ and satd. bicarb and the aqueous portion was extracted 3x CH₂Cl₂. The organic portion was dried (Na₂SO₄) and concentrated *in vacuo*. The resulting material was purified by reversed-phase chromatography (10-60% ACN in water (with 2 ml/l NH₄OH) over 20 min at 20 ml/min, 20x100 mm Phenomenex Gemini C18 column). Desired fractions were concentrated *in vacuo*. 50.5 mg, 73%.



N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethyl]cyclohexanecarboxamide

To 1-methyl-3-({[2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethyl]amino}methyl)quinolin-2(1H)-one (46.5 mg, 0.124 mmol) in CH₂Cl₂ (3 ml) and added DIEA (0.043 ml, 0.247 mmol) then cyclohexanecarbonyl chloride (0.018 ml, 0.136 mmol). The reaction was stirred for 1 hour and then concentrated *in vacuo*. Purified by reversed-phase chromatography (15-75% ACN in water (with 0.5 ml/l NH₄OH), 20x100 mm Phenomenex Gemini C18 column). Desired fractions were concentrated *in vacuo*. HRMS [M+H]⁺ 487.2962. 400 MHz ¹H NMR (CDCl₃) δ 7.59-7.47 (m, 2 H), 7.37 (d, J = 8.52 Hz, 1 H), 7.33-7.13 (m, 7 H), 4.26 (d, J = 18.4, 1 H), 4.17-3.95 (m, 2 H), 3.88-3.76 (m, 2 H), 3.74 (s, 3 H), 3.44-3.23 (m, 3 H), 2.97-2.91 (m, 0.8 H, rotational isomer A), 2.67-2.62 (m, 0.2 H, rotational isomer B), 2.42-2.19 (m, 0.2 H, rotational isomer B), 2.15-2.08 (m, 0.8 H, rotational isomer A), 1.95-0.95 (m, 15 H). 29.4 mg, 49%.

Analogous hydroxyl-substituted compounds were obtained by omitting the SOCl₂-mediated elimination step:



2-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-phenylethanaminium chloride

5 To (4-hydroxytetrahydro-2H-pyran-4-yl)(phenyl)acetonitrile (50 mg, 0.230 mmol) in ethanol (2 ml) was added HCl (0.190 ml, 2.301 mmol) then 10% Pd/C (49.0 mg, 0.046 mmol) as a slurry in ethanol. The reaction mixture was put under H₂ balloon pressure for 15 hours. The reaction was filtered through a 0.45 μm syringe-tip filter, then concentrated *in vacuo*. The product was used without further purification. 49.6 mg, 84%.

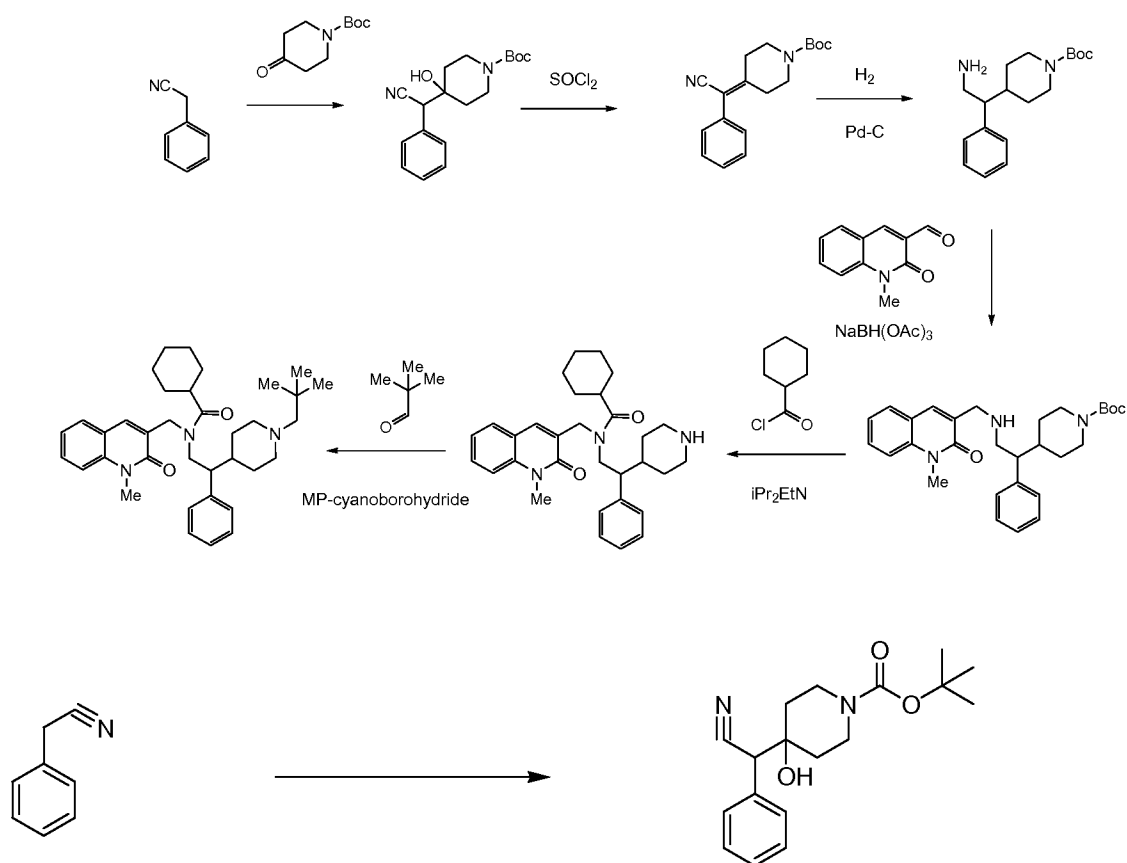
10

The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without

15 undue experimentation.

Name	MS <i>m/z</i> (M+H)
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N-[2-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	503.2927
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethyl]cyclohexanecarboxamide	487.2962
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-phenyl-2-(tetrahydro-2H-pyran-3-yl)ethyl]cyclohexanecarboxamide	487.2989

EXAMPLE 4

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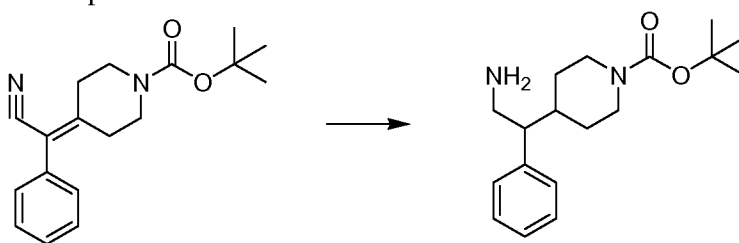
tert-butyl 4-[cyano(phenyl)methyl]-4-hydroxypiperidine-1-carboxylate

Benzyl cyanide (2.96 ml, 25.6 mmol) in THF (125 ml) was cooled to -78 °C. *n*BuLi (16.17 ml, 25.9 mmol) was added dropwise over 20 min via syringe pump, and the reaction stirred for 30 min. 1-BOC-4-piperidone (5.10 g, 25.6 mmol) in THF (20 ml) was added over 20 min via syringe pump and the reaction stirred for 2.5 hours. While still cold, the reaction was quenched with satd. NH₄Cl and allowed to warm overnight. The mixture was partitioned between CH₂Cl₂ and satd. NH₄Cl, the aqueous portion extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. The resulting material was carried on without further purification.



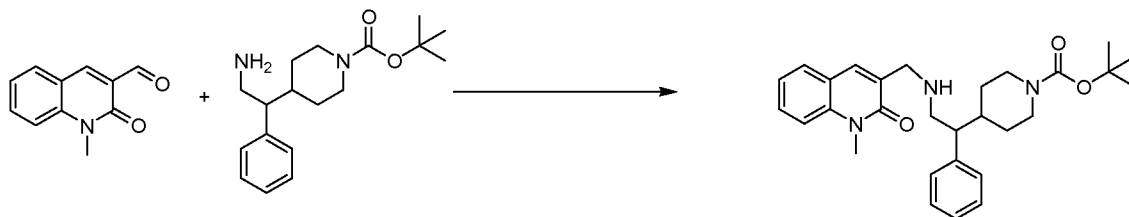
10 *tert*-butyl 4-[cyano(phenyl)methylene]piperidine-1-carboxylate

To *tert*-butyl 4-[cyano(phenyl)methyl]-4-hydroxypiperidine-1-carboxylate (1.8 g, 5.69 mmol) in pyridine (4 ml) was added SOCl₂ (2.076 ml, 28.4 mmol) and the reaction was stirred for 10 min. The reaction mixture was concentrated *in vacuo*. The resulting crystalline solid was adsorbed onto silica gel and purified by silica gel chromatography in an Isco Companion. The desired fractions were combined and concentrated *in vacuo*. 1.18 g, 70% over two steps.



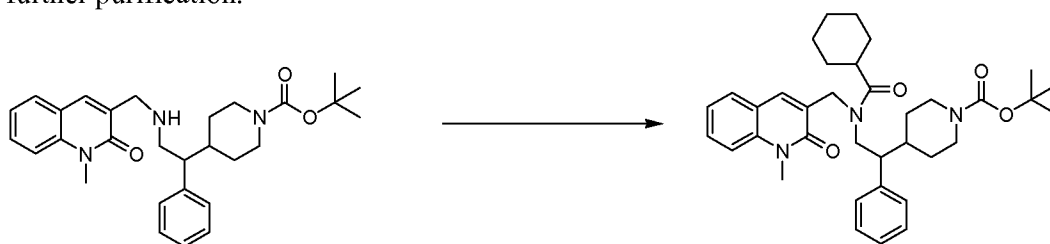
20 *tert*-butyl 4-(2-amino-1-phenylethyl)piperidine-1-carboxylate

tert-butyl 4-[cyano(phenyl)methylene]piperidine-1-carboxylate (1.18 g, 3.95 mmol) in ethanol (15 ml) was saturated with NH₃ at ambient temperature and Raney nickel (1 ml, 3.95 mmol) in water was added. The reaction was placed on a Parr reactor under H₂ pressure (48 psi) for 19 hours. The reaction mixture was then re-saturated with NH₃ and additional Raney nickel (1 ml, 3.95 mmol) was added before placing back on the Parr reactor for an additional 5.5 hours. The reaction mixture was filtered through Celite, washing with EtOH, and concentrated *in vacuo*. The product was carried on without further purification.



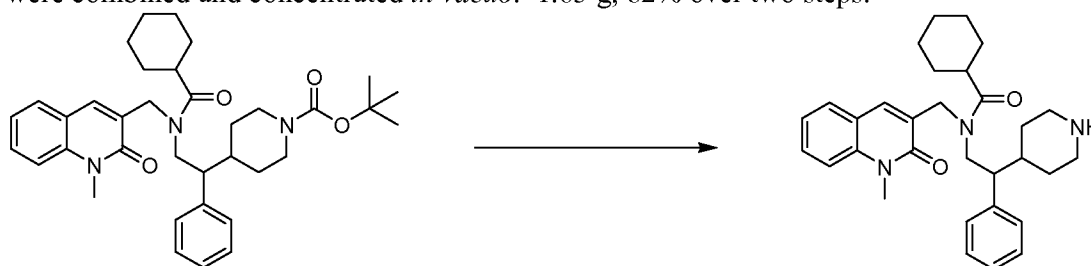
tert-butyl 4-(2-((1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)-1-phenylethyl)piperidine-1-carboxylate

1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (0.590 g, 3.15 mmol), *tert*-butyl 4-(2-amino-1-phenylethyl)piperidine-1-carboxylate (1.2 g crude, 3.94 mmol), and acetic acid (0.677 ml, 11.83 mmol) were combined in CH₂Cl₂ (20 ml). Sodium triacetoxyborohydride (2.506 g, 11.83 mmol) was added and the reaction stirred for 16 hours. The mixture was partitioned between CH₂Cl₂ and satd. bicarb, the aqueous portion extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. The product was carried on without further purification.



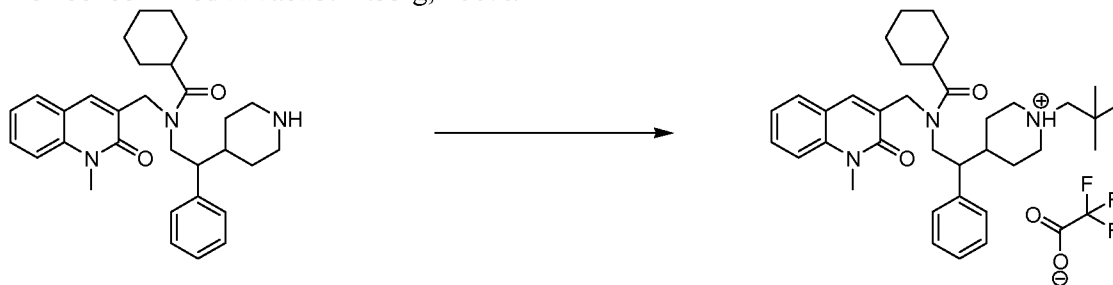
tert-butyl 4-(2-(cyclohexylcarbonyl)((1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)-1-phenylethyl)piperidine-1-carboxylate

tert-butyl 4-(2-((1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)-1-phenylethyl)piperidine-1-carboxylate (1.61 g crude, 3.39 mmol), EDC (1.298 g, 6.77 mmol), HOAT (0.461 g, 3.39 mmol), DIEA (1.182 ml, 6.77 mmol), and cyclohexanecarboxylic acid (0.504 ml, 4.06 mmol) were combined in CH₂Cl₂ and the reaction stirred for 15 hours. The mixture was partitioned between CH₂Cl₂ and satd. bicarb, the aqueous portion extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. The resulting material was purified by silica gel chromatography on an Isco Companion. The desired fractions were combined and concentrated *in vacuo*. 1.63 g, 82% over two steps.



N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-*N*-(2-phenyl-2-piperidin-4-ylethyl)cyclohexanecarboxamide

tert-butyl 4-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-1-phenylethyl)piperidine-1-carboxylate (1.63 g, 2.78 mmol) in CH₂Cl₂ (5 ml) was added to 4 M HCl in dioxane (20 mL, 80 mmol) at 0 °C and the reaction stirred for 1.5 hours before being poured into satd. bicarb. The mixture was partitioned between CH₂Cl₂ and satd. bicarb, the aqueous portion extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. 1.35 g, 100%.



4-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-1-phenylethyl)-1-(2,2-dimethylpropyl)piperidinium trifluoroacetate

Reaction was run in a library format; only the amine starting material was accurately measured. MP-cyanoborohydride (~0.165 mmol) and trimethylacetaldehyde (~21.3 mg, ~0.247 mmol) were combined. *N*-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-*N*-(2-phenyl-2-piperidin-4-ylethyl)cyclohexanecarboxamide (40 mg, 0.082 mmol) in CH₂Cl₂ (2 mL) and AcOH (0.014 ml, 0.247 mmol) were then added. The reaction vial was sealed and put on a rotator for 15 hours, after which time the mixture was filtered and concentrated. The resulting material was taken up in DMSO and sent to a purification group for reversed-phase purification, sample concentration, analysis, dilution, and plating. HRMS [M+H]⁺ 556.3899. ¹H NMR (400 MHz, CDCl₃): δ 7.76-7.73 (m, 1 H), 7.64-7.60 (m, 1 H), 7.55 (d, J = 8.42, 1 H), 7.46 (s, 1 H), 7.37-7.18 (m, 6 H), 4.22-4.14 (m, 1 H), 3.83-3.77 (m, 1 H), 3.69-3.61 (m, 4 H), 3.04-2.89 (m, 5 H), 2.55 (s, 3 H), 2.41-2.28 (m, 1 H), 2.10-1.92 (m, 2 H), 1.82-1.73 (m, 1 H), 1.61-1.52 (m, 4 H), 1.45-1.38 (m, 1 H), 1.32-1.25 (m, 3 H), 1.20-1.05 (m, 4 H), 1.00 (s, 9 H). 5 mg, 11%.

The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, as described in the foregoing Reaction Schemes and Examples, in particular by omitting the SOCl₂ –mediated elimination step. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

Name	MS <i>m/z</i> (M+H)
N-[2-(4-hydroxy-1-methylpiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	516.319
tert-butyl 4-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-1-phenylethyl)-4-hydroxypiperidine-1-carboxylate	602.3607
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-4-ylethyl)cyclohexanecarboxamide	484.3001
N-[2-(4-hydroxypiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	502.31
N-{2-[1-(2-hydroxyethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	530.3364
N-{2-[4-hydroxy-1-(2-hydroxyethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	546.336
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(1,3-oxazol-5-ylmethyl)piperidin-4-yl]-2-phenylethyl}cyclohexanecarboxamide	567.3365
N-{2-[1-(2,3-dihydroxypropyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	560.3512

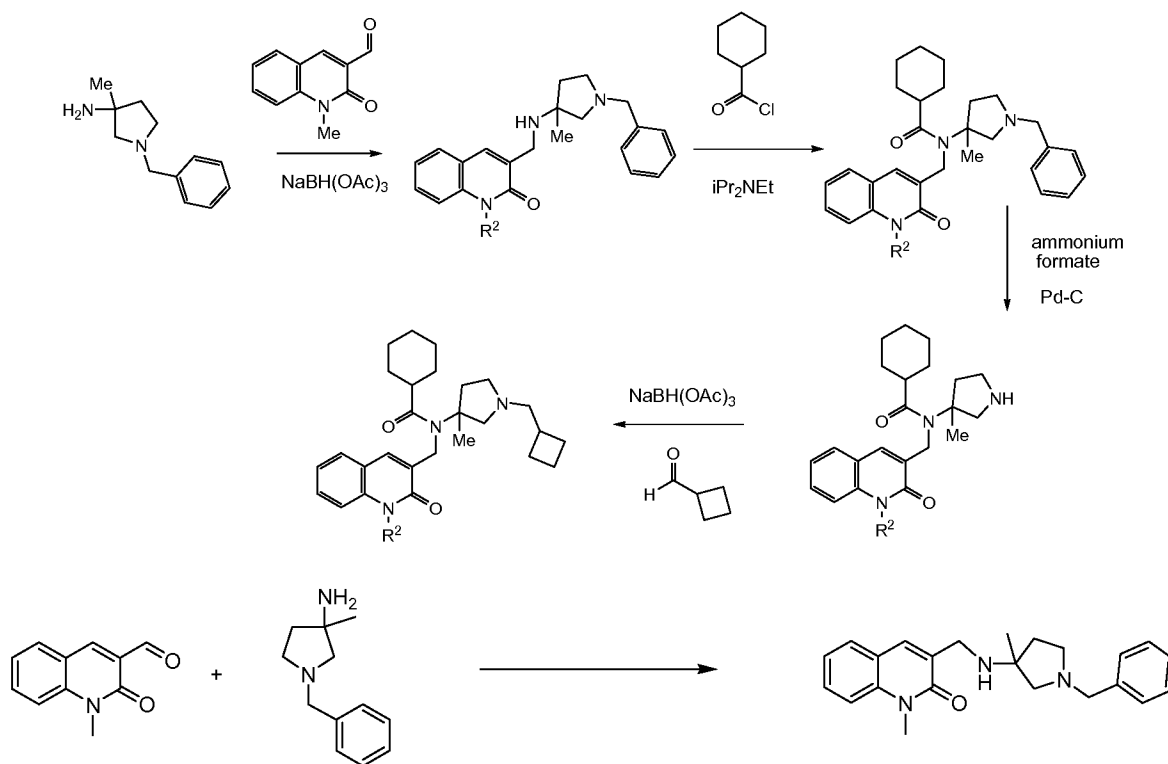
[4-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-1-phenylethyl)piperidin-1-yl]acetic acid	544.3184
N-{2-[1-(cyclopropylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	540.3602
N-{2-[1-(2,2-dimethylpropyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	556.3899
N-{2-[1-(cyclopentylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	568.3917
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(2-methylpropyl)piperidin-4-yl]-2-phenylethyl}cyclohexanecarboxamide	542.3753
N-[2-(1-butylpiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	542.3754
N-{2-[1-(3-methylbutyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	556.391
N-{2-[1-(1H-imidazol-2-ylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	566.3518
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(1,3-oxazol-2-ylmethyl)piperidin-4-yl]-2-phenylethyl}cyclohexanecarboxamide	567.3359

N-[2-(1-benzylpiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	576.362
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(pyridin-2-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	577.3563
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	577.3573
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(pyridin-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	577.3573
N-(2-{1-[(1-methyl-1H-imidazol-2-yl)methyl]piperidin-4-yl}-2-phenylethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	580.3684
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1,3-thiazol-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	583.3136
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(1,3-oxazol-4-ylmethyl)piperidin-4-yl]-2-phenylethyl}cyclohexanecarboxamide	567.3369
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1H-pyrazol-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	566.3538
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1H-pyrazol-5-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	566.352

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1H-1,2,3-triazol-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	567.3477
N-{2-[1-(cyclopropylmethyl)piperidin-4-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	464.3271
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(1H-pyrazol-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide	490.3177
N-{2-[1-(1H-imidazol-2-ylmethyl)piperidin-4-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	490.3176
N-{2-[1-(2,2-dimethylpropyl)piperidin-4-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	480.3584
N-{2-[1-(cyclopropylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	540.3577
N-{2-[1-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	556.3528
N-{2-[4-hydroxy-1-(1H-pyrazol-4-ylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	582.3446
N-{2-[4-hydroxy-1-(1H-imidazol-2-ylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	582.3445

N- {2-[1-(2,2-dimethylpropyl)-4-hydroxypiperidin-4-yl]-2-phenylethyl} -N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	572.3844
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EXAMPLE 5



3- {[(1-benzyl-3-methylpyrrolidin-3-yl)amino]methyl} -1-methylquinolin-2(1H)-one

1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (956 mg, 5.11 mmol), 1-benzyl-3-methylpyrrolidin-3-amine (972 mg, 5.11 mmol), and acetic acid (0.877 ml, 15.32 mmol) were combined in CH₂Cl₂ (25 ml) and stirred for 30 min. Sodium triacetoxyborohydride (3248 mg, 15.32 mmol) was added and the reaction stirred for 2.5 hours before being partitioned between CH₂Cl₂ and satd. bicarb. The aqueous portion was extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. The resulting material was carried on crude.

15



N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(3-methylpyrrolidin-3-yl)cyclohexanecarboxamide

To 3-[[1-(1-benzyl-3-methylpyrrolidin-3-yl)amino]methyl]-1-methylquinolin-2(1H)-one (1846 mg, 5.11 mmol) in CH₂Cl₂ (25 ml) was added DIEA (1.338 ml, 7.66 mmol). Cyclohexane carbonyl chloride (0.757 ml, 5.62 mmol) was added and the reaction stirred for 2 hours. The reaction was quenched with MeOH then concentrated *in vacuo*. The resulting material was twice purified by silica gel chromatography on an Isco Companion (5-35% acetone/hexane for first run, 5-25% acetone/hexane for second run). 2.12 g, 88% over two steps.

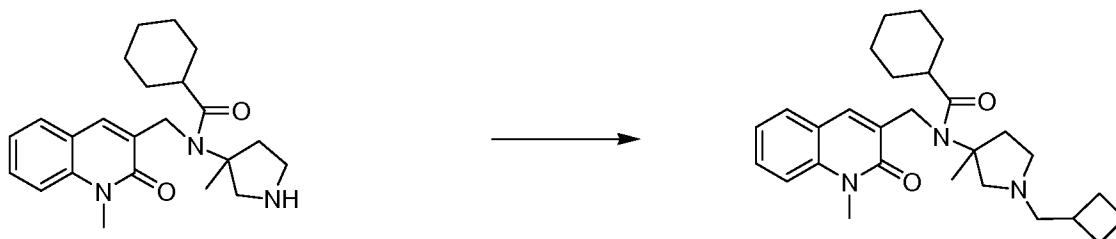
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N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(3-methylpyrrolidin-3-yl)cyclohexanecarboxamide

N-(1-benzyl-3-methylpyrrolidin-3-yl)-*N*-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide (1750 mg, 3.71 mmol) and ammonium formate (936 mg, 14.84 mmol) were combined in MeOH (37mL). 10% Pd/C (350 mg, 3.288 mmol) was added as a slurry in MeOH and the reaction heated to 60 °C for 15 hours. The reaction mixture was filtered through a 0.45 um syringe-tip filter and concentrated *in vacuo*. The resulting material was partitioned between CH₂Cl₂ and satd. bicarb, the aqueous portion extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. This material was carried on without further purification. 1.5 g, 106%.

20



N-[1-(cyclobutylmethyl)-3-methylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide

N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(3-methylpyrrolidin-3-yl)cyclohexanecarboxamide (300 mg, 0.786 mmol), cyclobutanecarbaldehyde (99 mg, 1.180 mmol), and acetic acid (0.090 ml, 1.573 mmol) were combined in CH₂Cl₂ (70 ml). Sodium triacetoxyborohydride (333 mg, 1.573 mmol) was added and the reaction stirred for 2.5 hours. The reaction mixture was partitioned between CH₂Cl₂ and satd. bicarb, the aqueous portion extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. The resulting material was purified in two batches by reversed phase chromatography (15-95% ACN in water (with 0.5 ml/l NH₄OH) over 20 min at 50 ml/min, 30x100 mm Phenomenex Gemini C18 column). Desired fractions were combined and concentrated *in vacuo*. HRMS [M+H]⁺ 450.3099. ¹H NMR (400 MHz, CDCl₃): δ 7.62-7.55 (m, 3 H); 7.42 (d, J = 8.5 Hz, 1 H); 7.29 (t, J = 7.6 Hz, 1 H); 4.44 (s, 2 H); 3.80 (s, 3 H); 2.99 (d, J = 10.0 Hz, 1 H); 2.85 (d, J = 10.2 Hz, 1 H); 2.53 (t, J = 7.9 Hz, 1 H); 2.47-2.35 (m, 4 H); 2.09-1.92 (m, 5 H); 1.92-1.64 (m, 14 H); 1.28-0.99 (m, 3 H). 210 mg, 59%.

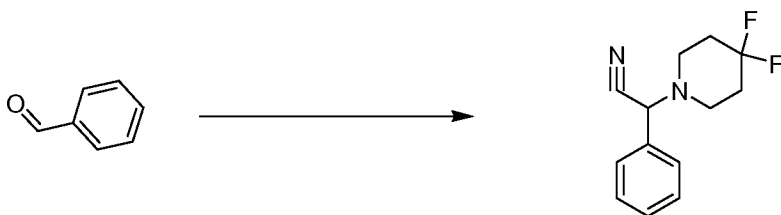
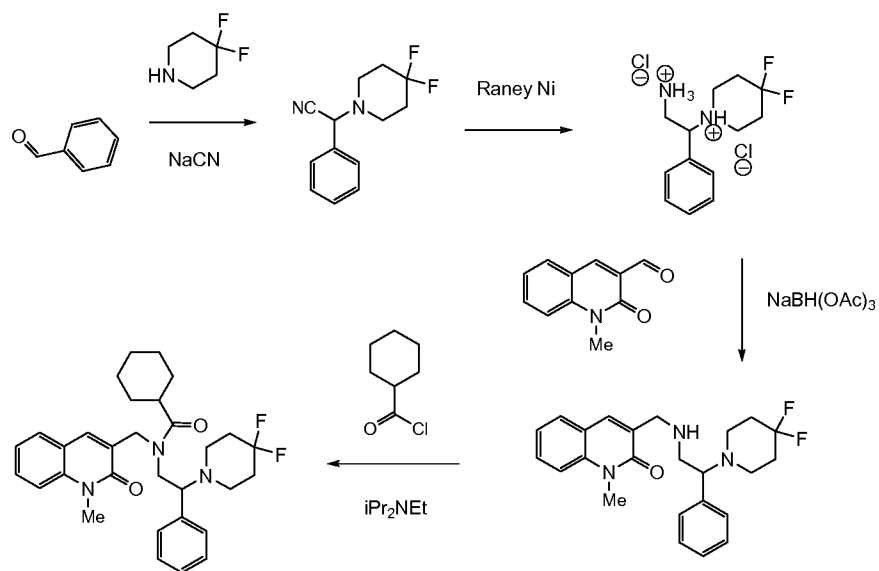
The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

Name	MS <i>m/z</i> (M+H)
N-(1-benzyl-3-methylpyrrolidin-3-yl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	472.2957
. tert-butyl 4-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino]piperidine-1-carboxylate	482.3042
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-piperidin-4-ylcyclohexanecarboxamide	382.2503

N-[1-(cyclopropylmethyl)piperidin-4-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	436.2967
N-[1-(cyclobutylmethyl)piperidin-4-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	450.3126
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1-methylpiperidin-4-yl)cyclohexanecarboxamide	396.2653
N-[1-(cyclopropylcarbonyl)piperidin-4-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	450.2766
N-[1-(cyclobutylmethyl)-3-methylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	450.16
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3R)-pyrrolidin-3-yl]cyclohexanecarboxamide	368.2335
N-(1,1-dimethyl-2-piperidin-1-ylethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	438.312
N-(1-benzylpiperidin-4-yl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	472.2952
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3R)-1-methylpyrrolidin-3-yl]cyclohexanecarboxamide	382.2484

N-[(3R)-1-ethylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	396.2651
N-[(3R)-1-(cyclopropylmethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	422.2808
N-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	367.2
N-[(3R)-1-acetylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	410.2462
N-[(3R)-1-(cyclopropylcarbonyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	436.2628
N-[(3R)-1-(cyclobutylmethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	436.2978

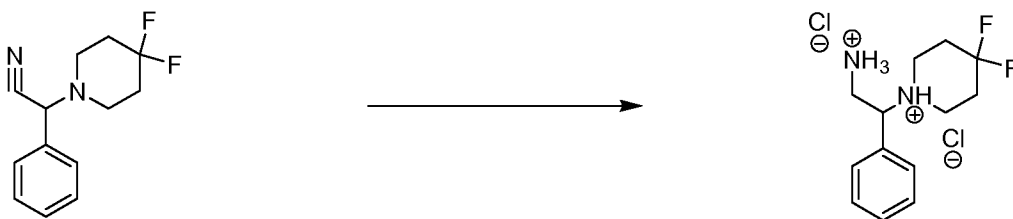
EXAMPLE 6



(4,4-difluoropiperidin-1-yl)(phenyl)acetonitrile

5 Benzaldehyde (1.284 ml, 12.63 mmol), 4,4-difluoropiperidine (1.53 g, 12.63 mmol), and NaCN (0.619 g, 12.63 mmol) were combined in MeOH (20 ml). Acetic acid (0.759 ml, 13.26 mmol) was added dropwise over 30 min via syringe pump and the mixture heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between water and CH₂Cl₂, the aqueous portion extracted 2x

10 CH₂Cl₂, and the organic portion dried (Na₂SO₄) and concentrated *in vacuo*. The resulting material was used without further purification.



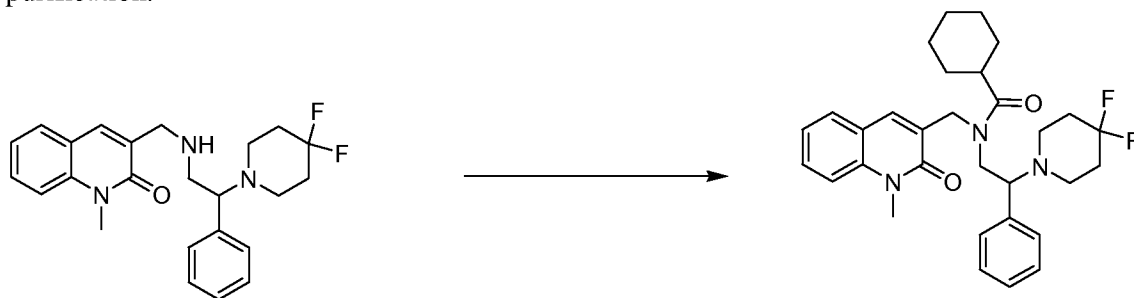
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1-(2-ammonio-1-phenylethyl)-4,4-difluoropiperidinium dichloride

(4,4-difluoropiperidin-1-yl)(phenyl)acetonitrile (500 mg, 2.116 mmol) was dissolved in EtOH (15 ml) and the solution saturated with NH₃ at ambient temperature. Raney nickel (1 ml, 2.116 mmol, 50% in water) was added and the reaction was put under H₂ balloon pressure for 1.5 hours. Additional Raney nickel (1 ml, 2.116 mmol, 50% in water) was added and the reaction resubmitted to H₂ for 2 hours. Additional Raney nickel (1 ml, 2.116 mmol, 50% in water) was added and the reaction resubmitted to H₂ for 3.5 hours. The reaction mixture was filtered through a 0.45 um syringe-tip filter, washing with EtOH, and concentrated *in vacuo*. The material was converted to the corresponding HCl salt by concentrating from HCl in ether and carried on crude.

3-({[2-(4,4-difluoropiperidin-1-yl)-2-phenylethyl]amino}methyl)-1-methylquinolin-2(1H)-one

1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (35 mg, 0.187 mmol), sodium acetate (19.94 mg, 0.243 mmol), and 1-(2-ammonio-1-phenylethyl)-4,4-difluoropiperidinium dichloride (51.7 mg, 0.187 mmol) were combined in 1,2-dichloroethane (2 ml). Acetic acid (0.021 ml, 0.374 mmol) and sodium triacetoxyborohydride (119 mg, 0.561 mmol) were added and the reaction stirred for 1 hour. The reaction mixture was partitioned between CH₂Cl₂ and satd. bicarb, the aqueous portion extracted 3x CH₂Cl₂, and the organic portion dried (Na₂SO₄) then concentrated *in vacuo*. The material was carried on without further purification.

N-[2-(4,4-difluoropiperidin-1-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide

3-([2-(4,4-difluoropiperidin-1-yl)-2-phenylethyl]amino)methyl)-1-methylquinolin-2(1H)-one (52 mg, 0.126 mmol), HATU (57.7 mg, 0.152 mmol), cyclohexanecarboxylic acid (0.019 ml, 0.152 mmol), and DIEA (0.026 ml, 0.152 mmol) were combined in DMF (1.5 ml) and the reaction heated at 50 °C for 0.75 hours. The mixture was purified directly by reversed-phase chromatography (15-95% ACN in water (with 0.5 ml/l NH₄OH) over 20 min at 20 ml/min, 20x100 mm Phenomenex Gemini C18 column). Fractions containing desired material were concentrated *in vacuo* and repurified by reversed-phase chromatography (5-50% ACN (with 0.1% TFA) in water (with 0.1% TFA) over 20 min at 20 ml/min, 20x100 mm Phenomenex Gemini C18 column). Desired fractions were free-based via Phenomenex Strata X-C cartridge. HRMS [M+H]¹⁺ 522.2936. ¹H NMR (400 MHz, CDCl₃): δ 7.60-7.55 (m, 1 H), 7.53-7.49 (m, 1 H), 7.39 (d, J = 8.52 Hz, 1 H), 7.35-7.28 (m, 4 H), 7.25-7.19 (m, 3 H), 4.50-4.35 (m, 2 H), 4.16-4.07 (m, 1 H), 3.88 (t, J = 7.6 Hz, 1 H), 3.76 (s, 3 H), 3.31 (dd, J = 7.38 Hz, 13.42 Hz, 1 H), 2.69-2.65 (m, 2 H), 2.53-2.43 (m, 2 H), 2.28-2.20 (m, 1 H), 2.01-1.88 (m, 4 H), 1.74-1.34 (m, 7 H), 1.25-1.05 (m, 3 H). 29.8mg, 45%.

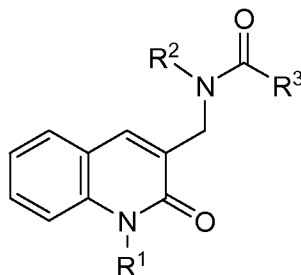
The following compounds were prepared using the foregoing methodology, but substituting the appropriately substituted reagent, as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

Name	MS <i>m/z</i> (M+H)
N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide	490.6
N-[2-(4,4-difluoropiperidin-1-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide	522.2936
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-morpholin-4-yl-2-phenylethyl)cyclohexanecarboxamide	488.2912

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

5

wherein:

R^1 is hydrogen or C_{1-6} alkyl, which is unsubstituted or substituted with $-O-C_{1-6}$ alkyl;

R^2 is $-C_{0-6}$ alkyl, which is substituted with one or more substituents selected from R^4 ,

10

wherein R^4 is selected from the group consisting of:

- (1) $-C_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{13} ,
- (2) $-C_{3-8}$ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13} , or where the cycloalkyl may be fused to a phenyl, where the phenyl is unsubstituted or substituted with one or more substituents selected from R^{13} ,
- 15 (3) $-C_{3-8}$ cycloalkoxyl, where the cycloalkoxyl is unsubstituted or substituted with one or more substituents selected from R^{13} , or where the cycloalkyl may be fused to a phenyl, where the phenyl is unsubstituted or substituted with one or more substituents selected from R^{13} ,
- (4) $-phenyl$ or $-naphthyl$, where the phenyl or naphthyl is unsubstituted or substituted with one or more substituents selected from R^{13} ,
- (5) $-heterocycle$, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13} ,
- 20 (6) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from the group consisting of:
 - (a) hydrogen,
 - (b) C_{1-6} alkyl, which is unsubstituted or substituted with R^{13} ,
 - (c) C_{3-6} alkenyl, which is unsubstituted or substituted with R^{13} ,

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- (d) C₃₋₆alkynyl, which is unsubstituted or substituted with R¹³,
- (e) C₃₋₆cycloalkyl which is unsubstituted or substituted with R¹³,
- (f) phenyl, which is unsubstituted or substituted with R¹³, and
- (g) heterocycle, which is unsubstituted or substituted with R¹³;

5

R³ is selected from the group consisting of:

- (1) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- (2) -C₃₋₆cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- (3) -phenyl or -naphthyl, where the phenyl or naphthyl is unsubstituted or substituted with one or more substituents selected from R¹³,
- (4) -heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R¹³,
- (5) -NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are independently selected from the group consisting of:
 - (a) hydrogen,
 - (b) C₁₋₆alkyl, which is unsubstituted or substituted with R¹³,
 - (c) C₃₋₆alkenyl, which is unsubstituted or substituted with R¹³,
 - (d) C₃₋₆alkynyl, which is unsubstituted or substituted with R¹³,
 - (e) C₃₋₆cycloalkyl which is unsubstituted or substituted with R¹³,
 - (f) phenyl, which is unsubstituted or substituted with R¹³, and
 - (g) heterocycle, which is unsubstituted or substituted with R¹³;

25 R¹³ is selected from the group consisting of:

- (1) halogen,
- (2) hydroxyl,
- (3) -(C=O)_m-O_n-C₁₋₆alkyl, where m is 0 or 1, n is 0 or 1 (wherein if m is 0 or n is 0, a bond is present) and where the alkyl is unsubstituted or substituted with one or more substituents selected from R¹⁴,
- (4) -O_n-(C₁₋₃)perfluoroalkyl,
- (5) -(C=O)_m-O_n-C₃₋₆cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R¹⁴,
- (6) -(C=O)_m-C₂₋₄alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R¹⁴,

35

- (7) $-(C=O)_m-C_{2-4}$ alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R^{14} ,
- (8) $-(C=O)_m-O_n$ -phenyl or $-(C=O)_m-O_n$ -naphthyl, where the phenyl or naphthyl is unsubstituted or substituted with one or more substituents selected from R^{14} ,
- 5 (9) $-(C=O)_m-O_n$ -heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{14} ,
- (10) $-(C=O)_m-NR^{15}R^{16}$, where R^{15} and R^{16} are independently selected from hydrogen and $-C_{1-6}$ alkyl, which is unsubstituted or substituted with phenyl,
- (11) $-S(O)_2-NR^{15}R^{16}$,
- 10 (12) $-S(O)_q-R^{12}$, where q is 0, 1 or 2 and where R^{12} is $-C_{1-6}$ alkyl, which is unsubstituted or substituted with phenyl;
- (13) $-CO_2H$,
- (14) $-CN$, and
- (15) $-NO_2$;

15

R^{14} is selected from the group consisting of:

- (1) hydroxyl,
- (2) halogen,
- (3) C_{1-6} alkyl,
- 20 (4) $-C_{3-6}$ cycloalkyl,
- (5) $-O-C_{1-6}$ alkyl,
- (6) $-O(C=O)-C_{1-6}$ alkyl,
- (7) $-NH-C_{1-6}$ alkyl,
- (8) phenyl,
- 25 (9) heterocycle,
- (10) $-CO_2H$, and
- (11) $-CN$;

or a pharmaceutically acceptable salt thereof.

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2. The compound of Claim 1 wherein R^1 is hydrogen or methyl.

3. The compound of Claim 2 wherein R^1 is methyl.

4. The compound of Claim 1 wherein R^2 is selected from the group consisting

35 of:

- 5
- (1) tetralone,
 - (2) -CH₂-cyclohexyl, where the cyclohexyl is unsubstituted or substituted with one or more substituents selected from R¹³,
 - (3) -CH₂-morpholinyl, where the morpholinyl is unsubstituted or substituted with one or more substituents selected from R¹³, and
 - (4) -CH₂-CH-(phenyl)heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R¹³.

10 of: 5. The compound of Claim 1 wherein R³ is selected from the group consisting

- (1) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from -C₃₋₆cycloalkyl and phenyl, where the cycloalkyl and phenyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of:

15

 - (a) halogen,
 - (b) hydroxyl,
 - (c) C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or naphthyl, and
 - (d) -O-C₁₋₆alkyl, which is unsubstituted or substituted with halogen,

20

hydroxyl or phenyl;
- (2) -C₃₋₆cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from -C₁₋₆alkyl and phenyl, where the alkyl and phenyl are independently unsubstituted or substituted with one or more substituents selected from the group consisting of:

25

 - (a) halogen,
 - (b) hydroxyl,
 - (c) C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or naphthyl, and
 - (d) -O-C₁₋₆alkyl, which is unsubstituted or substituted with halogen,

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hydroxyl or phenyl;
- (3) -phenyl, which is unsubstituted or substituted with one or more substituents selected from the group consisting of:

35

 - (a) halogen,
 - (b) hydroxyl,
 - (c) C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl or naphthyl, and

(d) -O-C₁₋₆alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl.

6. The compound of Claim 5 wherein R³ is selected from the group consisting of: cyclohexyl, cyclopentyl, sec-butyl, neo-pentyl and phenyl.

7. The compound of Claim 6 wherein R³ is cyclohexyl.

8. A compound which is selected from the group consisting of:

- 10 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)oxepan-3-yl)methyl}cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{4-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl}cyclohexanecarboxamide;
- 15 N-({4-[4-(1-methylethyl)piperazin-1-yl]tetrahydro-2H-pyran-4-yl}methyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{4-(4-phenylpiperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl}cyclohexanecarboxamide;
- N-{{4-(4-benzylpiperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 20 N-({4-[4-(2-hydroxyethyl)piperazin-1-yl]tetrahydro-2H-pyran-4-yl}methyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(4-piperazin-1-yl)tetrahydro-2H-pyran-4-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-({4-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]tetrahydro-2H-pyran-4-yl}methyl)cyclohexanecarboxamide;
- 25 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}cyclohexanecarboxamide;
- N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 30 4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}-N-2-(2,2,2-trifluoroethyl)-L-valinamide
- N-[3-methoxy-2-methyl-2-(4-methylpiperazin-1-yl)propyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 35

- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} cyclohexanecarboxamide;
- 5 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3-piperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} cycloheptanecarboxamide;
- 2-ethyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} butanamide;
- 10 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}-2-propylpentanamide
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} cyclopentanecarboxamide;
- 15 2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} acetamide
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydrofuran-3-yl)methyl} cyclohexanecarboxamide;
- N-{{3-(4-methyl-1,4-diazepan-1-yl)tetrahydro-2H-pyran-3-yl)methyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 20 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(2-phenylpiperidin-1-yl)ethyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(2-phenylpyrrolidin-1-yl)ethyl]cyclohexanecarboxamide;
- 25 N-{{2-[benzyl(methyl)amino]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-5-phenyl-1,2-dihydropyridin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} cyclohexanecarboxamide;
- (1S,4R)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} bicyclo[2.2.1]heptane-2-carboxamide;
- 30 3-methoxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}-4-(trifluoromethyl)cyclohexanecarboxamide;
- 35 2-methyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{{3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl} cyclohexanecarboxamide;

- 4-(1-methylethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}cyclohexanecarboxamide;
- 4-tert-butyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}cyclohexanecarboxamide;
- 5 2-cyclohexyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}acetamide
- 4-methyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}pentanamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}benzamide
- 10 3-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}propanamide
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}-2-phenylacetamide
- 15 2-cycloheptyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}acetamide
- 3,3-difluoro-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}cyclopentanecarboxamide;
- 4,4-difluoro-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[3-(4-methylpiperazin-1-yl)tetrahydro-2H-pyran-3-yl)methyl}cyclohexanecarboxamide;
- 20 N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-benzothiophene-2-carboxamide;
- N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-3-phenylpropanamide;
- 25 (1R,2R,4R)-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]bicyclo[2.2.1]hept-5-ene-2-carboxamide;
- (1S,2S)-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-2-phenylcyclopropanecarboxamide;
- N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclopropanecarboxamide;
- 30 3-methyl-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]butanamide;;
- 3-cyclopentyl-1- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]urea;
- 35 N-[(1-morpholin-4-ylcyclohexyl)methyl]-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;

- N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-yl)cyclohexyl)methyl]cyclohexanecarboxamide;
N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl]-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 5 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl} cyclohexanecarboxamide;
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclobutyl)methyl} cyclohexanecarboxamide;
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclopentyl)methyl} cyclohexanecarboxamide;
- 10 (1R,2R,4R)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclopentyl)methyl} bicyclo[2.2.1]hept-5-ene-2-carboxamide;
2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclopentyl)methyl} acetamide;
- 15 2-(1-hydroxycyclopentyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl} acetamide;
cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl} cyclohexanecarboxamide;
4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-
- 20 methylpiperazin-1-yl)cyclohexyl)methyl} cyclohexanecarboxamide;
cis-4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl} cyclohexanecarboxamide;
trans-4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl} cyclohexanecarboxamide;
- 25 N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl} cyclohexanecarboxamide;
N- {[1-(2-methoxyethyl)-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl} cyclohexanecarboxamide;
- 30 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-yl)cycloheptyl)methyl]cyclohexanecarboxamide;
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-yl)cyclopentyl)methyl]cyclohexanecarboxamide;
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-yl)cyclohexyl)methyl]cyclohexanecarboxamide;
- 35 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-yl)cyclohexyl)methyl]cyclohexanecarboxamide;

- cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-yl)cyclohexyl)methyl]cyclohexanecarboxamide;
- cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-yl)cyclohexyl)methyl]cyclohexanecarboxamide;
- 5 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-piperidin-1-yl)cyclopentyl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1-morpholin-4-yl)cycloheptyl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{[1-(4-methylpiperazin-1-yl)cyclohexyl)methyl}cyclohexanecarboxamide;
- 10 N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)benzamide;
- 3-methyl-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)butanamide;
- 3-tert-butyl-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(2-phenyl-2-piperidin-1-ylethyl)urea
- 15 2-methyl-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide;
- N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-2-phenyl-N-(2-phenyl-2-piperidin-1-ylethyl)acetamide;
- N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide;
- 20 N-[1-(2-methylphenyl)piperidin-4-yl]-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 3-methyl-N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1,2,3,4-tetrahydronaphthalen-1-yl)butanamide;
- N-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)thiophene-2-
- 25 carboxamide;
- 3-(2-chlorophenyl)-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(1,2,3,4-tetrahydronaphthalen-1-yl)urea;
- 3-(2-methoxyphenyl)-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(1,2,3,4-tetrahydronaphthalen-1-yl)urea;
- 30 3-cyclopentyl-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(2-phenyl-2-piperidin-1-ylethyl)urea;
- 3-cyclohexyl-1-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]-1-(2-phenyl-2-piperidin-1-ylethyl)urea;
- 2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-
- 35 1-yl)-2-phenylethyl]acetamide;

- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-1-yl)-2-phenylethyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide;
- 5 2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-1-yl)ethyl]acetamide;
- 2-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)acetamide;
- cis-4-(hydroxymethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide;
- 10 2-(1-hydroxycyclopentyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)acetamide;
- cis-4-hydroxy-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide;
- 15 N-(1-benzylpiperidin-3-yl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[2-(3,4-dihydroisoquinolin-2(1H)-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-{4-[2-(4-
- 20 methylphenyl)ethyl]piperidin-1-yl}ethyl)cyclohexanecarboxamide;
- N-[2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[2-(2,3-dihydro-1H-indol-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 25 N-[2-(4-benzylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[2-(4-benzylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[3-(2-methylphenyl)pyrrolidin-1-
- 30 yl]ethyl}cyclohexanecarboxamide;
- N-{2-[2-(1H-indol-2-yl)piperidin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 1-tert-butyl-2-methyl-(2S,4S)-4-{(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}pyrrolidine-1,2-dicarboxylate;
- 35 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(2-phenyl-5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-yl)ethyl]cyclohexanecarboxamide;

- benzyl-3-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-2-phenylpiperidine-1-carboxylate;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-piperidin-1-yl-2-pyridin-3-ylethyl)cyclohexanecarboxamide;
- 5 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[2-(phenoxyethyl)morpholin-4-yl]ethyl}cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(4-methylpiperazin-1-yl)ethyl]cyclohexanecarboxamide;
- N-[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 10 N-[2-(dimethylamino)-1-methylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- benzyl-{2-[(tert-butoxycarbonyl)amino]ethyl}{2-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}ethyl}carbamate;
- 15 N-{2-[4-(2,3-dihydro-1H-inden-2-yl)piperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- tert-butyl-[(3R,4R)-1-benzyl-4-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino]pyrrolidin-3-yl]carbamate;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[4-(phenylcarbonyl)piperazin-1-yl]ethyl}cyclohexanecarboxamide;
- 20 N-{2-[3-(1,3-benzoxazol-2-yl)piperidin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[2-(4-benzylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 25 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(2S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1S,2R)-2-phenylcyclopentyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3R,4R)-1-methyl-3-phenylpiperidin-4-yl]cyclohexanecarboxamide;
- 30 N-[2-(3,3-dimethylpiperidin-2-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1S,2S)-2-phenylcyclopentyl]cyclohexanecarboxamide;
- 35 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenylcyclopentyl)cyclohexanecarboxamide;

- N-[3-(diethylamino)-1,1-dimethylpropyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(1S,9aR)-octahydro-2H-quinolizin-1-ylmethyl]cyclohexanecarboxamide;
- 5 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1-methyl-3-pyrrolidin-1-ylpropyl)cyclohexanecarboxamide;
- N-(1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-(1,1-dimethyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 10 N-(1,1-dimethyl-3-pyrrolidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-(3-phenylpyrrolidin-1-yl)ethyl]cyclohexanecarboxamide;
- 15 N-[2-(dimethylamino)-2-pyridin-2-ylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[4-(1-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl} cyclohexanecarboxamide;
- tert-butyl-{[1-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)ethyl)piperidin-3-yl]methyl} carbamate
- 20 tert-butyl-1-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino) methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate;
- N-[(3R)-1-(1-methylethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 25 N-[[1-(1-methylethyl)pyrrolidin-2-yl]methyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[[1-(1-methylethyl)pyrrolidin-2-yl]methyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(3S)-1-benzylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 30 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-piperazin-1-ylethyl)cyclohexanecarboxamide;
- N-[(3R)-1-benzylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 35 N-(1,1-dimethyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;

- tert-butyl-4-(3-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-3-methylbutyl)piperazine-1-carboxylate;
tert-butyl-4-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)ethyl)piperidine-1-carboxylate;
- 5 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-piperidin-4-ylethyl)cyclohexanecarboxamide;
N-(1-ethyl-1-methyl-3-(4,4-difluoro-piperidin-1-yl)propyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]tetrahydro-2H-pyran-4-carboxamide;
- 10 N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-4,4-difluoro-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 15 N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]tetrahydro-2H-pyran-3-carboxamide;
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]tetrahydro-2H-pyran-2-carboxamide;
- 20 N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-2-(tetrahydrofuran-3-yl)acetamide;
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-2-(1-hydroxycyclopentyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]acetamide;
- 25 N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 30 N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-(1-ethyl-1-methyl-3-piperidin-1-ylpropyl)-N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 35 N-(1-ethyl-1-methyl-3-morpholin-4-ylpropyl)-N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]cyclohexanecarboxamide;

- N- {2-[2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N- {2-[4-(cyclopropylmethyl)-2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 5 N- {2-[4-(cyclopropylcarbonyl)-2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N- {2-[4-(cyclobutylmethyl)-2-phenylpiperazin-1-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[2-(4-benzyl-2-phenylpiperazin-1-yl)ethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 10 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethyl]cyclohexanecarboxamide;
- N-[2-(4-hydroxytetrahydro-2H-pyran-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 15 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-phenyl-2-(tetrahydro-2H-pyran-4-yl)ethyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[2-phenyl-2-(tetrahydro-2H-pyran-3-yl)ethyl]cyclohexanecarboxamide;
- 4-(2-{{cyclohexylcarbonyl}[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}-1-phenylethyl)-1-(2,2-dimethylpropyl)piperidine;
- 20 N-[2-(4-hydroxy-1-methylpiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- tert-butyl-4-(2-{{cyclohexylcarbonyl}[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}-1-phenylethyl)-4-hydroxypiperidine-1-carboxylate;
- 25 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-4-ylethyl)cyclohexanecarboxamide;
- N-[2-(4-hydroxypiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N- {2-[1-(2-hydroxyethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 30 N- {2-[4-hydroxy-1-(2-hydroxyethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N- {2-[1-(1,3-oxazol-5-yl)methyl]piperidin-4-yl]-2-phenylethyl} cyclohexanecarboxamide;
- 35 N- {2-[1-(2,3-dihydroxypropyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;

- [4-(2-((cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-1-phenylethyl)piperidin-1-yl]acetic acid;
- N-{2-[1-(cyclopropylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 5 N-{2-[1-(2,2-dimethylpropyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-{2-[1-(cyclopentylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(2-methylpropyl)piperidin-4-yl]-
- 10 2-phenylethyl}cyclohexanecarboxamide;
- N-[2-(1-butylpiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-{2-[1-(3-methylbutyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 15 N-{2-[1-(1H-imidazol-2-ylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(1,3-oxazol-2-ylmethyl)piperidin-4-yl]-2-phenylethyl}cyclohexanecarboxamide;
- N-[2-(1-benzylpiperidin-4-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-
- 20 yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(pyridin-2-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;
- 25 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(pyridin-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;
- N-(2-{1-[(1-methyl-1H-imidazol-2-yl)methyl]piperidin-4-yl}-2-phenylethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1,3-thiazol-4-
- 30 ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(1,3-oxazol-4-ylmethyl)piperidin-4-yl]-2-phenylethyl}cyclohexanecarboxamide;
- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1H-pyrazol-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;
- 35 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1H-pyrazol-5-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;

- N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-phenyl-2-[1-(1H-1,2,3-triazol-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;
N-{2-[1-(cyclopropylmethyl)piperidin-4-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 5 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-{2-[1-(1H-pyrazol-4-ylmethyl)piperidin-4-yl]ethyl}cyclohexanecarboxamide;
N-{2-[1-(1H-imidazol-2-ylmethyl)piperidin-4-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 10 N-{2-[1-(2,2-dimethylpropyl)piperidin-4-yl]ethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-{2-[1-(cyclopropylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-{2-[1-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 15 N-{2-[4-hydroxy-1-(1H-pyrazol-4-ylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-{2-[4-hydroxy-1-(1H-imidazol-2-ylmethyl)piperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 20 N-{2-[1-(2,2-dimethylpropyl)-4-hydroxypiperidin-4-yl]-2-phenylethyl}-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-[1-(cyclobutylmethyl)-3-methylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- N-(1-benzyl-3-methylpyrrolidin-3-yl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 25 tert-butyl-4-[(cyclohexylcarbonyl)[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}piperidine-1-carboxylate;
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-piperidin-4-ylcyclohexanecarboxamide;
- N-[1-(cyclopropylmethyl)piperidin-4-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 30 N-[1-(cyclobutylmethyl)piperidin-4-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(1-methylpiperidin-4-yl)cyclohexanecarboxamide;
- 35 N-[1-(cyclopropylcarbonyl)piperidin-4-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;

- N-[1-(cyclobutylmethyl)-3-methylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3R)-pyrrolidin-3-yl]cyclohexanecarboxamide;
- 5 N-(1,1-dimethyl-2-piperidin-1-ylethyl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-(1-benzylpiperidin-4-yl)-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-[(3R)-1-methylpyrrolidin-3-yl]cyclohexanecarboxamide;
- 10 N-[(3R)-1-ethylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[(3R)-1-(cyclopropylmethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 15 N-cyclopentyl-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[(3R)-1-acetylpyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[(3R)-1-(cyclopropylcarbonyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
- 20 N-[(3R)-1-(cyclobutylmethyl)pyrrolidin-3-yl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[2-(4,4-difluoropiperidin-1-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[(1-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl]-N-(2-phenyl-2-piperidin-1-ylethyl)cyclohexanecarboxamide;
- 25 N-[2-(4,4-difluoropiperidin-1-yl)-2-phenylethyl]-N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]cyclohexanecarboxamide;
 N-[(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl]-N-(2-morpholin-4-yl-2-phenylethyl)cyclohexanecarboxamide;
- 30 or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

- 35 10. A compound of Claim 1 or a pharmaceutically acceptable salt thereof for use in medicine.

11. Use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a sleep disorder.

5 12. A method for enhancing the quality of sleep in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

10 13. A method for treating insomnia in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

15 14. A method for treating or controlling anxiety in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

20 15. A method for treating or controlling depression in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

25 16. A method for treating or controlling inflammatory bowel disease in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

 17. A method for treating or controlling obesity in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/63030

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/42; A61K 31/47 (2009.01)

USPC - 514/311

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC - 514/311

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/187; 514/253.06 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: (oxo)quinolines, treatment, sleep disorders, anxiety, depression, obesity, inflammatory bowel disease, administer, mammals, compositions, carrier, 2-oxoquinoline, GPCR, screening, 5HT2C, CB2-ligand, docking, binding pocket. INTERNET search - Google - same

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/019940 A2 (FEVIG et al.) 23 February 2006 (23.02.2006) pg 1, ln 9-20; pg 3, ln 1-18, 23-26; pg 28, ln 13-22, 27-32; pg 30, ln 22-32; pg 42, ln 15-16; pg 48, ln 10 - pg 50, ln 29; Claim 1	1-17
Y	EP 1 142 877 A1 (INABA et al.) 10 October 2001 (10.10.2001) para [0020]-[0021], [0023], [0029], [0032], [0035].	1-17
Y	CHEN et al. GPCR Structure-Based Virtual Screening Approach for CB2 Antagonist Search. J Chem Inf Model, 2007, Vol 47(4), pp 1626-1637; Abstract; pg 1629 - Fig 1; pg 1630-1636	1-17

 Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

14 December 2009 (14.12.2009)

Date of mailing of the international search report

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